IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A05-10

Benefit assessment of long-term blood pressure reduction to levels in the lower normal range in patients with diabetes mellitus[1]

Executive Summary

[1] Translation of the executive summary of the rapid report "Nutzenbewertung einer langfristigen Blutdrucksenkung in den unteren normotonen Bereich bei Patienten mit Diabetes mellitus" (Version 1.0; Status: 21.06.2012). 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 pressure reduction to levels in the lower normal range in patients with diabetes mellitus

Contracting agency:

Federal Joint Committee

Commission awarded on:

22.02.2005

Internal Commission No.:

A05-10

Address of publisher:

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This report was prepared in collaboration with external experts. According to § 139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received." The Institute received the completed form "Disclosure of conflicts of interest" from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Appendix E of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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Background

Arterial hypertension is an important risk factor for the occurrence of cardiovascular events, both for persons with and those without diabetes mellitus (hereinafter referred to as "diabetes"). In addition, observational studies have also reported an increase in the risk of cardiovascular events in people without arterial hypertension, but with increasing blood pressure values. However, it remains unclear whether this relationship in the physiological range corresponds to a continuous increase or rather, a j-shaped or u-shaped association. Some international guidelines for antihypertensive treatment in patients with type 2 diabetes recommend target blood pressure values that are even below the general standard targets of 140/90 mmHg. These recommendations are based largely on the assumption that such an approach can achieve a reduction in the risk of cardiovascular morbidity and mortality to an extent as appears suggested by results of observational studies. Whether the risk – not only of serious cardiovascular events, but also of other late complications of diabetes – can be reduced in patients with type 2 or type 1 diabetes by such a treatment strategy, can only be proven by randomized controlled intervention studies.

Aim of the investigation

The aim of this rapid report was to assess the benefit of long-term blood pressure reduction in patients with type 1 or type 2 diabetes to blood pressure target levels (systolic and/or diastolic) that are lower than the standard targets for persons without diabetes, as compared with an attempted blood pressure reduction to standard targets (< 140 and/or < 90 mmHg) in respect of patient-relevant outcomes.

Methods

The assessment was conducted on the basis of relevant randomized controlled trials (RCTs). For this purpose, a systematic 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 up-to-date relevant systematic reviews was carried out in the databases MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (Cochrane Reviews), Database of Abstracts of Reviews of Effects (Other Reviews) and the Health Technology Assessment Database (Technology Assessments). The systematic reviews were screened for other relevant studies. The literature search covered the period up to 18.03.2011.

Studies of at least 24 weeks in adult patients with manifest type 2 or type 1 diabetes were included. In the intervention group, a long-term blood pressure reduction to targets that were lower for at least one value than the standard targets for persons without diabetes (140/90 mmHg), had to have been investigated. The use of at least one standard blood pressure target (< 140 and/or < 90 mmHg), but also lower levels – provided they were above those of the test intervention – was considered as comparator treatment. The following report-relevant outcomes, divided into patient-relevant outcomes and surrogate outcomes, were pre-defined: "all-cause mortality", "cardiovascular mortality", "cardiovascular morbidity", "end-stage renal failure", "amputation", "blindness", "health-related quality of life" and "all

adverse events" were specified as patient-relevant outcomes. In addition, the change in ocular fundus or visual acuity and the change in glomerular filtration rate (GFR) or in serum creatinine were considered as surrogate outcomes.

The studies and their results were shown separately for patients with type 2 and type 1 diabetes. The risk of bias of the results was rated for each study included in the benefit assessment and separately for each patient-relevant outcome. The results on the patient-relevant outcomes reported in the studies were described in comparative terms and, if applicable, summarized in a quantitative manner using meta-analyses. The influence of potential effect modifiers (e.g. "blood pressure at start of study") was investigated if this was reasonable and possible.

Results

Patients with type 2 diabetes

Four relevant RCTs with a total of 7313 patients with type 2 diabetes (ABCD [950 patients], ABCD-2V [129 patients], ACCORD [4733 patients] and HOT [1501 patients]) were found. The RCTs ABCD, ABCD-2V and ACCORD were conducted in North America, the HOT study additionally also in South America, Europe and Asia. The mean study duration was between 1.9 and 5.3 years. The mean age of the patients was between 56 and 63 years. The proportion of women in the comparator groups varied from 32% to 48%. Information about ethnicity was provided in 3 studies (ABCD, ABCD-2V and ACCORD), where the majority of patients were in each case of Caucasian origin. Exclusively patients with hypertension were investigated in the HOT study, whereas in the ABCD-2V study, only persons with normal blood pressure were enrolled. Both normotensive and hypertensive participants were enrolled in the other two RCTs, but in the ACCORD study, only a conjoint analysis was performed. In contrast, in the ABCD study the hypertensive cohort (Substudy ABCD-HT) and the normotensive cohort (Substudy ABCD-NT) were analysed separately and, in each case, reported in separate publications. Therefore, these two cohorts are also shown separately in this report. The mean duration of diabetes at the start of the study was about 7 to 10 years. The HOT study provided no information on this point. In the ABCD and ACCORD studies, 25% to 50% of participants had already had a cardiovascular event before the study began; in the other two RCTs (ABCD-2V and HOT) this number was far lower at 5% and 15% respectively.

All included RCTs were of an open-label design with a chronologically parallel group comparison. In addition, for most of the RCTs it was unclear whether or not at least one blinded outcome assessment took place.

In all RCTs an attempt was made in the intervention groups to achieve target blood pressures that were lower than the corresponding levels in the respective control groups. In accordance with the inclusion criteria of this rapid report, in the control groups these levels were at least a systolic blood pressure (SBP) < 140 mmHg and/or a diastolic blood pressure (DBP) < 90 mmHg.

In 3 studies only a diastolic target blood pressure was specified for the intervention group, which was defined in the ABCD-2V study and in the hypertensive cohort of the ABCD study (Substudy ABCD-HT) as < 75 mmHg and in the normotensive cohort of the ABCD study (Substudy ABCD-NT) as a reduction in DBP of 10 mmHg compared to the baseline value (mean baseline value was 84 mmHg). The HOT study had 2 intervention groups with target DBP < 85 mmHg or < 80 mmHg, results of the intervention group with the target of < 80 mmHg being used for the primary analyses of this report. The results of the other intervention group were considered in the context of sensitivity analyses. The fourth study (ACCORD) attempted only an SBP target, which, in the intervention group, was < 120 mmHg.

Two studies only specified DBP targets for the control groups (ABCD study: DBP 80-89 mmHg for both substudies; HOT study DBP < 90 mmHg). The ACCORD study specified an SBP target of < 140 mmHg. Only the ABCD-2V study specified diastolic as well as systolic blood pressure targets (DBP< 90 mmHg, SBP < 140 mmHg) for the control group.

The risk of bias of the results at study level was rated as low for the two studies ABCD-2V and ACCORD. Results of the ABCD and HOT studies were overall rated as having a high risk of bias. Key reasons for this were discrepant information in the publications and a non-transparent patient flow in the ABCD study. In the HOT study, these were the lack of information on basic characteristics and patient flow for the report-relevant group of patients with type 2 diabetes and possibly selective reporting.

For all outcomes, the outcome-specific risk of bias corresponded to the risk of bias at study level with the following exceptions: since for the outcome “all adverse events” normally only accumulations or unusual features are reported, in the ACCORD study these results were also assessed as having a high risk of bias. The results on the outcome “early stages of blindness in the sense of change in the ocular fundus” in the ABCD-2V and ACCORD studies were considered as having a high risk of bias. Likewise, the risk of bias for the outcome “moderate vision loss” in the ACCORD study was rated as high.

Where possible, the results of all studies were generally considered together to assess the effects of a treatment strategy using lower blood pressure targets. If heterogeneity was present, the influence of potential effect modifiers was considered. The effect modifier “specified target systolic or diastolic blood pressure” was regularly investigated because this was the only one that could be checked for all outcomes.

All studies reported on all-cause mortality. A meta-analysis showed a high heterogeneity (I^2 = 54 %) for this outcome, so that no overall point estimator could be stated. None of the individual studies showed a statistically significant effect. In the study with a target SBP (ACCORD), the proportion of persons who died was not statistically significantly different between the comparator groups. In contrast, an analysis of RCTs with a target DBP produced,

with lack of (statistical) heterogeneity, a statistically significant effect in favour of the intervention (overall effect[3]: 0.65; 95% CI [0.45; 0.94]).

Information on the frequency of occurrence of a fatal or non-fatal myocardial infarction could be found in the ACCORD and HOT studies and for the substudy ABCD-NT. The meta-analytical summary showed no statistically significant difference. There was no information about this outcome in the ABCD-2V study. In the ABCD-HT substudy it was reported that there was no statistically significant difference in fatal myocardial infarctions.

Data on the frequency of occurrence of a fatal or non-fatal stroke were available for the ACCORD and HOT studies and for the ABCD-NT substudy. No information about this outcome was provided in the ABCD-2V study, whereas in the ABCD-HT substudy it was merely reported that there was no statistically significant difference in fatal strokes. A meta-analytical summary of the events showed a statistically significant advantage in favour of the intervention with lack of (statistical) heterogeneity (overall effect[4]: 0.58; 95% CI [0.41; 0.81]).

Only 2 studies (ABCD-NT substudy and ACCORD) reported how frequently fatal or non-fatal heart failure occurred. The meta-analytical summary of the two RCTs showed no statistically significant difference for this outcome. The ABCD-HT substudy also reported no statistically significant difference for fatal heart failure.

Results for the outcome “death from cardiovascular causes” were available for the ABCD-NT substudy and from the ACCORD and HOT studies. The overall consideration of all data produced a high statistical heterogeneity (I^2 = 72 %), so that no overall point estimator could be given. An investigation of the effect modifier “specified target blood pressure” was carried out to clarify heterogeneity, which also produced a high statistical heterogeneity (I^2 = 83%) even for the results from the RCTs with DBP targets. The only study with specified target SBP (ACCORD) showed no statistically significant difference between the study groups. Whilst the ABCD-NT substudy also showed no statistically significant difference, there was a statistically significant advantage for the intervention group in the HOT study.

Results on a combined cardiovascular outcome were reported in 3 studies (ABCD-2V, HOT and ACCORD). The meta-analysis of the available results showed no statistically significant group difference.

Results on end-stage renal disease were available only from the ACCORD study, where the frequency of its occurrence due to a systolic blood pressure reduction below 120 mmHg was not statistically significantly different.

[3] Result of a meta-analysis that included the relative risk (RR) and hazard ratio (HR).

[4] Result of a meta-analysis that included the relative risk (RR) and hazard ratio (HR).

The included RCTs contained no information on the outcomes “amputation”, “blindness” and “health-related quality of life”.

Information about the proportion of patients with adverse events was only provided in the ACCORD study and is therefore only available for a specified target SBP. Serious adverse events related to the antihypertensive medication occurred statistically significantly more frequently in patients of the intervention group (IG) (IG vs. control group (CG): 3.3% vs. 1.3%; $p < 0.001$).

Information about the surrogate outcome “early stages of blindness in the sense of changes in the ocular fundus” was provided in all RCTs apart from the HOT study. However, in the ACCORD study, results were only available for some of the participants from a substudy (ACCORD-EYE). A meta-analysis of all study results found a high heterogeneity ($I^2 = 41\%$). If the results of studies with target SBP or DBP were considered separately, then the results varied: in the ACCORD study with the target SBP, there was no difference, whereas a meta-analysis of RCTs with a target DBP provided, with homogeneous effects, a statistically significant result in favour of the intervention (RR: 0.80; 95% CI [0.67; 0.95]).

Moreover, in the ACCORD-EYE substudy, there were also results on the change in visual acuity, for which no statistically significant difference between the intervention and the control groups could be shown (HR: 1.17; 95% CI [0.96; 1.42]; $p = 0.12$).

Relevant information about the early stages of end-stage renal disease in the sense of a change in GFR or in serum creatinine was available from the ABCD, ABCD-2V and ACCORD studies. The meta-analysis of all study results on the change in GFR showed a high heterogeneity ($I^2 = 71.4\%$). When the results from studies with target SBP or DBP were considered separately, the results varied: the ACCORD study found a statistically significant disadvantageous effect ($p < 0.001$). The meta-analysis of the studies with a target DBP showed no statistically significant difference with low heterogeneity.

The meta-analytical summary of the results of the early stages of end-stage renal disease in the sense of a change in serum creatinine showed a statistically significant disadvantage of the intervention with lack of (statistical) heterogeneity (overall effect: 0.10; 95% CI [0.07; 0.13]).

In addition to the considerations of the different blood pressure targets (diastolic/systolic), analyses of a possible effect modification were also possible only in relation to the factor “blood pressure at the start of the study” and this only for the outcome “all-cause mortality” for which analysis across all studies had shown heterogeneity. In this context, there were no signs of an effect modification. Due to the lack of data, further analyses for all other outcomes were not possible. Analyses of possible effect modifiers for the other previously planned factors “age” and “gender” were not practicable because the studies did not differ substantially in respect of these factors. There were also no corresponding analyses on the level of the specified targets, since, on the one hand, a target SBP was only specified in one

single study and, on the other hand, the specified target DBP in the remaining studies differed only slightly. However, supplementary sensitivity analyses that included results of the second intervention group of the HOT study (DBP target < 85 mmHg) alone or the combination of both intervention groups were undertaken for the outcomes "all-cause mortality", "myocardial infarctions", "strokes", "death from cardiovascular causes" and for the combined cardiovascular outcome. For the outcomes "all-cause mortality" and "death from cardiovascular causes", there were deviations from the results of the main analyses in respect of the statistical significance or statistical heterogeneity. However, the results of the main analyses were not called into question. As, however, there is a high risk of bias for all results of the HOT study, the results of these sensitivity analyses show a high degree of uncertainty. Therefore, no conclusions can be drawn regarding possible differing effects of different DBP targets.

In summary, for the patient-relevant outcomes "all-cause mortality" and "death from cardiovascular causes" there is neither proof nor an indication of a benefit or harm from a strategy to reduce blood pressure to levels in the lower normal range in patients with type 2 diabetes. The meta-analyses show a high statistical heterogeneity for both outcomes. The subsequent analyses on the effect modifier "specified target blood pressure systolic/diastolic" provided an indication of a benefit of a blood pressure reduction to diastolic targets of < 75 to 80 mmHg for the outcome "all-cause mortality". However, this result is based largely on studies with a high risk of bias. Furthermore, the extent to which this also applies to normotensive patients is still unclear, because this result is predominantly based on studies with participants with hypertension. No indication or proof of a benefit or harm is given from these analyses for the outcome "all-cause mortality" for a specified systolic blood pressure target or on consideration of the outcome "death from cardiovascular causes".

Regarding the outcome "stroke" (fatal and/or non-fatal) there was overall proof of a benefit of the strategy of reducing blood pressure to the lower normotensive range in patients with type 2 diabetes. There is neither indication nor proof of a benefit or harm for the outcomes "myocardial infarction" and "heart failure" – in each case fatal and non-fatal combined – or for the combined cardiovascular outcome.

There were no data for the patient-relevant outcomes "amputation", "blindness" and "health-related quality of life", whilst for the outcomes "end-stage renal disease" and "all adverse events" there was at least information from one study with a specified SBP target. From these results, an indication could be derived of harm from an SBP target < 120 mmHg in respect of serious adverse drug reactions of the antihypertensive medication. For the outcome "end-stage renal disease", there was neither an indication nor proof of benefit or harm.

For the surrogate outcome "early stages of blindness" there was overall neither proof nor an indication of an effect from the strategy of reducing blood pressure to levels in the lower normal range in patients with type 2 diabetes. Heterogeneous results were obtained across all studies for the early stages of blindness in the sense of changes in the ocular fundus; an

analysis taking into account the effect modifier "specified target blood pressure systolic/diastolic", produced an indication of an advantageous effect of reducing blood pressure to diastolic targets of < 75 to 80 mmHg, but not for a specified target SBP.

For the surrogate outcome "early stages of end-stage renal disease" in the sense of a change in GFR there was overall neither proof nor an indication of an effect from the strategy of reducing blood pressure to levels in the lower normal range in patients with type 2 diabetes. Here too, results were heterogeneous across all studies. If the results are considered separately according to specified target SBP or DBP, there is, on the one hand, an indication of an effect to the disadvantage of a strategy with SBP targets < 120 mmHg, while, on the other hand, there is neither an indication nor proof for DBP targets of <75 to 80 mmHg. For the surrogate outcome "early stages of end-stage renal disease" in the sense of a change in serum creatinine there was, however, overall proof of a disadvantageous effect for the strategy of reducing blood pressure to levels in the lower normal range in patients with type 2 diabetes.

Patients with type 1 diabetes

Only information from one RCT (Lewis et al.) from the USA on patients with type 1 diabetes was available. In this 2-year study, 129 patients with diabetic nephropathy who had already taken part in a previous study were enrolled (Study of ACE Inhibition in Diabetic Nephropathy). The mean age of the patients was 37 years and approx. 53% were female and almost all were Caucasian. Normotensive as well as hypertensive patients were included and the mean blood pressure at the start of the study was approx. 132/79 mmHg. The mean duration of diabetes when the study began was about 26 years. There was no information on the number of participants who has already suffered a cardiovascular event. The RCT had an open-label study design with a chronologically parallel group comparison. In addition, it was unclear whether a blinded outcome assessment took place.

The target levels were defined via the mean arterial blood pressure and were ≤ 92 mmHg in the intervention group and 100 to 107 mmHg in the control group.

The risk of bias was already rated at study level as high, so all results were potentially subject to a high degree of bias.

Only results on the outcomes "all adverse events" and "early stages of end-stage renal disease" were reported. No information about any of the other outcomes defined as patient-relevant for the report was available.

There was a statistically significant disadvantage for the intervention group in respect of an orthostatic drop in blood pressure, whereas oedema, bronchitis or sinusitis occurred less often in the intervention group. No information about significance was provided. The Institute's calculations showed that only the difference in frequency of sinusitis was statistically significant (oedema: $p = 0.12$; bronchitis: $p = 0.11$; sinusitis: $p = 0.003$).

There were no statistically significant differences between the comparator groups in terms of the mean annual reduction in GFR and the change in serum creatinine.

In summary, it can be said that there is neither proof nor an indication of a benefit or harm from a reduction in blood pressure to the lower near-normal range in patients with type 1 diabetes.

Conclusions

In order to derive conclusions about the benefits of attempted blood pressure reduction to levels in the lower normal range as compared with an attempted blood pressure reduction in the normal range to merely standard target levels, studies that specify a target for the systolic *and* the diastolic blood pressure for both the test and the comparator intervention are primarily of interest. No such studies were identified for this report so that the conclusions drawn below are subject to the proviso that the standard targets were not necessarily reached in the control group.

Overall consideration of all studies in patients with type 2 diabetes for the patient-relevant outcome “stroke” (fatal and/or non-fatal) produces proof for the benefit of an attempted blood pressure reduction with blood pressure targets that are lower than the standard targets compared to an attempted blood pressure reduction to a standard target.

For the patient-relevant outcome “all-cause mortality”, there is an indication of a benefit of a reduction in blood pressure to diastolic targets < 75 to 80 mmHg compared to an attempted blood pressure reduction to a standard target. This indication does not arise from the study with a blood pressure reduction targeted to an SBP in the lower normotensive range.

There is an indication of harm in respect of serious adverse events related to the antihypertensive medication arising from a reduction in blood pressure to systolic targets < 120 mmHg, compared to an attempted blood pressure reduction to a systolic standard target.

For all other patient-relevant outcomes (“cardiovascular mortality”, “myocardial infarction”, “heart failure”, “combined cardiovascular outcome”, “end-stage renal disease”, “minor and major amputations”, “blindness”, “health-related quality of life” and “all adverse events”) no indication or proof can be derived in patients with type 2 diabetes for a benefit or harm from a blood pressure reduction with blood pressure targets that are lower than the standard targets for at least one systolic or diastolic value, compared to an attempted blood pressure reduction to standard targets.

In patients with type 1 diabetes, neither benefit nor harm is proven from a reduction in blood pressure to levels in the lower normal range compared to an attempted blood pressure reduction to standard targets for the patient-relevant outcomes investigated here. Furthermore, no such indications can be deduced from the only available study. An advantageous or

disadvantageous effect on the early stages of blindness or early stages of end-stage renal disease is also not demonstrated.

Keywords: hypertension; blood pressure control; diabetes mellitus, type 1; diabetes mellitus, type 2; systematic review; benefit assessment

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