Prevention of Sudden Cardiac Death with Beta Blockers

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Summary: Beta blockers have been shown to reduce the risk of sudden cardiac death in more than 50 randomized trials involving more than 55,000 patients. Relative reductions (vs. placebo) in cardiac death in some of these trials ranged from 30 to 50%. These reductions are substantially greater than trials of other drug classes including angiotensin-converting enzyme inhibitors. However, not all beta blockers confer equal benefit to patients at risk of sudden cardiac death. Results from various trials suggest that lipophilic beta blockers—such as timolol, metoprolol, propranolol, bisoprolol, and carvedilol—may be more beneficial than hydrophilic beta blockers. Results of animal studies have indicated that sudden cardiac death is mediated, at least in part, by the central nervous system, which may account for why lipophilic agents have more pronounced clinical effects.

Based on the results of numerous clinical and mechanistic studies, it is suggested that beta blockers should be given to all patients at risk for sudden cardiac death, including those patients with previous myocardial infarction, hypertension, or congestive heart failure.

Key words: beta blockers, sudden cardiac death, trials

Introduction

It is known that about half of all deaths among patients with ischemic heart disease is due to sudden cardiac death. Sudden cardiac death is responsible for about 300,000–400,000 deaths each year in the US.1 In the majority of cases, the cause of sudden death is thought to be ventricular fibrillation shortly after onset of acute ischemia. In some patients ventricular fibrillation occurs without any prior symptoms. To reduce the incidence of sudden cardiac death, patients at risk of developing sudden cardiac death should be identified; therapies with proven effects on sudden cardiac death have to be identified; and such therapies ought to be given to all patients at risk, considering contraindications and side effects.

During the past two decades, several treatments have been found to reduce mortality in patients with ischemic heart disease, including coronary artery revascularization and administration of beta blockers, aspirin, thrombolytic agents, and angiotensin-converting enzyme (ACE) inhibitors. In selected groups of patients, these therapies have been found to reduce total mortality significantly.2 On the other hand, other groups of drugs, including antiarrhythmic agents, calcium antagonists, and nitrates, have failed to reduce mortality in patients with ischemic heart disease. Only one group of drugs, beta blockers, has been found to have an even more marked effect on sudden cardiac death than on other modes of death.

Myocardial Infarction

In 1981, three placebo-controlled trials, the Norwegian Timolol,3 the Beta-Blocker Heart Attack Trial (BHAT),4 and the Göteborg Metoprolol5 trials, were published. They showed for the first time that medical treatment started after onset of myocardial infarction reduced total mortality. The two studies on timolol and propranolol were started 1–2 weeks after onset of acute myocardial infarction with a follow-up time of about 2 years. Total mortality was reduced by 36 and 26%, respectively. In the Metoprolol Trial, the beta blocker was given to patients with suspected acute myocardial infarction within the first 24 hours of the incident. The ISIS-1 Trial reduced cardiovascular mortality by 14% after 7 days and the MIAMI Trial showed a 13% nonsignificant difference of 15 days total

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mortality. Pooling all early intervention trials starting with intravenous administration of a beta blocker, there are 28 trials including more than 27,000 patients. The pooled data showed a significant 13% reduction in total mortality (Table I).

In 16 of the postinfarction trials, sudden cardiac death—mostly deaths within 1–24 h after onset of symptoms—has been reported (Tables I, II). In the BHA T Trial, death occurring within 1 h after onset of symptoms was reduced by 28%, while in the trials on timolol and metoprolol sudden death defined as death within 24 h after onset of symptoms was reduced by 40–50% (Table II, Fig. 1). It is of interest to note that the Sotalol Trial from the United Kingdom showed no effect at all on sudden cardiac death despite the fact that the study was large enough to demonstrate a significant reduction in reinfarction rate and had a favorable trend toward total mortality (14%). Sotalol is the only beta blocker which, in a larger study, has not shown a favorable effect on sudden death that has not been more marked than the effect on total mortality. In the two large trials, ISIS-1 and MIAMI, there were no reports on sudden cardiac death defined as death within 1–24 h after onset of symptoms. Both studies, however, reported a major effect on early cardiac rupture within 24 h, which could also be a cause of sudden cardiac death, especially during the short-term follow-up after acute myocardial infarction.

The cause of death is thought to be due to ventricular fibrillation in the majority of patients. Animal studies on experimental infarction have clearly demonstrated that some beta blockers can prevent ventricular fibrillation following coronary artery ligation. In two clinical studies, beta blockers have been found to reduce the incidence of ventricular fibrillation in patients suffering an acute myocardial infarction. These studies were the Göteborg Metoprolol Trial and a study on propranolol from New Zealand. In these trials, beta blockers

### Table I Total mortality and sudden cardiac deaths in beta-blocker trials

<table>
<thead>
<tr>
<th></th>
<th>No. of deaths/patients</th>
<th>Reduction (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Beta blocker</td>
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</tr>
<tr>
<td>Total mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All long-term studies</td>
<td>1,199/12,431</td>
<td>1,027/13,815</td>
<td>20</td>
</tr>
<tr>
<td>All short-term studies</td>
<td>586/13,721</td>
<td>513/13,815</td>
<td>13</td>
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<tr>
<td>Sudden deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>480/9,441</td>
<td>333/9,887</td>
<td>34</td>
</tr>
</tbody>
</table>

*Two-year follow-up.

### Table II Sudden cardiac deaths in beta-blocker trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of deaths/patients</th>
<th>Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwegian Multicenter Study (timolol)</td>
<td>95/939</td>
<td>47/495</td>
</tr>
<tr>
<td>BHAT (propranolol)</td>
<td>89/1,921</td>
<td>64/1,916</td>
</tr>
<tr>
<td>All metoprolol (5 studies)</td>
<td>104/2,721</td>
<td>62/2,753</td>
</tr>
<tr>
<td>APSI (acebutolol)</td>
<td>9/309</td>
<td>6/298</td>
</tr>
<tr>
<td>United Kingdom (sotalol)</td>
<td>27/583</td>
<td>41/873</td>
</tr>
<tr>
<td>All other (7 studies)</td>
<td>156/2,968</td>
<td>113/3,102</td>
</tr>
</tbody>
</table>

*Abbreviations: APSI = Acebutolol Prévention Secondaire de l’Infarctus; BHAT = Beta Blocker Heart Attack Trial.*

![Fig. 1](cumulative_number_of_deaths.png) Cumulative number of sudden cardiac death from pooled results of five double-blind placebo-controlled postinfarction trials. Solid line shows sudden death in the placebo group (n = 2,721) and the dotted line sudden death in the metoprolol group (n = 2,753). The effect was highly significant (p = 0.002).
reduced ventricular fibrillation markedly by prophylactic use of metoprolol (Fig. 2) and propranolol.

Primary Prevention

The Framingham heart study\textsuperscript{14} demonstrated that hypertension is a highly significant risk factor for development of coronary artery disease and sudden cardiac death. The impact of treating hypertension has been assessed in many prospective clinical trials, and diuretics and beta blockers have been found to reduce morbidity and mortality.\textsuperscript{15} The most marked effect has been found on prevention of cerebrovascular events. Effects of ACE inhibitors, calcium antagonists, and alpha blockers have not yet convincingly demonstrated effects on mortality and morbidity. The only study that has demonstrated a significant effect on sudden cardiac death in patients with hypertension is the Metoprolol Atherosclerosis Prevention in Hypertension Trial (MAPHY).\textsuperscript{15} In this study, with a mean 5-year follow-up of middle-aged men with hypertension, metoprolol was found to reduce total mortality more markedly than did thiazide diuretics. There was a marked difference in the incidence of sudden cardiac death between patients treated with metoprolol and diuretics (Fig. 3). Subgroup analyses from other studies on hypertension have also shown favorable effects of beta blockers on sudden cardiac death. Besides the beta blockers, none of the other agents used for the treatment of hypertension have been found to reduce sudden cardiac death.

Congestive Heart Failure

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) was the first to show that the ACE inhibitor enalapril reduced total mortality in patients with severe congestive heart failure.\textsuperscript{16} The major effect was due to a prevention of progressive heart failure causing death, while there was no effect on sudden cardiac death. Similar effects with a reduction of total mortality and less clear effects on sudden cardiac death were also found in other placebo-controlled trials including the Studies of Left Ventricular Dysfunction (SOLVD).\textsuperscript{17} The effect on sudden cardiac death observed in some studies with ACE inhibitors seems to be indirectly due to prevention of remodeling, a progression of the disease. In the CONSENSUS II Trial\textsuperscript{18} of about 6,000 patients, there were more than 200 cases of sudden cardiac death during the first 6 months after myocardial infarction and there was no difference between enalapril and placebo. This study included patients both with and without congestive heart failure and no effect was seen on sudden death even in subgroups.

Very recently, two large studies on beta blockers in patients with mild to severe heart failure have also shown a significant reduction in sudden cardiac death. The Cardiac Insufficiency Bisoprolol Study (CIBIS) II, including 2,647 patients (class III–IV) reported a 34\% reduction in total mortality and an even more marked effect on sudden cardiac death, that is, 44\%.\textsuperscript{19} In the Metoprolol Randomised Intervention Trial in Heart Failure (MERIT-HF) including 3,991 (class II–IV) patients with congestive heart failure, metoprolol CR/XL reduced total mortality, also by 34\%, and sudden death by 41\% compared with placebo.\textsuperscript{20} Also, in the US Carvedilol program,\textsuperscript{21} retrospectively pooling four different studies in patients with heart failure, there was a significant reduction in total mortality, and on both sudden cardiac death and progressive heart failure.

Possible Mode of Action

Three beta blockers, timolol, metoprolol, and propranolol, have been found to reduce sudden cardiac death significantly by about 30–50\%. These beta blockers have two properties in common: beta\textsubscript{1}-receptor blockade and a higher degree of lipophilicity. In this context it can be stated that the beta blockers carvedilol and bisoprolol also reduced sudden cardiac death by 40–50\% in patients with congestive heart failure.\textsuperscript{19, 21} Car-
vedilol has several different properties of action, but the two factors in common for timolol, metoprolol, propranolol, beta1-blockade, and a higher degree of lipophilicity, are also properties of carvedilol. It is well known that beta1-receptor blockade reduces the sympathetically overstimulation of the ventricular myocardium and the metabolic demand, mainly by a reduction of heart rate work and prolongation of diastolic perfusion time. The high sympathetic activity per se has been found to reduce the ventricular fibrillation threshold, which is also the effect of myocardial ischemia. It is likely that these mechanisms are involved in the prevention of ventricular fibrillation and sudden cardiac death.

A probable role of a higher degree of lipophilicity of beta blockers has been brought up during the last decade. Parker et al. reported that injection of propranolol into the brain markedly reduced the risk of ventricular fibrillation in pigs after coronary artery ligation. This was found despite the fact that with this mode of administration of the beta blocker there was very little direct effect of the beta blocker on the myocardium. The intracerebral injection was far more effective than intravenous administration of propranolol to pigs, despite the fact that in this situation there was a marked effect directly on the ischemic myocardium. The authors propose that there have to be central nervous mechanisms involved in the prevention of ventricular fibrillation by beta blockade. Åblad et al. studied this hypothesis in a rabbit model, in which the animals were pretreated with beta blockers [metoprolol (lipophilic) or atenolol (hydrophilic)] using osmotic pumps during 3 weeks prior to coronary artery occlusion under anesthesia. After coronary artery occlusion, death from ventricular fibrillation occurred in most controls and also in atenolol-treated animals, whereas metoprolol markedly reduced the risk of ventricular fibrillation. In this study the degree of myocardial ischemia, assessed by ST-segment elevation, heart rate, and systolic blood pressure, was reduced similarly by the two beta blockers. In contrast, the level of vagal tone as measured by heart rate variability was significantly higher in the metoprolol group than in the atenolol group and in controls. Assessment of vagal activity by using cholinergic antagonists demonstrated that vagal tone was better maintained in this situation of stress and acute coronary ligation in animals treated with metoprolol than in treatment with atenolol. It was thus proposed that metoprolol, as it is more lipophilic, penetrates into the brain and thereby causes better maintenance of vagal activity during stress in contrast to the hydrophilic atenolol.

Selection of Patients

Patients with depressed cardiac function and more widespread coronary artery disease are at higher risk of ventricular fibrillation. It was reported from the BHAT Trial that propranolol given to patients after myocardial infarction had a more marked effect on reduction of total mortality as well as on sudden cardiac death in patients with compared with those without congestive heart failure at onset of treatment (Fig. 4). The patients with congestive heart failure had about twice as high total mortality as well as sudden death compared with patients without heart failure. Propranolol reduced sudden cardiac death by 47% in patients with congestive heart failure. In the two early intervention trials with metoprolol, the Göteborg Metoprolol and the MIAMI trials, it was found that mortality reduction was more marked in patients at high risk.

In a recent analysis of patients who have congestive heart failure prior to randomization in the Göteborg Metoprolol Trial, metoprolol reduced total mortality by 50% at 3 and 12 months after myocardial infarction. Patients with diabetes after myocardial infarction are known to be at high risk of death, and in several studies beta blockade has reduced short- and long-term mortality by as much as 50%.

Thus patients at higher risk of death—and most likely of sudden cardiac death—will benefit most from postinfarct prophylactic treatment with a beta blocker.

Conclusion

In more than 50 randomized controlled trials including about 55,000 patients, beta blockers have been found to reduce total mortality, and even more markedly, sudden cardiac death. The effect on sudden cardiac death in some of these studies is 30–50%. Also, in patients with hypertension, some beta block-
ers have been reported to reduce sudden cardiac death. Very recently, two large trials in patients with congestive heart failure have shown a 34% reduction in total mortality and 41–44% reduction in sudden cardiac death. There is no other therapy with such marked and well-documented effect on sudden cardiac death as the beta blockers. An important question is whether all beta blockers have similar favorable effects on sudden cardiac death. The beta blockers that have been reported to reduce sudden cardiac death are both beta1-selective and nonselective agents, but they have two properties in common: beta1-receptor blockade and a higher degree of lipophilicity (timolol, metoprolol, propranolol, bisoprolol, and carvedilol). It has been suggested from animal experimental observations that reduction in sudden cardiac death is at least in part mediated through central nervous system mechanisms that might explain the importance of a higher degree of lipophilicity. It can be concluded that beta blockers with proven clinical effect should be given to patients at risk of sudden cardiac death, including those with previous myocardial infarction, hypertension, and congestive heart failure.

References