

IQWiG Reports - Commission No. A05-07

Benefit assessment of long-term blood glucose lowering to near- normal levels in patients with type 2 diabetes mellitus¹

Executive Summary

¹ Translation of the executive summary of the rapid report “Nutzenbewertung einer langfristigen, normnahen Blutzuckersenkung bei Patienten mit Diabetes mellitus Typ 2” (Version 1.0; Status: 06.06.2011). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Benefit assessment of long-term blood glucose lowering to near-normal levels in patients with type 2 diabetes mellitus

Contracting agency:

Federal Joint Committee

Commission awarded on:

22.02.2005

Internal Commission No.:

A05-07

Address of publisher:

Institute for Quality and Efficiency in Health Care

Dillenburger Str. 27

51105 Cologne

Germany

Tel: +49-(0)221/35685-0

Fax: +49-(0)221/35685-1

E-mail: berichte@iqwig.de

Website: www.iqwig.de

Executive summary

Background

Epidemiological studies in patients with type 2 diabetes mellitus show a clear positive association between blood glucose (BG) levels and elevated microvascular and macrovascular morbidity and mortality, whereby the risk rises continuously with increasing BG levels. In order to avoid diabetes-related late complications, clinical practice guidelines on BG lowering recommend therapy goals in a “near-normal” range (“intensive BG control”). Even if higher BG levels have been associated with a higher risk of late complications in non-interventional epidemiological studies, this does not necessarily mean that the lowering of elevated BG levels also leads in any case to a decrease in the risk of diabetes-related late complications. Only randomized controlled intervention trials can prove whether efforts to achieve low BG levels by means of BG-lowering therapy can actually reduce the risk of serious cardiovascular, cerebrovascular or other vascular events, or other late complications of diabetes.

Aim of the investigation

The aim of the present investigation is the benefit assessment of measures with the goal of long-term adjustment of BG to near-normal levels compared to measures with no goal or a less intensive goal of BG adjustment in patients with type 2 diabetes mellitus in respect of patient-relevant outcomes.

Methods

The assessment was conducted on the basis of relevant randomized controlled trials (RCTs). For this purpose, a literature search was performed in the following databases: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search for current relevant systematic reviews was undertaken in the following databases: MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), the NHS Economic Evaluation Database (Economic Evaluations), and the Health Technology Assessment Database (Technology Assessments). The systematic reviews were screened for any further relevant studies. The literature search covered the period up to 23 July 2009. In justified individual cases, the authors of relevant publications were contacted.

Eligible studies were those of at least 6 months' duration investigating adult patients with manifest type 2 diabetes mellitus. The goal in the test intervention group had to be long-term BG adjustment to near-normal levels (long-term lowering of HbA1c to levels at least lower than 7.5%, or long-term lowering of fasting BG to levels at least lower than 126 mg/dl or 7 mmol/l). Comparator interventions were those with no goal or a less intensive goal of long-term BG adjustment to near-normal levels. The primary outcome of the investigation was all-cause mortality. Secondary outcomes were late complications of diabetes mellitus such as

myocardial infarction (MI), stroke, end-stage renal disease, amputation, blinding, health-related quality of life, as well as therapy-related factors in terms of severe hypoglycaemia and serious adverse events (SAEs). In addition, the following outcomes were assessed as surrogates: changes in the ocular fundus or in vision, as well as changes in the glomerular filtration rate (GFR) or serum creatinine levels.

The risk of bias of the results was assessed for each study included in the benefit assessment, and separately for each patient-relevant outcome. The results for the patient-relevant outcomes reported in the studies were described and compared, and, if appropriate, pooled quantitatively by means of meta-analyses. The influence of potential effect modifiers, e.g. caused by the age and gender of participants or by different specifications of target levels in the studies were, among other things, examined with meta-regression methods.

Results

Seven relevant RCTs were identified including a total of nearly 28,000 participants. The ACCORD, ADVANCE and VADT studies were conducted after the year 2000; the remaining ones (KUMAMOTO, UGDP, UKPDS, van der Does) took place between the 1960s and 1990s. Patients were on average between 47 and 66 years old, had been suffering from manifest type 2 diabetes mellitus for about 4 to 12 years, or, in 2 studies (UKPDS, UGDP), had a new manifestation of the disease. The mean HbA1c baseline levels were between 7.1% and 9.4%. In the 3 newer studies (ACCORD, ADVANCE, VADT), 32% to 41% of participants had already experienced a cardiovascular event before the start of the study; in the other studies this proportion was in part considerably lower. The gender ratio varied substantially (proportion of women between 3% and 77%). Information on body weight was lacking in the UGDP study; in the other studies patients were overweight, with a mean Body Mass Index (BMI) of 28 to 32, except for the participants in the Japanese KUMAMOTO study, who were of normal weight, with a BMI of 20 to 22. A blinded assessment of outcomes was performed only in individual cases.

Whereas in the ACCORD, ADVANCE and VADT studies intensive BG control was exclusively orientated towards HbA1c specifications, for the participants in the KUMAMOTO study, in the test intervention group HbA1c target levels as well as target levels for fasting BG and postprandial BG were defined. The target levels in the UGDP study considered fasting BG levels as well as levels 1.5 hours after breakfast and one hour after an oral glucose stress test (50g) performed within the framework of routine monitoring. The target levels in the UKPDS and van-der-Does studies only concerned the fasting BG levels to be achieved.

The risk of bias of results was largely assessed as low in the two newer ADVANCE and VADT studies. Overall, the results of the ACCORD, KUMAMOTO, UGDP, UKPDS and van-der-Does studies were classified as potentially having a high risk of bias.

For all outcomes, the risk of bias on an outcome level corresponded to that on the study level, with the following exceptions:

The results for all outcomes of the ACCORD study were deemed as potentially having a high risk of bias because of the premature study termination due to increased mortality and the unclear influence of competing risks, as well as to the fact that for all other outcomes it was ultimately insufficiently certain that the corresponding results were actually independent of mortality.

The results for severe hypoglycaemia were seen as potentially carrying a high risk of bias in the case of the ADVANCE study due to the study-specific definition used for this outcome and a lack of blinding of the outcome assessment. With regard to pre-stages of blindness, on the outcome level all available results (except for the photocoagulation / vitrectomy results of the VADT study) showed a potentially high risk of bias.

Except for the van-der-Does study, all studies reported all-cause mortality and none showed a statistically significant reduction for this outcome through intensive BG control. In contrast, in one study (ACCORD), the risk of dying was statistically significantly higher in patients whose therapy goal was BG lowering to near-normal levels than in those with a more liberal target level. This study was terminated prematurely. Meta-analytic pooling of all studies showed no significant effect for this outcome.

Except for the KUMAMOTO and van-der-Does studies, complete information was available on the frequency of both fatal and non-fatal MI for all included studies. Meta-analytic pooling of results for fatal MI showed no statistically significant difference (pooled effect for hazard ratio or risk ratio: 1.01 [95% CI: 0.83; 1.23]; $p=0.944$).

In contrast, meta-analytic pooling of the ACCORD, ADVANCE, UGDP, UKPDS and VADT studies yielded a statistically significant reduction in non-fatal MI (pooled effect 0.84 [95% CI: 0.75; 0.94]; $p=0.002$). However, this result seems to be uncertain overall. In this analysis, the results of the ACCORD study are considered with a weight of 34%. In the ACCORD study, on the one hand, the risk of a non-fatal MI was significantly reduced in the intensive-therapy group, while on the other hand all-cause mortality was significantly increased. This contrary effect could indicate competing events and thus a relevant risk of bias. A meta-analysis excluding the ACCORD study showed a reduction in the risk of non-fatal MI, which was however not significant (pooled effect 0.88 [95% CI: 0.76; 1.01]; $p=0.072$). Due to these uncertainties, the results allow no inference of proof of a benefit in respect of the prevention of non-fatal MI; however, the data provide an indication in this regard. In respect of fatal MI, the data provide neither proof nor an indication of a benefit.

Information on the frequency of stroke was complete in the ACCORD, ADVANCE, UKPDS and VADT studies. A meta-analysis showed no advantage of the test intervention, neither for

fatal nor non-fatal stroke (pooled effect fatal stroke: 0.88 [95% CI: 0.64; 1.21]; p=0.447; pooled effect non-fatal stroke: 1.01 [95% CI: 0.87; 1.16]; p=0.903).

Only the UKPDS and ACCORD studies provided concrete information on the outcome “end-stage renal disease”. In both studies no statistically significant group difference was found. In the ADVANCE study a composite outcome was reported that comprised end-stage renal disease and death through renal disease. Here, too, no significant advantage for the test intervention was shown. Meta-analytic pooling showed no statistically significant difference between groups (pooled effect: 0.86 [95%-CI: 0.69; 1.08]; p=0.207).

Information on amputation rates was provided in the VADT, UKPDS and UGDP studies, which did not distinguish between minor and major amputations. Meta-analytic pooling showed no statistically significant difference between groups (pooled effect: 0.67 [95% CI: 0.42; 1.05]; p=0.083).

Only the UKPDS study reported on the outcome “blindness”; no statistically significant group difference was shown here (HR: 0.84 [95% CI: 0.51; 1.40]; p=0.39).

Results that were relevant to the report and referred to changes in health-related quality of life were not available in any publication.

Despite the different and largely bias-prone definitions of outcomes and despite the different absolute frequencies of events, the ACCORD, ADVANCE, UKPDS and VADT studies consistently found that intensive BG control considerably increased the risk of severe hypoglycaemia, as the examples from the current studies presented below also illustrate. In the other studies, either no information was available or no events occurred. Overall, for severe hypoglycaemia the data provide a clear indication of harm from intensive BG control; however, due to the high risk of bias no proof of harm is inferred.

Information on the proportion of patients with SAEs was available only in the ACCORD and VADT studies. In both studies the test intervention was significantly more frequently associated with SAEs. As in the case of the VADT study, the results for this outcome overlap with the results for the outcome “severe hypoglycaemia”, and otherwise are solely based on the results of the prematurely terminated ACCORD study, the data only provide an indication of potential harm from intensive BG control.

The present data, which indicate an advantage of intensive BG control regarding pre-stages of blindness, only refer to changes in the ocular fundus, and not to vision. In the comparatively small KUMAMOTO study, a favourable effect was reported with regard to changes in the ocular fundus on a retinopathy scale. A favourable effect was also reported on the basis of the results from a sub-analysis of the ACCORD study, which, however, was not completely based on an improvement on a retinopathy scale. In contrast, the results of the ADVANCE study do not indicate an advantage. The UKPDS study found a statistically significant advantage for

the outcome “photocoagulation”; this was shown neither in the VADT nor in the ACCORD study (the latter analysed a composite outcome). There is consequently insufficient information to assess the effect of intensive BG control in respect of the incidence as well as the progression of diabetic retinopathy. With regard to vision, no individual results reporting an advantage were available. Studies reporting a disadvantage were not available. Nearly all results for this surrogate parameter were deemed as having a potentially high risk of bias; consequently, the data provide neither proof nor an indication of a favourable or unfavourable effect of intensive BG control in respect of pre-stages of blindness. The same applies to vision.

Relevant information on pre-stages of end-stage renal disease in terms of changes in the GFR or serum creatinine was available in the ACCORD, ADVANCE and VADT studies. The results showed no favourable effect of intensive BG control with regard to GFR or serum creatinine. In the ACCORD study, an unfavourable effect was found for an outcome combining a deterioration in the GFR rate and a doubling of the serum creatinine level. The data therefore provide neither proof nor an indication of a favourable or unfavourable effect of intensive BG control on pre-stages of end-stage renal disease.

An effect modification due to the factors age, gender, different specifications for target levels, or different BG-lowering medication was not demonstrated. The impact of the risk of bias could not be reliably examined. Moreover, inspection of the HbA1c values actually observed during the course of the study, as well as of the study results, did not produce further findings.

In summary, a benefit of intensive BG control is not proven for any of the patient-relevant outcomes investigated here.

Relevant residual uncertainty remains in the assessment of benefit and harm in the case of the outcomes “non-fatal MI”, “severe hypoglycaemia”, as well as “SAEs”. Therefore, in these cases the respective effect observed is seen as an indication, and not as proof of a benefit or harm. This means that for intensive BG control, the data provide, on the one hand, an indication of harm through an increased rate of severe hypoglycaemia and SAEs, while on the other, they provide an indication of a benefit of such an intervention with regard to the prevention of non-fatal MI.

The Number Needed to Treat (NNT, or NNTB for benefit and NNTH for harm) is a measure for comparing and illustrating these contrary effects on the basis of the newer and very large studies ACCORD and ADVANCE.

These studies did not provide, or provided insufficient, NNTs for outcomes relevant to the report. The necessary information for our own calculations of NNTs was largely unavailable. Therefore NNTs were only calculated approximately; however, information on premature study discontinuation by patients was not considered, so that the results are potentially biased. Even if no concrete signs for this were present, the calculations should only serve as a rough

orientation and illustration, and not be misunderstood as actual results of the report. Furthermore, the estimated data are largely subject to considerable uncertainty, which is illustrated by the wide confidence intervals for most NNTs.

On the basis of the ACCORD study, the only study in which patients in the intensive-therapy group experienced a non-fatal MI significantly less often than those in the control group, an NNTB of 104 (95% CI: [57.7; 523]) was calculated for a period of 3.5 years. In contrast, the NNTH for the occurrence of severe hypoglycaemia requiring third-party assistance by medical staff was about 14 for the same period of time (NNTH 14.3; 95% CI: 12.5; 16.6). On the basis of the point estimates, this would mean that for 104 patients treated more intensively, one non-fatal MI would be prevented; however, 7 to 8 additional cases of severe hypoglycaemia would occur. This illustrates that, subject to the proviso of the methodological limitations of the calculations, in order to prevent a non-fatal MI in a single patient substantially more patients would suffer from an additional severe hypoglycaemic episode. Regardless of this, the increased overall risk of mortality needs to be considered (NNTH of 95.3 for all-cause mortality; 95% CI: [53.9; 404]). If in the above case 104 patients were to receive more intensive treatment, one additional death would also be expected.

In the ADVANCE study, there was on the one hand only a minor non-significant relative reduction in non-fatal MI of 2%, corresponding to an NNTB of 1823 over a 5-year period (95% CI: NNTB 150 to ∞ to NNTH 179). On the other hand, there was a significant increase in severe hypoglycaemia with a NNTH over a 5-year period of 80.7 (95% CI: [56.3; 141]). According to these results, 1823 patients would need to be treated to prevent one non-fatal MI; however, this would be accompanied by about 23 cases of severe hypoglycaemia. Due to the great uncertainty of the estimate, even harm with regard to both outcomes cannot be excluded.

It can therefore be stated that the indication of a decrease in the risk of non-fatal MI is accompanied by a clear increase in the risk of severe hypoglycaemia. In addition, the data provide an indication of harm due to an increased rate of SAEs independent of hypoglycaemia.

Since the publication of the last milestone studies ACCORD, ADVANCE and VADT, several other author groups of systematic reviews and meta-analyses have also addressed the research question addressed here. A comparison of the results of these widely acknowledged reviews published in high-impact factor journals with the results of the present rapid report show that, even though approaches in part differ, all reviews reach largely consistent results, which also correspond to those of the present rapid report.

Conclusions

In patients with type 2 diabetes mellitus, a benefit or harm of intensive BG lowering is not proven for any of the patient-relevant outcomes investigated here, i.e. neither for all-cause

mortality nor diabetes-related late complications (fatal or non-fatal MI, fatal or non-fatal stroke, end-stage renal disease, amputation, or blindness), nor health-related quality of life. Likewise, there is no proven harm or benefit with regard to therapy-related factors (severe hypoglycaemia or SAEs), nor is a favourable or unfavourable effect proven on surrogate outcomes such as pre-stages of blindness or pre-stages of end-stage renal disease.

However, the data provide indications of harm through an increased rate of severe hypoglycaemia and SAEs independent of hypoglycaemia. This is accompanied by an indication of a benefit with regard to the prevention of non-fatal MI.

Keywords: intensive blood glucose control; diabetes mellitus, non-insulin dependent; systematic review; benefit assessment

The full report (German version) is published under www.iqwig.de