What Blood Pressure Goal in Type-2 Diabetes?

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Atherosklerose - PAVK Erstdiagnostik

Jeder 5. der über 65-Jährigen ist von einer behandlungsbedürftigen Gefäßerkrankung betroffen, 80 % davon sind unerkannt*

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Introduction

In 1921, the Austrian physician, Karl Hitzenberger (Figure 1), was one of the first to describe the association between elevated blood pressure (BP) and disturbances of glucose metabolism in the finding of hyperglycemia in patients with hypertension based on observations in his clinic in Vienna [1]. This skillful observation has thereafter been repeatedly confirmed in numerous studies describing patients with established type-2 diabetes or in various states of pre-diabetes, or the so-called metabolic syndrome, as reviewed [2]. Patients with type-2 diabetes run an increased cardiovascular risk [3] not only due to hyperglycemia, but to a cluster of other risk factors, most notably dyslipidemia, hypertension, impaired fibrinolysis, and risk of thrombosis. These risk factors should all be addressed by a strategy to reduce modifiable risk factor levels by lifestyle intervention and appropriate drug therapy, as documented in the Steno-2 study [4].

Elevated blood pressure is of special importance as observational studies have revealed a more or less linear relationship between the height of systolic blood pressure and the risk of coronary heart disease and stroke [5], which has not always been found in intervention studies. The treatment of hypertension in type-2 diabetes is thus of great importance to avoid costly complications and human suffering. The evidence-base for recommending a treatment target for blood pressure control has expanded due to the publication of several new studies and meta-analyses during recent years, which will be summarized and commented upon in this overview.

Tighter BP control in hypertensive patients with type-2 diabetes (by use of several antihypertensive drug classes versus placebo) has been documented to reduce the risk of both micro- and macrovascular disease in the UKPDS [6, 7] as well as in several other intervention studies [8–11]. Most guidelines have so far advocated a treatment target of BP < 130/80 mmHg for patients with type-2 diabetes [12–14], even the 2011 version of the „Medical Treatment Standards“ from the American Diabetes Association (ADA), although with some comments on the need of individualizing the treatment [15].
Evidence from Studies

A summary of the most important studies from recent years and their findings is presented below.

**ACCORD-BP**

The Action to Control Cardiovascular Risk in Diabetics (ACCORD) BP trial [24] in 4733 high-risk patients with type-2 diabetes (34% had previous CVD) analysed 2 randomly selected groups, one group assigned to intensive therapy targeting an SBP < 120 mmHg, and another group on standard therapy targeting an SBP < 140 mmHg. Mean SBP after one year was 119 mmHg and 134 mmHg, respectively, and mean follow-up was 4.7 years. The primary composite outcome was non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes. The study investigators found no significant difference between the 2 groups concerning the risk for the primary outcome or in risk for total mortality, with hazard ratios (HR) for intensive therapy of 0.88 (0.73–1.06; p = 0.2) and 1.07 (0.85–1.35; p = 0.5), respectively. However, the risk for the pre-specified secondary endpoint stroke was reduced with intensive therapy, HR 0.59 (0.39–0.89; p = 0.01). Serious adverse events attributed to antihypertensive treatment occurred more frequently (p < 0.001) in the intensive-therapy group – 77 of the 2362 participants (3.3 %) – compared to the standard therapy group – 30 of 2371 (1.3 %).

**INVEST**

The International Verapamil-Trandolapril Study (INVEST) was a randomized controlled trial in 22,500 patients with hypertension and coronary heart disease (CHD), with the objective to compare the effects of treatment with verapamil – trandolapril or atenolol – hydrochlorothiazide on the risk for CVD. The primary outcome was first occurrence of all-cause mortality, non-fatal myocardial infarction, or stroke, mean follow-up was 2.7 years. A post-hoc observational subgroup follow-up analysis of 6400 hypertensive patients with diabetes and CHD has been presented [25], showing a higher risk for the primary endpoint with an SBP ≥ 140 mmHg (outcome rate 19.8%, adjusted HR 1.46 [1.25–1.71; p < 0.001]), and a similar risk with an SBP < 130 mmHg (outcome rate 12.7%, adjusted HR 1.11 [0.93–1.32; p = 0.2]), compared to usual control 130–139 mmHg as reference (outcome rate 12.6%).

**NDR-BP**

This observational study from the Swedish National Diabetes Register (NDR) of 12,677 patients with type-2 diabetes treated with antihypertensive drugs [26] analysed the effect of SBP levels on risks for fatal/non-fatal CHD, stroke, and CVD, when followed for 5 years from 2002–2007 after exclusion of patients with a history of heart failure. Risk curves of CHD and stroke increased progressively with higher baseline or updated mean SBP across 110–180 mmHg in a Cox regression model, and no J-shaped risk curves were seen at low SBP levels in all patients, or in 2 subgroups without (n = 10,304) or with (n = 2373) a history of CVD. With an updated mean SBP 110–129 mmHg (mean 123 mmHg) as reference, SBP ≥ 140 mmHg (mean 152 mmHg) showed an adjusted HR 1.37 (1.12–1.68) for CHD, 1.86 (1.34–2.59) for stroke and 1.44 (1.21–1.72) for CVD (p = 0.003–< 0.001), while an SBP 130–139 mmHg (mean 135 mmHg) showed a non-significant risk increase for these outcomes. Furthermore, a with baseline SBP 110–129 mmHg, a further SBP reduction from baseline to follow-up was associated with an increase in risks for CHD and CVD, adjusted HR 1.7 (p = 0.002) compared to no further SBP reduction, although this was not seen for stroke. However, with a baseline SBP of ≥ 130 mmHg, strong benefits of further SBP reduction were seen with considerable risk reductions for CHD, stroke, and CVD, adjusted HR 0.5–0.7 (p = 0.02–< 0.001). Similar results have been reported in the ONTARGET post-hoc analysis in patients on antihypertensive treatment (38% with diabetes) with a baseline SBP < 130 mmHg [21, 22], in which cardiovascular mortality was increased with a further SBP reduction from baseline to follow-up (p < 0.001).

The NDR-BP results [26] are in accordance with both ACCORD-BP [24] and the post-hoc INVEST [25] studies showing strong benefits in CVD risk with an SBP < 140 mmHg, although no obvious difference in benefits between lower intervals in the SBP range 110–139 mmHg, though it must be taken into account that NDR-BP is an observational study. Thus, these recent studies support the reappraisal of the European guidelines aiming for an SBP well below 140 mmHg [16]. In a further analysis from the NDR study, different statistical methods were applied to illustrate the same data [27, 28]. The conclusion was that some spline statistics (graphs) are maybe not so accurate as to show the data by defined blood pressure intervals because the uncertainty at both ends of the spline curve makes it less reliable and can even be interpreted as an exaggerated graphical illustration, as used in the post-hoc analysis of attained blood pressure levels and coronary risk in the Treatment to New Targets (TNT) statin intervention trial [20, 29].

**ADVANCE**

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial [11] was a randomised controlled trial in 11,140 patients with type-2 diabetes, analysing the effect of treatment with a fixed combination of an ACE inhibitor (perindopril) and a thiazide (indapamide) compared to placebo, for the effect on micro- and macrovascular complications, with a mean follow-up of 4.3 years. The SBP was reduced to < 135 mmHg in drug-treated patients, compared with patients on placebo in whom
Two New Meta-Analyses from 2011

It is customary to try to collect the evidence for performing a meta-analysis if a controversy exists in clinical science in order to look for results based on the bulk of evidence available. In May 2011, a new meta-analysis was published to investigate the appropriate blood pressure goal in patients with type-2 diabetes, based on extensive searches via PubMed and other databases until October 2010 [34]. Studies were included based on patients with type-2 diabetes mellitus or impaired fasting glucose/impaired glucose tolerance that enrolled at least 100 patients with an achieved SBP of ≤ 135 mmHg in the intensive blood pressure control group and ≤ 140 mmHg in the standard blood pressure control group, had a follow-up of at least one year, and evaluated macro- or microvascular events. Finally, the authors were able to identify 13 randomized clinical trials enrolling 37,736 participants. Intensive blood pressure control was associated with a 10%-reduction in all-cause mortality, odds ratio (OR) 0.90 (95%-CI: 0.83–0.98), a 17%-reduction in stroke, and a 20%-increase in serious adverse effects, but with similar outcomes for other macro- and microvascular (cardiac, renal, and retinal) events compared with standard blood pressure control. The results were similar in a sensitivity analysis using a so-called Bayesian random effects model. More intensive blood pressure control (≤ 130 mmHg) was associated with a greater reduction in stroke, but did not reduce other events.

The authors concluded that in patients with type-2 diabetes mellitus/impaired fasting glucose/impaired glucose tolerance, an SBP treatment goal of 130–135 mmHg is acceptable [34].

However, with more aggressive goals (< 130 mmHg), they observed target organ heterogeneity in that the risk of stroke continued to fall, but there was no benefit regarding the risk of other macro- or microvascular (cardiac, renal, and retinal) events, and the risk of SAEs even increased. These facts underscore the importance of a balanced approach to blood pressure control in patients with type-2 diabetes.

In a second recent meta-analysis, estimates of the effects of blood pressure reduction on the risks of myocardial infarction and stroke in diabetic patients were investigated [35]. A number of 73,913 patients with diabetes (295,652 patient years of exposure) were included, randomized in 31 intervention trials. Abstract-retrieved data were used. Overall, experimental treatment reduced the risk of stroke by 9% (p = 0.006), and that of myocardial infarction by 11% (p = 0.002). Allocation to more-tight, compared with less-tight, blood pressure control reduced the risk of stroke by 13% (p = 0.006), but that of myocardial infarction by 11% (p = 0.002). Allocation to more-tight, compared with less-tight, blood pressure control reduced the risk of stroke by 13% (p = 0.006), and that of myocardial infarction by 11% (p = 0.002). Allocation to more-tight, compared with less-tight, blood pressure control reduced the risk of stroke by 13% (p = 0.006), and that of myocardial infarction by 11% (p = 0.002).
The 2 new meta-analyses [34, 35] taken together thus suggest that even if stroke is prevented by lower attained blood pressure levels, this does not involve myocardial infarction or prevention of cardiovascular mortality. As there is a price to be paid regarding increased costs and risk of serious adverse events, it is recommendable to go for a flexible blood pressure goal taking into account significant background factors in each patient for individual evaluation. This often leads to the aim of a systolic blood pressure goal in the range of 130–135 mmHg in most patients, somewhat higher than recommended in most current guidelines. The inevitable conclusion thus has to be that these guidelines do not reflect the summary of available evidence at present.

**Discussion**

Even if observational studies show a linear relationship between increasing systolic blood pressure levels and risk of ischemic heart disease [5], this does not mean that a reduction of blood pressure by treatment will show the expected benefits (Table 1). On the contrary, there might even exist a risk of increased risk in some susceptible elderly patients with longer diabetes duration and a number of comorbidities. This should, however, not preclude clinicians from realising that still a very large number of patients with diabetes have not reached an acceptable blood pressure control of <140 mmHg systolic blood pressure. A high BP ≥140/90 mmHg was reported in 29% of patients with type-1 diabetes and in 46% of patients with type-2 diabetes in the national register [36]. The frequency was 40% in a representative sample of patients with diabetes (mean age 59 years, 54% on oral agents alone, and 17% on insulin alone) in NHANES 1999–2000 [37]. In a recent report on trends from the NDR, it was shown that even if blood pressure control improved from 2005–2009, still almost half of all patients with established type-2 diabetes is not <140/90 mmHg [38]. This underlines that strong efforts should be carried out in order to reduce this category of patients in poor control.

The ESH statement [16] of an SBP treatment target in patients with type-2 diabetes far below 140 mmHg points to the value of not recommending a specific lowest SBP target which is as yet unproven. ACCORD-BP [24] had a mean SBP of 119 mmHg in those on intensive treatment targeting SBP below 120 mmHg, and ADVANCE [11] had a mean SBP < 135 mmHg with intensive drug treatment. Furthermore, the INVEST post-hoc analysis also reported that a subgroup with very tight control of SBP <110 mmHg had an increased risk of total mortality, HR 2.18 (1.17–4.09; p = 0.02), compared to SBP 125–129 mmHg, adjusting for but not excluding previous heart failure [25]. NDR-BP found an increased risk of CHD, but not of stroke, with a further SBP reduction during follow-up below baseline 110–129 mmHg, excluding previous heart failure [26]. Increased risks of MI, CVD, total mortality, but not of stroke, with very tight SBP control <110–120 mmHg was recently reported in the post-hoc observational analysis of the Treating to New Targets (TNT) trial of 10,003 patients with a history of CHD in the general population [29], a phenomenon that could also be influenced by reversed causality as previous heart failure was adjusted for but only excluded for an ejection fraction <30%. A useful clinical approach may be an individualized lowest target well below 140 mmHg, taking into account individual clinical factors and comorbidities of importance. The presence of a history of CVD might be one of these factors, even if NDR-BP [26] showed no sign of a J-shaped risk curve at the lowest SBP levels down to 110 mmHg in 2373 patients with a history of CVD after exclusion of patients with heart failure. It can also be argued that a lower SBP target might be of value in patients ex-

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**Table 1. Summary of results from recent intervention trials, observational studies, and meta-analyses in patients with combination of type-2 diabetes and hypertension.**

<table>
<thead>
<tr>
<th>Study [Reference]</th>
<th>Participants</th>
<th>Design</th>
<th>Major outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE-BP [11]</td>
<td>11,140</td>
<td>RCT</td>
<td>Reduced major micro- and macrovascular events and mortality with SBP &lt; 135 versus ~140 mmHg</td>
</tr>
<tr>
<td>ACCORD-BP [24]</td>
<td>4733</td>
<td>RCT</td>
<td>No difference in risk of fatal/non-fatal CVD between SBP &lt; 120 and &lt; 140 mmHg</td>
</tr>
<tr>
<td>INVEST [25]</td>
<td>6400</td>
<td>Post-hoc observational analysis of RCT</td>
<td>No difference in risk of total mortality, non-fatal myocardial infarction, or stroke between SBP &lt; 130 and 130–139 mmHg, but increased risk of total mortality with SBP &lt; 110 versus 125–129 mmHg</td>
</tr>
<tr>
<td>ONTARGET-DM [22]</td>
<td>9300</td>
<td>Post-hoc observational analysis of RCT</td>
<td>Increased cardiovascular mortality with SBP &lt; 125 mmHg compared to SBP &lt;130 mmHg</td>
</tr>
<tr>
<td>VADT [23]</td>
<td>1791</td>
<td>Post-hoc observational analysis of RCT</td>
<td>Increased risk with DBP ≥70 mmHg even if SBP was within range recommended by guidelines</td>
</tr>
<tr>
<td>NDR-BP [26]</td>
<td>12,677</td>
<td>Observational national study</td>
<td>No difference in risk of fatal/non-fatal CVD between SBP 110–129 and 130–139 mmHg, but increased risk with baseline SBP 110–129 mmHg and further SBP reduction from baseline to follow-up</td>
</tr>
<tr>
<td>Meta-analysis I [34]</td>
<td>37,736</td>
<td>Meta-analysis of 13 RCT with DM2 or IFG patients</td>
<td>More intensive SBP control ≤130 mmHg was associated with greater reduction of stroke but not with other outcomes. Recommended goal: SBP 130–135 mmHg.</td>
</tr>
<tr>
<td>Meta-analysis II [35]</td>
<td>73,913</td>
<td>Meta-analysis of 31 RCT with DM2 patients</td>
<td>Protection of stroke increases with SBP reduction but this was not seen for myocardial infarction</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; SBP: systolic blood pressure; CVD: cardiovascular disease; DM2: type-2 diabetes; IFG: impaired fasting glucose
expected to have a higher risk of future stroke than CHD, as ACCORD-BP found a significant risk reduction of 41 % (\(p = 0.01\)) for the pre-specified secondary endpoint stroke with intensive therapy aiming at an SBP < 120 mmHg [24]. This could apply to some populations at high risk for stroke, e.g. in East Asian countries such as China and Japan.

**Combination of Blood Pressure and Glycemic Control**

The ADVANCE, UKPDS 75, and NDR data on combined intensified treatment of both SBP and HbA1c underline the importance of a multifactorial approach in order to reduce risks of macro- and microvascular complications, as demonstrated in the Steno-2 study as well [4]. The fact that reductions of both SBP and HbA1c seem to have additive effects on these endpoints points to the need to obtain an HbA1c target of < 7 % generally, although individualised based on e.g. comorbidity conditions, adults with limited life expectancy, and severe hypoglycemia in patients with advanced disease. The DCCT/EDIC observational study [39] and a recent observational NDR study [36] of patients with type-1 diabetes have demonstrated significant risk reductions of 40 % for fatal/non-fatal CVD and CHD, when groups of baseline HbA1c mean > 7 % were compared with groups of HbA1c mean 9 %. The role of intensified glycemic control in type-2 diabetes has been a subject of debate, although the benefits on microvascular complications are well-established for treatment of both type-1 and type-2 diabetes.

Antihypertensive drug treatment has been re-evaluated in recent guidelines [16]. In 2005, a large meta-analysis of available trials [10] showed that in diabetes all major antihypertensive drug classes protect against cardiovascular complications, probably because of the protective effect of BP lowering per se. Combination treatment is commonly needed to effectively lower BP. An agent that blocks the renin-angiotensin system should always be included because of the evidence of its superior protective effect against initiation or progression of nephropathy. A diuretic can be added in those with an estimated glomerular filtration rate (GFR) of \(\geq 30\) ml/min/1.73 m\(^2\), if needed, or a loop diuretic for those with GFR < 30 ml/min/1.73 m\(^2\). The ADVANCE trial used a fixed combination of an ACE inhibitor and a diuretic often on top of pre-existing antihypertensive drugs to produce some further BP reduction [11]. This resulted in benefits on the combined major and microvascular endpoints and mortality. However, ACCOMPLISH [40], including 60 % of diabetic patients among 11,000 individuals, has reported superiority of an ACE inhibitor combined with a calcium antagonist, compared to the combination of an ACE inhibitor and a diuretic, with a relative risk reduction of 20 % (\(p < 0.001\)) for the primary endpoint fatal/non-fatal CVD.

The results from recent randomised clinical trials and observational studies support a systolic blood pressure goal in type-2 diabetes well below 140 mmHg, and < 135 mmHg based on data from ADVANCE [27]. This corresponds well with findings from recent meta-analyses [34, 35] stating a goal of 130–135 mmHg for systolic blood pressure [34]. In populations at high risk for stroke, the blood pressure goal could be even lower, although taking into account the increased risks of CHD and total mortality seen with a very tight SBP control < 110 mmHg. In addition, there are benefits with combined blood pressure and glycemic control [41]. In patients with chronic kidney disease, similar conclusions have been drawn, indicating that tight blood pressure control is only of proven benefit in patients with overt albuminuria > 500 mg/day [42]. Future studies could hopefully include a randomized design to compare all 3 systolic blood pressure goals 140, 130, and 120 mmHg. The prediction, however, is that we will have to wait for such studies and therefore the view expressed in this review reflects the current evidence that we will have to live with for a number of years to come.

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**Conflict of Interest**

None.

**Relevanz für die Praxis**

Vorrangiges Ziel bei Typ-2-Diabetikern mit Hypertonie sollte es sein, bei möglichst allen Patienten den systolischen Blutdruck dauerhaft auf < 140 mmHg, am besten auf etwa 130–135 mmHg zu senken. Für eine stärkere Blutdrucksenkung (< 130 mmHg) ist kein Nutzen für das kardiovasculäre Risiko belegt; der bewiesene Benefit für das Schlaganfallrisiko wird durch vermehrte Nebenwirkungen und möglicherweise eine erhöhte kardiovaskuläre Morbidität und Mortalität erkauf.

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