EFFECT OF ALPHA-GLUCOSIDASE INHIBITORS ON PREDIABETES

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ABSTRACT

Systematic Review

BACKGROUND: Prediabetes is a precursor stage of type 2 diabetes mellitus (T2DM). T2DM is an increasing global problem, leading to many clinical complications. Alpha-glucosidase inhibitors slow down uptake of glucose in the small intestine resulting in decreased blood sugar fluctuations, which makes it a treatment for T2DM. It is not yet known whether it is also beneficial for people with prediabetes.
OBJECTIVE: The purpose of this evidence-based systematic review is to research the effect of alpha-glucosidase inhibitors on the development of prediabetes to type 2 diabetes mellitus, glucose levels, macro vascular morbidity, mortality and side effects in prediabetic people.
METHODS: The PubMed and Embase databases were used to search for articles, using synonyms of the determinant, alpha-glucosidase inhibitors, and the domain, prediabetic people. All investigators abstracted data and evaluated study quality independently. Each article was evaluated by at least two researchers. The critical appraisals were based on the Cochrane risk of bias tool. The results were evaluated by meta-analyses.
RESULTS: The search strategy resulted in a total of 917 articles, of which eight were relevant to our question and were included in this systematic review.. There was a significant reduction in development to T2DM and in HbA1c values in the intervention group compared to the placebo group. There was no significant difference in fasting glucose. One study reported a reduction in cardiovascular events in the intervention group. The intervention had no association with mortality.
CONCLUSION: The risk of development to T2DM decreases with alpha-glucosidase inhibitors treatment. Furthermore, alpha-glucosidase inhibitors lower the blood glucose levels and decrease macrovascular morbidity. It is not associated with mortality. However, there are side effects and no account is taken of the complications other than macrovascular morbidity that accompany T2DM. Even though alpha-glucosidase inhibitors have positive effects, we cannot yet recommend to prescribe alpha-glucosidase inhibitors to prediabetic people.

KEY WORDS: Prediabetes, Alpha-glucosidase Inhibitors, Acarbose, Glucose Levels, Macrovascular Morbidity

*Supplementary material is marked with * and can be found online at www.ramsresearch.nl*

Introduction

Type 2 diabetes mellitus is a major global health problem. There were 382 million people with diabetes in 2013, and this number is expected to rise to 592 million by 2035. The incidence is rising rapidly, due to obesity, decreased physical activity and aging of the population [1]. T2DM increases the risk of cardiovascular diseases, diabetic nephropathy and blindness. Prediabetes is a precursor stage of T2DM and increases the risk of hypertension and other cardiovascular diseases [2]. It is therefore important that prediabetes is treated, so that T2DM can be prevented [3,4].

Prediabetes is an intermediate metabolic state between normoglycaemia and diabetes. Prediabetic patients have impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). IGT is characterized as 2-hour plasma glucose of 7,8-11,0 mmol/L after ingestion of 75 g of oral glucose. If this value gets above 11 mmol/L it indicates T2DM. IFG is a similar condition, defined as fasting plasma glucose of 5,6 - 6,9 mmol/L, according to American Diabetes Association (ADA) [5]. A value higher than this is an indication for T2DM. Additionally, glycated hemoglobin (HbA1c) values reflect the average blood glucose levels over a period of twelve weeks [6,7].

In 2015 the prevalence of IGT was estimated to be 318 million worldwide. The International Diabetes Federation predicts that this number would increase to 481 million worldwide by 2040 [8]. The only current treatment for prediabetes is a lifestyle change. People have to lose weight by exercising and a healthy eating habit [9]. Therefore it is important that more research is done to prevent the development of T2DM.

Acarbose, voglibose and miglitol are prescribed to patients with T2DM. These drugs are alpha-glucosidase inhibitors, which slow down the uptake of glucose in the small intestine. This causes the postprandial blood sugar to increase less rapidly, which decreases the fluctuations in blood sugar. Alpha-glucosidase inhibitors can cause gastrointestinal side effects and it has not yet been proven whether they can prevent the progression of prediabetes to T2DM [6]. Hence, the goal of this systematic review is to investigate the effect of alpha-glucosidase inhibitors on the development of T2DM, glucose levels, macro vascular morbidity, mortality and side effects in prediabetic people.

Research question

What is the effect of alpha-glucosidase inhibitors on the development of prediabetes to type 2 diabetes mellitus, glucose levels, macro vascular morbidity, mortality and side effects in prediabetic people?

Methods

Search strategy and selection

We used the PubMed and Embase databases to search for relevant articles. A search filter was designed by using all relevant synonyms of the determinant, alpha-glucosidase inhibitors, and the domain, prediabetic people (Table 1*). In the PubMed search alpha-glucosidase was used as a term for the determinant instead of alpha-glucosidase inhibitors. The

latter is a relatively new term and is classified under glycoside hydrolase inhibitors, which is a MeSH term that includes many other, irrelevant enzymes that were not applicable for our research.

Articles were included if they met the inclusion criteria shown in the flow chart (Figure 1). We excluded all non-clinical studies and studies not written in English. Furthermore, articles that were not available online were excluded due to insufficient resources.

Further relevant articles were found using the snowball method, which entails going through the citations of an article to find more relevant studies.

Critical appraisal

Two researchers independently judged the trustworthiness, value and relevance of each article. Bias was examined by looking at randomization, allocation concealment, blinding of participants, researchers and analysts, incomplete outcome data selective outcome reporting and other sources of bias. These appraisals were combined to form a final evaluation. One article was deemed not valid enough for inclusion, because it was a very small pilot study and had a very high risk of bias. The critical appraisal of the remaining eight articles has been summarized in a Cochrane risk of bias summary and a risk of bias graph (Figure 2).

Analysis

First, the characteristics of the included studies were defined and summarized (Table 2). The relative risk (RR) and mean differences were compared between the studies. The significance was defined as $\alpha<0,05$. The outcomes of development to T2DM, fasting plasma glucose and HbA1c were analyzed in a meta-analysis in Review Manager. Secondly, we summarized the outcomes macrovascular morbidity and the side effects.

Results

Using the aforementioned search strategy, 917 publications were obtained. After the removal of duplicates, 807 articles remained. In the first selection step these articles were screened based on title and abstract, which led to a selection of 131 articles. The references of the reviews were checked to make sure no relevant publications were missed. In the second selection step, abstracts and full articles were screened and the critical appraisal was executed, which narrowed the number of publications down to eight. These eight articles are summarized in Table 2.

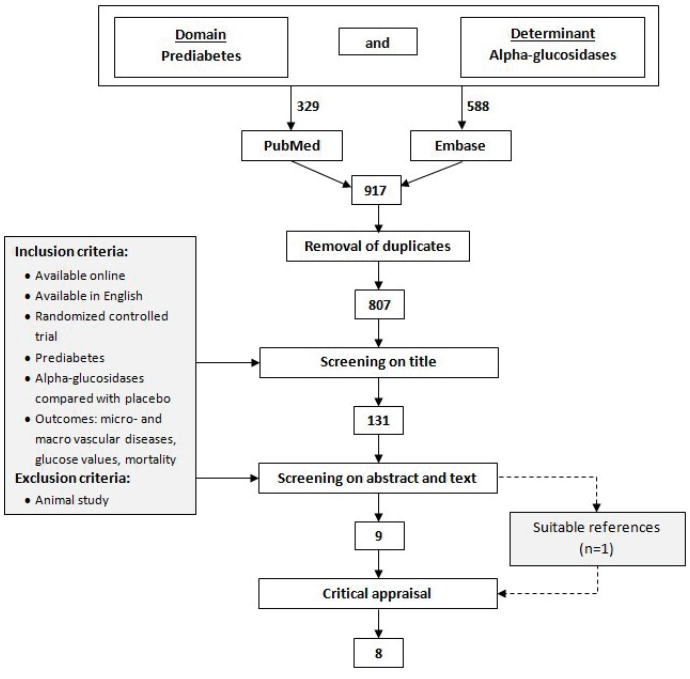

Figure 1: *Flowchart of the search process.*

Table 2: **three times a day, ** STOP-NIDDM trial, ***IOC country codes*

Author (publication year)	Study design	Setting	Study period (weeks)	Amount of included patients (n)	Alpha-glucosidase (n)	Placebo (n)	Female (%)	Mean age (years)	Mean BMI (kg/m²)	Baseline HbA1c (%)	Baseline glucose values (mmol/L)	Dose
Kawamori et al. (2007) [10]	Randomized controlled trial	Japanese institutions	208	1505	786	737	*Voglibose:* 40 *Placebo:* 40	55,7	*Voglibose:* 25,76 *Placebo:* 25,89		*Voglibose:* 5,80 (0,55) *Placebo:* 5,85 (0,56)	0,2 mg t.i.d.*
Kirkman et al. (2006) [11]	Randomized controlled trial	IU School of Medicine, WUSM	343	219	109	110	*Acarbose:* 67,0 *Placebo:* 65,4	53,7	*Acarbose:* 35,1 *Placebo:* 35,2	*Acarbose:* 6,35 (0,65) *Placebo:* 6,33(0,63)	*Acarbose:* 6,78 (0,77) *Placebo:* 6,70 (0,74)	100 mg t.i.d.
Nijpels et al. (2008) [12]	Randomized controlled trial	Residents of Hoorn	182	66	30	36	*Acarbose:* 49,2 *Placebo:* 50	*Acarbose:* 58,5 *Placebo:* 56,5	*Acarbose:* 28,4 *Placebo:* 29,5	*Acarbose:* 5,9 (0,5) *Placebo:* 5,6 (0,6)	*Acarbose:* 6,6 (0,5) *Placebo:* 6,5 (0,6)	50 mg t.i.d.
Rudovich et al. (2011) [13]	Randomized controlled cross-over study		12	63	31 (acarbose-placebo)	32 (placebo-acarbose)	44,4	58,2	31,6	5,7 (0,5)	*Acarbose:* 5,3 (0,6) *Placebo:* 5,3 (0,6)	100 mg t.i.d.
Pan et al. (2002) [14]	Randomized controlled trial	Five centers in the mainland of China	16	252	125	127	*Acarbose:* 60,8 *Placebo:* 59,1	*Acarbose:* 53,4 *Placebo:* 55,6	*Acarbose:* 25,6 *Placebo:* 25,8	*Acarbose:* 6,51 (0,72) *Placebo:* 6,61 (0,62)		50 mg t.i.d.
Hanefeld et al. (2004) [15]**	Randomized controlled trial	Hospitals in CAN, GER, AUT, NOR, DEN, SWE, FIN, ISR, ESP***	160	115	56	59	*Acarbose:* 44,6 *Placebo:* 33,9	*Acarbose:* 54,8 *Placebo:* 55,6	*Acarbose:* 29,5 *Placebo:* 28,6	*Acarbose:* 5,92 (0,50) *Placebo:* 5,73 (0,55)	*Acarbose:* 6,44 (0,50) *Placebo:* 6,34 (0,58)	100 mg t.i.d.
Chiassion et al. (2002, 2003) [16, 17]**	Randomized controlled trial		160	115	682	686	*Acarbose:* 52 *Placebo:* 50	*Acarbose:* 54,3 *Placebo:* 54,6	*Acarbose:* 31,0 *Placebo:* 30,9		*Acarbose:* 6,23 (0,50) *Placebo:* 6,24 (0,53)	100 mg t.i.d.

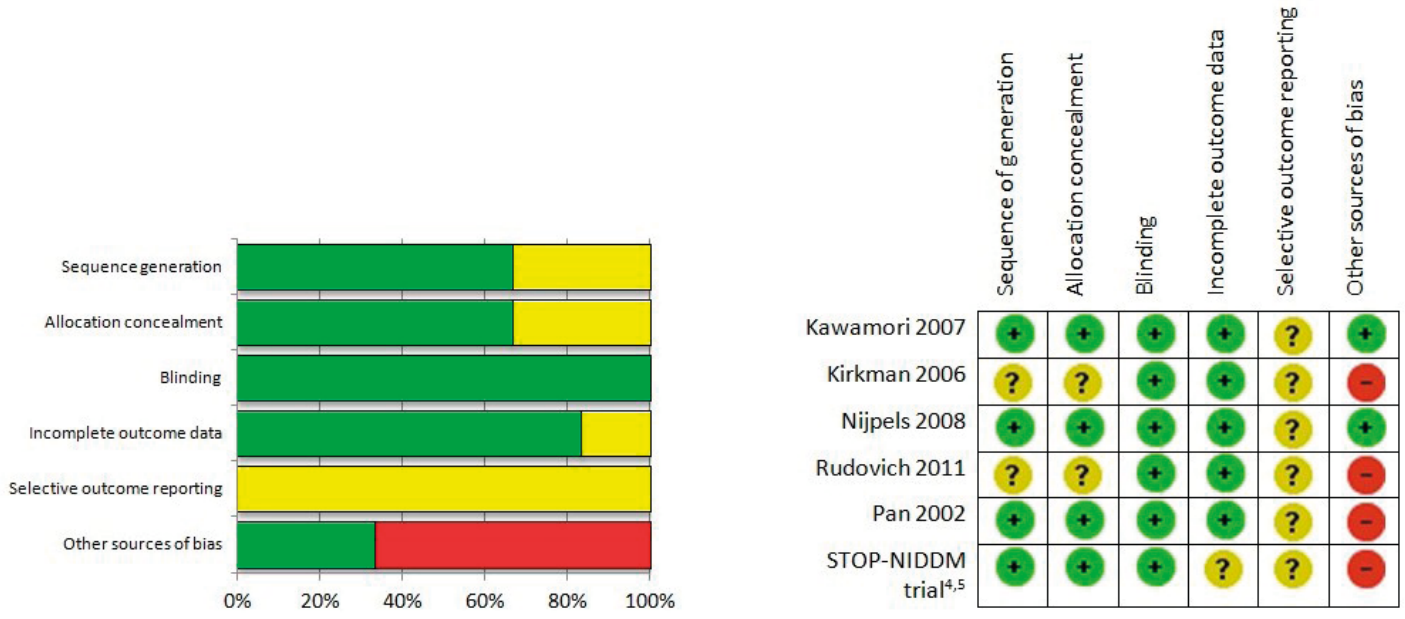

Figure 2: *Risk of bias graph and summary for studies included in the systematic review of the effect of alpha-glucosidase inhibitors on the prevention of T2DM in prediabetic people. Green = low chance of bias; yellow = unclear; red = high chance of bias. +, adequate; –, inadequate; ?, unknown, no information given. a Standardized criteria for validation in therapeutic research as stated in the Cochrane collaboration.*

Four studies reported the number of patients that developed T2DM during follow-up. A meta-analysis was performed in which the number of events was compared to the total number of patients in the intervention or placebo group (Figure 3A). In the study of Nijpels et al. (2008) [12], only the percentage of events and the total number of patients in the group were given. The number of events was calculated by multiplying the number of patients in the group with the percentages of events.After pooling the results, there was a significant effect of alpha-glucosidase inhibitors compared to placebo on development to T2DM (Relative Risk (RR): 0,80 [0,70; 0,91]). The risk difference (0,08 [0,03; 0,13]) was used to calculate the number needed to treat (NNT) [5, 12]. The results of the studies were homogeneous (I2=0%).

Three of the remaining studies reported the fasting plasma glucose levels of the baseline and endpoint. The difference between baseline and endpoint was calculated and reported, in order to take the, differences in baseline values into account. The standard deviation of the difference was calculated by pooling the standard deviations of the baseline and endpoint levels. A meta-analysis of the difference in fasting plasma glucose levels of the three studies was performed (Figure 3B). After pooling the results, no significant difference was observed between the alpha-glucosidase inhibitors and placebo (mean difference: -0,25 [-0,50; 0,01]). The results of the studies were homogeneous (I2= 0%).

The baseline and endpoint levels of HbA1c were given by three of the included studies (Figure 3C). The difference between the baseline and endpoint levels was calculated and reported. This was to correct for the variation between baseline levels. The standard deviation was calculated as mentioned before. There was a significant effect of alpha-glucosidase inhibitors compared to placebo after pooling the results (mean difference: -0,51 [-0,76;-0,26]). The results of the studies were homogeneous (I2=24%).

In the STOP-NIDDM Trial the development of major cardiovascular events (coronary heart disease, cardiovascular death, congestive heart failure, cerebrovascular event and peripheral vascular disease) was described [15,17]. At least one cardiovascular event was experienced by 32 patients from the placebo group and 15 patients from the intervention group. The cumulative annual incidence was 4.7% in the placebo group versus 1.4% in the intervention group. Myocardial infarction occurred significantly less often in the intervention group compared to the placebo group [17].

In the study of Kawamori et al. (2007) [10], six deaths occurred in the intervention group and none in the placebo group. These include accidents, suicide and lung cancer. None of these deaths were considered to be related to the use of voglibose [10]. In the study of Nijpels et al. (2008) [12], one death occurred in the intervention group eight months after the last treatment due to colon carcinoma, but this death was not considered related to the drug [12]. In the STOP-NIDMM Trial three deaths occurred in the placebo group and six deaths occurred in the intervention group [16, 17].

Besides the glucose inhibiting effect of alpha-glucosidase inhibitors, some side-effects were noticed. The STOP-NIDDM trial noted that the most common side-effects are gastrointestinal symptoms, for example gastrointestinal adverse events (RR: 1,4) flatulence (RR: 2,5), diarrhea (RR: 1,9) and abdominal pain (RR: 1,4) [16]. These effects were considered as mild or moderate in severity by the data safety and quality review committee and decrease over time after the last treatment.

The study of Kawamori et al. (2007) [10] found similar results, with flatulence occurring more often in the intervention group than in the placebo group (RR: 2,5). There were more patients with diarrhea in the intervention group (RR: 2,6) [10].

The study of Nijpels et al. (2008) [12] found that the intervention group also had more side effects than the placebo group: abdominal pain (relative risk of 4,0), diarrhea (RR: 11,6) and flatulence (RR: 13,5) [12].

Discussion

The aim of this study was to investigate the effect of alpha-glucosidase inhibitors on macrovascular morbidity, glucose levels and mortality in prediabetic people. A literature search was performed to find relevant articles. There was a significant reduction in development to T2DM and in HbA1c values in the intervention group compared to the placebo group. There was no significant difference in fasting glucose. One study reported a reduction in cardiovascular events in the intervention group. The intervention had no association with mortality.

Remarkable was that the studies where the population had lower baseline glucose values have significance, whereas the studies with higher baseline glucose values have no significance. This could suggest that alpha-glucosidase inhibitors are more effective in patients who have less developed prediabetes.

Our study contains a few drawbacks. Potentially interesting articles could have been missed, due to the exclusion of articles that were not available online or not written in English.

Furthermore, it was not possible to evaluate potential selective outcome reporting, because we were not able to find the protocols of the included studies'. Because we could not find the protocols, we cannot verify if the researchers left out data. This could potentially damage the credibility of this review, as the data that disrepute alpha-glucosidase inhibitors could be left out.

Bayer, a pharmaceutical company, funded four of the included studies. In Europe this company sells acarbose under the brand name Glucobay and has an interest in selling this drug [19]. Bayer would therefore benefit from studies recommending acarbose as a treatment for prediabetic patients.

Unfortunately, not all articles reported the outcome data that were required for our meta-analyses. For example, some studies reported the baseline HbA1c values, but not the HbA1c values after intervention. This made it difficult to include articles in the meta-analyses.

Table 3: *Summary of findings.*

Outcomes and studies	Alpha-glucosidase inhibitors	Placebo	Association measures
Development to T2DM	*Incidence*	*Incidence*	RR *[95% CI]*
- **Chiasson et al. (2002, 2003) [16, 17]**	32,4 %	41,5 %	0,78 [0,68; 0,90]
- **Kawamori et al. (2007) [10]**	5,6 %	12,0 %	0,46 [0,34; 0,64]
- **Kirkman et al. (2006) [11]**	34,4 %	34,0 %	1,01 [0,69; 1,49]
- **Nijpels et al. (2008) [12]**	16,7 %	25,0 %	0,67 [0,25; 1,78]
Fasting blood glucose	*Mean*	*Mean*	Mean difference *[95% CI]*
- **Hanefeld et al. (2004) [15]**	0,29 (SD 1,06)	-0,17 (SD 1,26)	-0,12 [-0,55; 0,31]
- **Nijpels et al. (20080 [12]**	-0,2 (SD 0,95)	0,08 (SD 1,21)	-0,28 [-0,67; 0,11]
- **Rudovich et al. (2011) [13]**	-0,1 (SD 1,00)	0,3 (SD 1,00)	-0,40 [-0,97; 0,17]
HbA1c	*Mean*	*Mean*	*Mean difference [95% CI]*
- **Hanefeld et al. (2004) [15]**	-0,39 (SD 0,87)	0,27 (SD 1,05)	-0,66 [-1,01; -0,31]
- **Kirkman et al. (2006) [11]**	-0,32 (SD 0,96)	0,08 (SD 1,09)	-0,40 [-0,76; -0,13]
- **Pan et al. (2002) [14]**	-0,38 (SD 0,86)	-0,38 (SD 0,80)	0,00 [-0,21; 0,21]
Macrovascular events	*Cumulative incidence*	*Cumulative incidence*	*RR [(95% CI])*
- **Chiasson et al. (2002, 2003) [16, 17]**	1,4 %	4,7 %	0,47 [0,26; 0,86]
Mortality	*Incidence*	*Incidence*	*RR [95% CI]*
- **Kawamori et al. (2007) [10]**	0,7 %	0 %	-
- **Nijpels et al. (2008) [12]**	1,7 %	0 %	-
- **Chiasson et al. (2002, 2003) [16, 17]**	0,9 %	0,4 %	2,01 [0,51; 8,01]
Side effects	*Incidence*	*Incidence*	*RR*
- **Flatulence**			
o **Chiasson et al. (2002, 2003) [16, 17]**	68,0 %	27,0 %	2,5
o **Kawamori et al. (2007) [10]**	17,0 %	7,0 %	2,5
o **Nijpels et al. (2008) [12]**	44,3 %	3,3 %	13,5
- **Diarrhea**			
o **Chiasson et al. (2002, 2003) [16, 17]**	32,0 %	17,0 %	1,9
o **Kawamori et al. (2007) [10]**	13,0 %	5,0 %	2,6
o **Nijpels et al. (2008) [12]**	19,7 %	1, 7 %	11,6
- **Abdominal pain**			
o **Chiasson et al. (2002, 2003) [16, 17]**	17,0 %	12,0 %	1,4
o **Nijpels et al. (2008) [12]**	13,1 %	3,3 %	4,0

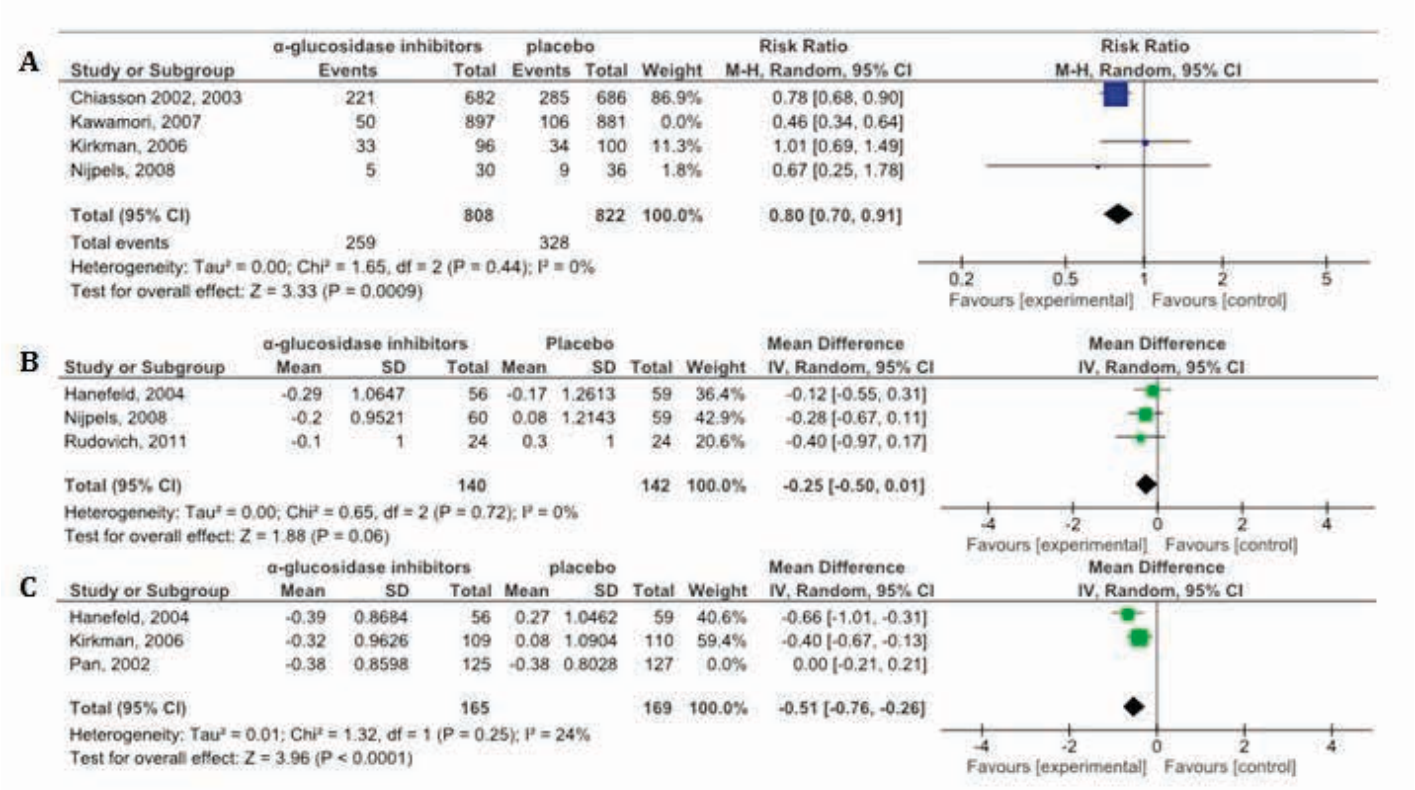

Figure 2: *Forest plots. A) Development to T2DM with risk ratio. B) Fasting glucose with mean difference. C) HbA1c with mean difference. Square size = study population. Diamond = average value with 95%-CI.*

Cardiovascular events were only reported in the STOP-NIDDM trail. In this trial, alpha-glucosidase inhibitors decrease the risk of cardiovascular events suggesting that alpha-glucosidase inhibitors could be beneficial. This conclusion is based on the results of one trial, thus this is not substantial evidence. This study did have many participants and the effect that was found was strong. We recommend further research, since alpha-glucosidase inhibitors have a potential to prevent macrovascular events.

We did not look at microvascular morbidity, because it was not studied in any article. Therefore, we cannot draw a conclusion about the benefit of alpha-glucosidase inhibitors on micro morbidities.

We excluded the study of Kawamori in the meta-analysis on the development to T2DM (Figure 3A), because this was the only study that used voglibose as an intervention instead of acarbose. In the study of Nijpels, we calculated the number of events, because only the percentage of events and the total number of patients in the group was given. This is questionable, because we did not get a rounded number of events after calculation. The study of Chiasson weighed a lot more than the other two studies, so the result of the meta-analysis is predominantly based on this study. The result is significant, but not convincingly. On the other hand, the NNT was low, therefore a small amount of people needs to be treated to prevent one person from developing T2DM.

The difference in fasting glucose between the intervention group and the placebo group (Figure 3B) was not significant. A reason for this could be that after a period of fasting there is only a small amount of glucose in the intestines, so alpha-glucosidase inhibitors have less of an effect on the blood glucose. Another reason could be that the results of the Rudovich study are less reliable, as it is a cross-over trial. The effect of the intervention could potentially contaminate the outcome of the placebo.

The study of Pan was excluded in the meta-analysis on HbA1c (Figure 3C) because the study had a follow-up of 16 weeks, whereas the studies of Hanefeld and Kirkman had a follow-up of respectively 160 and 343 weeks. Moreover, Pan used a dose of 50 mg three times a day, while the other two studies used a dose of 100 mg three times a day. The fact that this meta-analysis now consists of only two studies, makes the conclusion less reliable.

By definition, alpha-glucosidase inhibitors lower the blood glucose level in people, which is also what we found in our review. As the diagnosis of T2DM is based on blood glucose levels, this leads to fewer diagnoses in the intervention group compared to the placebo group. However, whether this effect decreases the morbidity associated with T2DM is unclear. In none of the studies mortality correlated with the treatment of alpha-glucosidase inhibitors. Hence, we can conclude that alpha-glucosidase inhibitors are safe to use and do not cause a higher risk of mortality.

Treatment with alpha-glucosidase inhibitors can cause side effects, but these are considered mild. Even so, these could lead to drug non-compliance. However, not all included articles mentioned the drug compliance. In the studies that did mention compliance, it was shown to be quite high [11,14,16].

This treatment has a lot of implications for the life of prediabetic people. They have to use the medication three times a day, with a meal. It is unclear if this treatment needs to be taken life-long. These implications could also lead to drug non-compliance. People may find taking a drug three times a day too much or they forget to take the drug.

The costs of treatment with alpha-glucosidase inhibitors are not included in this review.

A study has shown that there is a difference in blood glucose levels, depending on whether you measure the blood glucose from capillary or venous sources [20]. This was not taken into account in this analysis, as

the included studies did not mention from which source the blood glucose was measured.

We noted that the studies with an asian population had, on average, a lower BMI than the studies with a western population, which influences the comparability between the included articles. Therefore, studies with an asian population are less applicable when it comes to drawing a conclusion intended for a western population.

Conclusion

Alpha-glucosidase inhibitors decrease the risk of major cardiovascular events, decrease the blood glucose values, and there is no association with mortality. The risk of development to T2DM decreases with alpha-glucosidase inhibitors treatment. This would help tackle a major health problem. However, there are side effects that need to be considered and the effect of alpha-glucosidase inhibitors on complications that are associated with T2DM have not all been studied.

The current recommendation for prediabetic people in the Netherlands is to change their lifestyle by healthy dietary changes and more exercise in order to reduce the risk of developing prediabetes into T2DM [21]. Two large prevention studies have shown a beneficial effect in the reduction of the development of prediabetes into diabetes due to lifestyle changes [22,23]. Alpha-glucosidase inhibitors could perhaps be prescribed when lifestyle changes are not effective enough.

More research needs to be done on the effects of alpha-glucosidase inhibitors on T2DM related morbidity. Alpha-glucosidase inhibitors decrease the chance of T2DM diagnosis. However, there are health effects associated with T2DM that could still be problematic, even without a T2DM diagnosis, which is based on blood glucose levels.

Further research should be done on the cost-effectiveness of the treatment and the implications it has on a patient's life.

Even though alpha-glucosidase inhibitors have positive effects, we cannot yet recommend to prescribe alpha-glucosidase inhibitors to prediabetic people.

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