Clinical research

Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies

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Aims To assess if treatment with the α-glucosidase inhibitor acarbose can reduce cardiovascular events in type 2 diabetic patients.

Methods and results This meta-analysis included seven randomized, double-blind, placebo-controlled acarbose studies with a minimum treatment duration of 52 weeks. Type 2 diabetic patients valid for safety were randomized to either acarbose (n=1248) or placebo (n=932). The primary outcome measure was the time to develop a cardiovascular event. Primary analysis was conducted using Cox regression analysis. The effect of acarbose on metabolic parameters was also investigated. Acarbose therapy showed favourable trends towards risk reduction for all selected cardiovascular event categories. The treatment significantly reduced the risk for 'myocardial infarction' (hazards ratio=0.36 [95% CI 0.16–0.80], P=0.0120) and 'any cardiovascular event' (0.65 [95% Cl 0.48–0.88], P=0.0061). Glycaemic control, triglyceride levels, body weight and systolic blood pressure also improved significantly during acarbose treatment.

Conclusion Intervention with acarbose can prevent myocardial infarction and cardiovascular disease in type 2 diabetic patients while most of them are already on intensive concomitant cardiovascular medication.

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KEYWORDS Acarbose; Cardiovascular events; Meta-analysis; Myocardial infarction; Risk reduction; Type 2 diabetes

Introduction

The prevalence of diabetes is increasing worldwide to epidemic proportions.1 Owing to its association with an increased incidence of and mortality from cardiovascular (CV) disease,2 a rapid worldwide rise in diabetes-related CV events is also occurring. Study data suggest that type 2 diabetic patients without previous myocardial infarction (MI) have a similar risk of MI to non-diabetic patients with a previous MI event.3 The mortality rate of diabetic patients after their first MI was also markedly higher.4 The OASIS study reports diabetes as an independent risk factor for long-term morbidity and mortality after an episode of unstable coronary artery disease.5 The UK-PDS is so far the only controlled trial showing that improved glycaemic control achieved with metformin reduces the incidence of coronary heart disease events in patients with type 2 diabetes.6 Also intensified treatment with insulin and glibenclamide showed a reduction of 16% what however failed to be significant (P=0.052).7

In order to prevent these macrovascular events, physicians are currently restricted to tools such as lifestyle intervention and pharmacological intervention using
A recent meta-regression analysis reported a continuous relationship between 2h-postprandial glucose levels and cardiovascular risk below the diabetic threshold and there is growing epidemiological evidence for the association of postprandial hyperglycaemia and macrovascular complications in diabetic individuals.

The α-glucosidase inhibitor acarbose is an oral antidiabetic agent which delays glucose release from complex carbohydrates and thus leads to a reduction of postprandial blood glucose levels. It has been proven efficacious as monotherapy and in combination with other antidiabetic agents in numerous clinical trials with type 2 diabetic patients (see review) and has shown sustained efficacy in long-term studies. The recent results of the STOP-NIDDM trial also point to its use for delaying the development of type 2 diabetes in patients with impaired glucose tolerance (IGT). Acarbose reduces HbA1c and postprandial insulin levels, improves insulin sensitivity and is not associated with weight gain. Further metabolic effects triggered by the reduction of hyperglycaemia in type 2 patients include improvement in blood lipid levels, reduction of coagulation activation/oxidative stress and systolic blood pressure. Based on the current pathophysiological understanding of the effects of the postprandial state on cardiovascular disease development, acarbose should therefore exercise a preventive effect on the endothelium and vasculature of type 2 diabetic patients. The first study to investigate the relationship between lowering postprandial blood glucose by acarbose therapy and the development of CV events has been the STOP-NIDDM trial in IGT patients. The study reported a significant reduction using acarbose in the development of CV events of any type, of MI and in the reduction of new cases of hypertension. These results obtained in subjects at an early stage of the type 2 diabetes disease continuum triggered the following analysis reported here.

The analysis used a database of seven double-blind, placebo-controlled, randomized long-term trials with acarbose in type 2 diabetic patients in order to investigate if acarbose therapy could also achieve a reduction of CV events in these patients.

### Methods

#### Study population

This meta-analysis was to include all patients with type 2 diabetes from a database of randomized, double-blind, placebo-controlled acarbose studies with a minimum treatment duration of 52 weeks. Only studies with at least 50 patients were considered. Table 1 summarizes the seven studies selected for this analysis. The studies were carried out in adult, type 2 diabetes patients (except for study 3 which also enrolled type 1 patients but whose data were not included in this analysis). Other inclusion criteria such as metabolic parameters or concomitant antidiabetic medication varied according to the primary objective of the different studies. The following exclusion criteria applied to most of the studies: type 1 diabetes, recent CV events, major debilitating diseases, malignant tumours, hepatic or renal impairments, uncontrolled hypertension, concurrent infections, documented gastrointestinal diseases and intake of medication likely to alter gut mobility or absorption. Pregnant or nursing women and women of childbearing age without a medically approved contraceptive method were excluded as were patients participating in another clinical trial 30 days prior to screening. All studies followed the guidelines for Good Clinical Practice and all study protocols were approved by the relevant ethical committees. Written informed consent was obtained from all participants.

All patients valid for safety were included in this meta-analysis, regardless of the duration of their participation in the trial. Validity was defined as either all randomized patients (studies 1 and 2) or randomized patients who had taken the study medication on at least one occasion (studies 3–7).

#### Outcome measures

The primary variable was the time to develop a CV event. These events had been reported as adverse events in the original studies (COSTART term) and were prospectively clustered to

### Table 1 Summary of the seven randomized, double-blind, placebo-controlled studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number of patients on Acarbose</th>
<th>Acarbose dosage (mg t.i.d.)</th>
<th>Acarbose Placebo</th>
<th>50</th>
<th>100</th>
<th>200</th>
<th>Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No. 541&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Israel</td>
<td>69</td>
<td>-</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>78</td>
</tr>
<tr>
<td>2 Chiasson et al. 1994&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Canada</td>
<td>172</td>
<td>182</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>52</td>
</tr>
<tr>
<td>3 No. 656&lt;sup&gt;b&lt;/sup&gt;</td>
<td>USA</td>
<td>190</td>
<td>96</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>56</td>
</tr>
<tr>
<td>4 Hasche et al. 1999&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Germany</td>
<td>35</td>
<td>38</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>104</td>
</tr>
<tr>
<td>5 Campbell et al. 1998&lt;sup&gt;d&lt;/sup&gt;</td>
<td>United Kingdom</td>
<td>507</td>
<td>259</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>164</td>
</tr>
<tr>
<td>6 Bachmann et al.</td>
<td>Austria, Germany, Greece, Latvia, Lithuania</td>
<td>183</td>
<td>188</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>78</td>
</tr>
<tr>
<td>7 Josse et al. 2003&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Canada</td>
<td>92</td>
<td>99</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>52</td>
</tr>
</tbody>
</table>

<sup>a</sup>Unpublished data (Bayer AG).
<sup>b</sup>Also described in Holman et al. 1999<sup>f</sup>
<sup>c</sup>In preparation.
<sup>d</sup>Also described in Holman et al. 1999<sup>g</sup>
<sup>e</sup>In preparation.
match as closely as possible the pre-specified CV event categories in the STOP-NIDDM Study. Table 2 lists the COSTART terms and the allocation to cardiovascular event categories. If necessary, investigator statements from the different studies were used for clarification. The selection was performed blind and prior to the analyses for this study.

All laboratory measures were carried out according to standard procedures as previously described.

Statistical analysis

Descriptive statistical procedures were employed for the demographic characteristics of the pooled patient population of the seven studies.

Event rates of cardiovascular events were calculated as the number of patients with CV-adverse events occurring during or within 30 days after treatment relative to the total number of subjects. The first occurrence of each type of event was analysed. If an event occurred several times and the last resulted in death, the event was counted only in the category ‘cardiovascular death’. If two or more different types of event occurred in one patient during treatment, each event was counted as a separate event. In the composite analysis of ‘any CV event’, however, only the first CV event of a patient was included.

Cox Proportional Hazard models were used for analysis. Kaplan–Meier curves were utilized to examine the assumption of proportional hazards. The question of heterogeneity was addressed by including study-by-treatment interactions into the model. A Wald-test statistic for the combined hypothesis, that all study-by-treatment interactions equal zero yielded a $P$-value of 0.7457. Hence homogeneity of treatment effect could be assumed. The model without stratification by study was compared to the stratified one. Both produced similar results.

Covariate analysis was performed for those parameters that may have had an impact on the outcome. Study adjusted means were calculated for metabolic parameters and vital signs of the pooled study population for baseline and end of study.

Changes from baseline were computed using for each subject individual baseline values and his or her last measurement under treatment. Risk factors from the cardiovascular risk factor analysis with $P<0.05$ were chosen for examination as additional covariates for the Cox proportional hazard model.

Table 2  Description of cardiovascular events selected for analysis

<table>
<thead>
<tr>
<th>Cardiovascular event category</th>
<th>COSTART term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>Heart arrest</td>
</tr>
<tr>
<td></td>
<td>Aortic stenosis (with outcome death)</td>
</tr>
<tr>
<td></td>
<td>All other selected COSTART terms with outcome death</td>
</tr>
<tr>
<td>Stroke/Cerebrovascular accident</td>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td></td>
<td>Cerebral ischaemia hemiplegia</td>
</tr>
<tr>
<td>Peripheral vascular disorder/Occlusion</td>
<td>Cardiovascular disorder</td>
</tr>
<tr>
<td></td>
<td>Occlusion</td>
</tr>
<tr>
<td></td>
<td>Carotid occlusion</td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular disorder</td>
</tr>
<tr>
<td>Angina</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Left heart failure</td>
</tr>
<tr>
<td>Revascularization procedure</td>
<td>Cardiovascular surgery</td>
</tr>
</tbody>
</table>

*a Only relevant events according to the investigator’s statement were selected

Table 3  Baseline demographic characteristics of the pooled study population (valid for safety)*

<table>
<thead>
<tr>
<th></th>
<th>Acarbose $(n=1248)$</th>
<th>Placebo $(n=932)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.2±10.1</td>
<td>61.5±10.0</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>59.8</td>
<td>55.7</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>92.1</td>
<td>92.5</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>76.5±76.8</td>
<td>84.6±75.1</td>
</tr>
<tr>
<td>(months)</td>
<td>403±293</td>
<td>412±407</td>
</tr>
</tbody>
</table>

*a Data are means±SD

The level of significance for all analyses was chosen to be $P<0.05$.

Results

Study population

All seven selected studies were conducted between 1987 and 1999. All were multicentric with a run-in period except for study 1. A total of 2180 patients who were all valid for safety analysis were included in the present study (acarbose $n=1248$, placebo $n=932$). Table 1 shows the distribution of patients to each treatment group in all studies. The study medication was increased stepwise in all studies for 3 to 8 weeks and patients were asked to swallow the medication with the first mouthful of the three main meals.

Baseline demographic and metabolic characteristics of the pooled study population were well matched for both treatment groups (Table 3 and Table 4).

The pre-specified diseases in the medical history of the trial participants compared well in the placebo and acarbose group.
In the acarbose group, 88.5% of the patients had a medical history finding at baseline compared to 87% in the placebo group. Patients were considered as having a history of cardiovascular disease at baseline if they had a CV event during the run-in period, a CV-relevant medical history finding or were taking anti-hypertensive medication prior to the start of study medication. Based on these criteria, acarbose patients had 1.4% more CV findings (57.5%) than placebo patients (56.1%) at baseline. More than 80% of the patients in both treatment groups received concomitant medication during the treatment phase (acarbose 84.9%, placebo 86.4%). Concomitant antidiabetic treatment consisted of sulfonylureas (31% vs 38%), metformin (4% vs 5%) and insulin (11% vs 12%). A large number of patients received concomitant cardiovascular medication: 56.5% for acarbose and 60.2% for placebo. The data for both treatment groups compared well, especially for lipid-lowering drugs (10.3% acarbose vs 9.9% placebo), agents acting on the renin-angiotensin-aldosterone system (18.8% vs 17.1%), other antihypertensives (5% vs 4.9%) and anti-thrombotic drugs (23.9% vs 24.4%).

**Effect of acarbose therapy**

Under acarbose treatment, a significant prolongation of time in which type 2 diabetes patients remained free of any newly diagnosed CV events was demonstrated ($P=0.0057$, log rank test; Fig. 1). Of the 1248 acarbose patients, 76 (6.1%) reported a CV event according to the terms given in Table 2 whereas in the placebo group ($n=932$) 88 (9.4%) experienced an event. The Cox proportional hazards model showed a significant relative risk reduction of 35% in developing any CV event for patients

![Figure 1](image-url)
on acarbose treatment compared to placebo with a hazards ratio of 0.65 (95% CI 0.48–0.88; \(P=0.0061\)). The hazards ratios of all other selected CV events also favoured acarbose treatment (Fig. 2). These results remain significant after adjustment for the covariates body weight, systolic blood pressure and triglycerides.

A substantial, highly significant relative risk reduction of 64% was achieved for ‘myocardial infarction’ (\(P=0.0120\)). The Kaplan–Meier survival curve (Fig. 3) shows the lower incidence of myocardial infarction in acarbose patients.

Long-term acarbose treatment significantly improved glycaemic control in the pooled study population (Table 4). HbA1c, fasting and postprandial blood glucose levels were significantly reduced by acarbose treatment. Triglyceride levels also significantly decreased during
Acarbose treatment compared to placebo (P<0.001). There was a small weight loss in both treatment groups (acarbose 1.1 kg, placebo 0.8 kg) which was also significant for acarbose (P=0.042). This is also reflected in the BMI data (Table 4). Furthermore, systolic blood pressure was significantly lower under acarbose treatment.

To avoid bias by different duration of the studies an adjustment to the study was performed.

Adverse effects and safety

No serious adverse events related to acarbose were reported. The most common complaints were gastrointestinal side-effects such as flatulence, diarrhoea and abdominal pain. The frequency of any adverse events varied from country to country, for example 52.7% for acarbose and 29.2% for placebo in the German Study16 and 73.2% and 39% respectively, in a large Canadian trial.32

Discussion

The current meta-analysis has shown for the first time that treatment with the α-glucosidase inhibitor acarbose can have a protective effect against cardiovascular events in type 2 diabetes patients.

A total of 164 pre-specified CV events were documented for the pooled study population, 76 (6.1%) in the acarbose and 88 (9.4%) in the placebo group (P=0.0061). The results for the type 2 patients compared well to the results for the IGT subjects in the recent STOP-NIDDM trial.24 In both studies, acarbose treatment was associated with a relative risk reduction for a cardiovascular event of any type (35% for type 2 patients, 49% for IGT subjects). The improvements were most pronounced for the category ‘myocardial infarction’ with a hazards ratio of 0.36 (95% CI 0.16–0.80) for type 2 patients and of 0.09 (95% CI 0.01–0.72) for IGT subjects. The effects of the study medication on most of the selected CV categories was not significant but the trend consistently favoured acarbose treatment in both investigations. The relative risk reductions were somewhat higher in IGT subjects (‘angina’ 22% in type 2 vs 5% in IGT subjects; ‘revascularization procedure’ 22% vs 39%; ‘CV death’ 38% vs 45%; ‘stroke/cerebrovascular accident’ 25% vs 44%). However, in general the data of the STOP-NIDDM trial and the meta-analysis in type 2 diabetes were remarkably consistent. The minor differences may be due to the fact that type 2 diabetes represents a more advanced stage of atherosclerosis.

The effect of acarbose was evident despite a high rate of state of the art concomitant CV medication (56.5% of all acarbose patients). Considering the different methodologies of analysis, the results can still be put into perspective and be compared with the results of other prospective outcome trials. The risk reductions achieved by acarbose therapy in type 2 diabetic patients in this study are comparable to a posthoc analysis of the effects of the cholesterol-lowering agent simvastatin on the diabetic subpopulation of the 4S study.25 Patients with coronary heart disease (CHD) on long-term simvastatin treatment had a relative risk reduction for a major CHD event (CHD death or nonfatal MI) of 55% (P=0.002). A subgroup analysis of 586 diabetic patients with MI in the CARE trial reported a 25% risk reduction of coronary events (CHD death, nonfatal MI, CABG and PTCA) using pravastatin (P=0.05).26 The pravastatin-treated diabetic patients also had significantly fewer revascularization procedures (PTCA or CABG) than those in the placebo group (relative risk 0.68, P=0.04).28

Acarbose treatment significantly improved glycaemic control and lowered triglyceride levels, body weight, BMI and systolic blood pressure. These factors are all associated with an increased risk for CV disease in type 2 diabetic patients.9,27–30 The α-glucosidase inhibitor acarbose acts by delaying the enzymatic breakdown of carbohydrates in the small intestine31 and thus reduces postprandial blood glucose increment directly. No evidence exists so far that other mechanisms of action of acarbose are involved. The same applies to its effect on blood lipids and blood pressure which is secondary owing to improved postprandial glucose regulation. Additional acarbose effects such as a reduction of insulin levels or improved insulin sensitivity are therefore directly attributable to reduced postprandial blood glucose levels. Excessive initial postprandial hyperglycaemia has been shown to trigger a cascade of atherogenic events, leading to changes in endothelial, mesangial, pericyte, smooth muscle and macrophage cell function in a manner which causes micro- and macrovascular disease.23 The metabolic effects of acarbose can thus lead to a protection of the cardiovascular endothelium and to a reduction in CV disease. The results of this meta-analysis and the recent STOP-NIDDM trial24 show that a reduction of postprandial blood glucose excursions by acarbose can lead to a reduced risk in developing MI or CV disease.

No acarbose related serious side-effects were reported in these pooled data base according to previously published long term observation in the STOP-NIDDM trial15 and a 5-year surveillance study on safety and efficacy with acarbose.16

In conclusion, acarbose treatment of type 2 diabetes has shown preventative effects on myocardial infarction and any cardiovascular events. This may be explained by a reduction of postprandial hyperglycaemia and improvement in other features of the metabolic syndrome.

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References


