

# Diabetes, Hypertension, and Outcome Studies: Overview 2010

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The treatment of hypertension in type 2 diabetes is of great importance in avoiding costly complications and human suffering. The evidence base for recommending a treatment target for blood pressure control has expanded as the result of the publication of new studies in 2010, which will be summarized and commented on in this overview.

Hypertension is a leading risk factor for mortality in both developing and developed countries (1) and a well established risk factor for cardiovascular disease (CVD) in patients with diabetes (2). An observational analysis from the UK Prospective Diabetes Study (UKPDS) has demonstrated a linear relationship between mean in-study systolic blood pressure (SBP) and the risk of macro- and microvascular complications (3). Tighter blood pressure control in hypertensive patients with type 2 diabetes by use of several antihypertensive drug classes versus placebo has been reported to reduce the risk of both micro- and macrovascular disease in the UKPDS (4,5) as well as several other intervention studies (6–9). Guidelines have so far advocated a treatment target blood pressure of <130/80 mmHg for patients with type 2 diabetes (10–12).

However, the 2009 European guidelines from the European Society of Hypertension (ESH) recommend that patients with diabetes lower their SBP well below 140 mmHg—without mentioning a specific lowest target (13)—against a background of the lower blood pressure goals

(<130/80 mmHg) recommended for patients with diabetes, which have never really been achieved in any single large trial and are even more rarely attained in medical practice. This ESH recommendation was also based on the results in some trials (14,15) and post hoc analyses of high-risk hypertensive patients (16,17), as in the Ramipril Global Endpoint Trial (ONTARGET) post hoc study (18,19) of high-risk patients (49% with a previous coronary heart disease [CHD] and 38% with diabetes) demonstrating a J-shaped risk curve with a nadir of around 130 mmHg for in-treatment SBP and all CVD outcomes except stroke. This underlines the value of some recently published randomized trials and observational studies that have performed further studies of the effect of various SBP levels on the risk for CVD and mortality (Table 1).

## ACCORD BLOOD PRESSURE STUDY

The recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial (ACCORD-BP) (20) in 4,733 high-risk patients with type 2 diabetes (34% had previous CVD) analyzed two randomly selected groups—one group assigned to intensive therapy targeting SBP of <120 mmHg, and another group on standard therapy targeting SBP of <140 mmHg. Mean SBP after 1 year was 119 mmHg and 134 mmHg, respectively, and mean follow-up was 4.7 years. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

The study investigators found no significant difference between the two groups in risk for the primary outcome or in risk for total mortality, with hazard ratios (HRs) for intensive therapy of 0.88 (95% CI 0.73–1.06;  $P = 0.2$ ) and 1.07 (0.85–1.35;  $P = 0.5$ ), respectively. However, the risk for the prespecified secondary end point stroke was reduced with intensive therapy (0.59 [0.39–0.89];  $P = 0.01$ ). Serious adverse events attributed to antihypertensive treatment occurred more frequently ( $P < 0.001$ ) in 77 of the 2,362 participants (3.3%) in the intensive-therapy group, compared with 30 of 2,371 (1.3%) with standard therapy.

**INVEST**—The International Verapamil-Trandolapril Study (INVEST) was a randomized controlled trial in 22,500 patients with hypertension and coronary heart disease, with the objective to compare the effects of treatment with verapamil-trandolapril or atenolol-hydrochlorothiazide on the risk for CVD (21). The primary outcome was first occurrence of all-cause mortality, nonfatal myocardial infarction, or stroke, and the mean follow-up was 2.7 years.

A post hoc observational subgroup follow-up analysis of 6,400 hypertensive patients with diabetes and CHD has recently been presented (22), showing higher risk for the primary end point with SBP  $\geq 140$  mmHg (outcome rate 19.8%, adjusted HR 1.46 [95% CI 1.25–1.71];  $P < 0.001$ ), and similar risk with SBP <130 mmHg (outcome rate 12.7%, 1.11 [0.93–1.32];  $P = 0.2$ ), compared with usual control 130–139 mmHg as reference (outcome rate 12.6%).

## SWEDISH NATIONAL DIABETES REGISTER BLOOD PRESSURE STUDY

The recently published observational study from the Swedish National Diabetes Register (NDR) of 12,677 patients with type 2 diabetes treated with antihypertensive drugs (23), analyzed the effect of SBP levels on risks for fatal/nonfatal CHD, stroke, and CVD, when followed for 5 years from 2002 to 2007 after exclusion of patients with a history of heart failure.

Risk curves of CHD and stroke increased progressively with higher baseline

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Table 1—Summary of recent studies in patients with type 2 diabetes and hypertension

	n	Design	Major outcomes	Ref.
ADVANCE-BP	11,140	RCT	Reduced major micro- and macrovascular events and mortality with SBP <135 versus ~140 mmHg	24
ACCORD-BP	4,733	RCT	No difference in risk of fatal/nonfatal CVD between SBP <120 and <140 mmHg	20
INVEST	6,400	Post hoc observational analysis of RCT	No difference in risk of total mortality, nonfatal myocardial infarction or stroke between SBP <130 and 130–139 mmHg, but increased risk of total mortality with SBP <110 versus 125–129 mmHg	22
NDR-BP	12,677	Observational study	No difference in risk of fatal/nonfatal 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	23

RCT, randomized controlled trial.

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 two subgroups without ( $n = 10,304$ ) or with ( $n = 2,373$ ) a history of CVD. With updated mean SBP 110–129 mmHg (mean 123 mmHg) as reference, SBP  $\geq 140$  mmHg (mean 152 mmHg) showed adjusted HR 1.37 (95% CI 1.12–1.68) for CHD, 1.86 (1.34–2.59) for stroke, and 1.44 (1.21–1.72) for CVD ( $P = 0.003$ – $<0.001$ ), whereas SBP 130–139 mmHg (mean 135 mmHg) showed a nonsignificant risk increase for these outcomes. Furthermore, with baseline SBP 110–129 mmHg, 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 with no further SBP reduction, although this was not seen for stroke. However, with baseline SBP of  $\geq 130$  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 baseline SBP <130 mmHg (18), in which cardiovascular mortality was increased with further SBP reduction from baseline to follow-up ( $P < 0.001$ ).

The results of the NDR blood pressure (NDR-BP) study are in agreement with those of both the ACCORD-BP (20) and the post hoc INVEST (21) studies, showing strong benefits in CVD risk with an SBP <140 mmHg. However, there was no obvious difference in benefits between lower intervals in the SBP range 110–139 mmHg, taking into account that the NDR blood pressure study is observational. Thus, these recent studies support the reappraisal of the European

guidelines aiming for SBP well below 140 mmHg (13).

**ADVANCE**—The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (24) was a randomized controlled trial in 11,140 patients with type 2 diabetes analyzing the effect of treatment with a fixed combination of an ACE inhibitor (perindopril) and a thiazide (indapamide) compared with placebo, for the effect on micro- and macrovascular complications, with a mean follow-up of 4.3 years. SBP was reduced to <135 mmHg in the drug-treated patients compared with patients on placebo in whom SBP remained at ~140 mmHg. The primary end point was a composite of major macro- and microvascular events, defined as death from CVD, nonfatal stroke or myocardial infarction, and new or worsening renal or diabetic eye disease. The relative risk of the primary end point was reduced by 9% (HR 0.91 [95% CI 0.83–1.00];  $P = 0.04$ ). The separate reductions in macro- and microvascular events were similar but not independently significant, whereas HR for fatal CVD and total mortality were significant (0.82 [0.68–0.98];  $P = 0.03$  and 0.86 [0.75–0.98];  $P = 0.03$ , respectively).

The ADVANCE trial also demonstrated a reduced risk of 18% (95% CI 1–32;  $P = 0.04$ ) for total mortality with a combination of antihypertensive drug treatment and intensive glucose control compared with placebo blood pressure treatment and standard glucose control (25). SBP was reduced below 140 mmHg in the combined treatment group, with a difference in SBP of 7 mmHg and in HbA<sub>1c</sub> of 0.6%. Combination treatment reduced the risks of new or worsening nephropathy by 33% (12–50;  $P = 0.005$ ), new onset of macroalbuminuria by 54% (35–68;

$P < 0.001$ ), new onset of microalbuminuria by 26% (17–34), and total mortality by 18% (1–32;  $P = 0.04$ ).

The effects of blood pressure and glucose were found to be additive in the ADVANCE trial, with no interaction between them. Similar finding of such additive combined effects have also been reported in observational data from UKPDS, the Swedish NDR, the Multiple Risk Factor Intervention Trial (2), and the Diabetes Intervention Study (26). UKPDS 75 (27) analyzed outcome incidences in an adjusted Poisson model in 4,320 newly detected patients with type 2 diabetes followed for 10 years and found that those in the highest HbA<sub>1c</sub> and SBP category ( $\geq 8\%$  and  $\geq 150$  mmHg), compared with those in the lowest category ( $<6.0\%$  and <130 mmHg), had a relative risk of 4.1 for fatal/nonfatal myocardial infarction, 12.8 for stroke, and 16.3 for microvascular disease (retinopathy or renal failure). The NDR study (28) found that 2,593 patients with type 2 diabetes on tight combined control (median HbA<sub>1c</sub> 6.5% and blood pressure and 130/80 mmHg), compared with 2,160 patients on adverse control (median 8.1% and 155/85 mmHg), had significantly reduced risks of fatal/nonfatal CHD and stroke when followed for mean 5.7 years, adjusted HR 0.69 (95% CI 0.55–0.86;  $P < 0.001$ ) and 0.62 (0.45–0.84;  $P < 0.001$ ), respectively. Baseline lower BMI and absence of microalbuminuria were associated with tight control. These findings in ADVANCE, UKPDS, and NDR jointly call for a multifactorial approach to improve HbA<sub>1c</sub>, blood pressure, and other risk factors.

**DISCUSSION**—Findings in recent studies of the effect of various SBP levels on risk for CVD and mortality, along with the recent ESH statement, should be

considered against the background of the importance of hypertension treatment in clinical practice. Hypertension is up to three times more common in patients with type 2 diabetes than in nondiabetic subjects and is frequent in type 1 diabetes as well (11). The frequency of hypertension (untreated blood pressure  $\geq 140/90$  mmHg or treated) was recently reported to be 45% in patients with type 1 diabetes in 2004 in a national diabetes register covering the majority of patients nationwide (29). A high blood pressure  $\geq 140/90$  mmHg was reported in 29% of patients with type 1 diabetes, and in 46% of patients with type 2 diabetes in the national register (29,30). 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 (National Health and Nutrition Examination Survey) 1999–2000 (31). Therefore, strong efforts should be made to reduce the number of patients with diabetes with SBP levels that are still  $\geq 140$  mmHg. Both INVEST, the NDR-BP, and ONTARGET have demonstrated that strong benefits of reduced risks for CHD, stroke, and CVD can be obtained with treated SBP  $< 140$  mmHg.

The ESH statement (13) of an SBP treatment target in patients with type 2 diabetes well below 140 mmHg supports the value of not recommending a specific lowest SBP target that is as yet unproven. The ACCORD-BP had a mean SBP of 119 mmHg in those on intensive treatment targeting SBP below 120 mmHg, the lowest SBP interval in NDR-BP was 110–129 mmHg with mean 123 mmHg, and ADVANCE had a mean SBP of  $< 135$  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 (95% CI 1.17–4.09;  $P = 0.02$ ), compared with SBP 125–129 mmHg, adjusting for but not excluding previous heart failure (22). NDR-BP found increased risk of CHD but not of stroke, with further SBP reduction during follow-up below baseline 110–129 mmHg, excluding previous heart failure. Increased risks of myocardial infarction, 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 statin-based Treating to New Targets trial of 10,000 patients with a history of CHD in the general population (32), a phenomenon

that could also be influenced by reversed causality as previous heart failure was adjusted for but not excluded in the Treating to New Targets study (33). A useful clinical approach may be an individualized lowest target well below 140 mmHg, taking into account individual clinical factors and comorbidities of importance (34). A history of CVD might be one of these factors, even if NDR-BP showed no sign of a J-shaped risk curve at the lowest SBP levels down to 110 mmHg in 2,373 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 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 prespecified secondary end point stroke with intensive therapy aiming at an SBP  $< 120$  mmHg. This could apply to some populations at high risk for stroke, e.g., in Asia.

The ADVANCE, UKPDS 75, and NDR data on combined intensified treatment of both SBP and HbA<sub>1c</sub> underline the importance of a multifactorial approach in order to reduce risks of macro- and microvascular complications, as also demonstrated in the Steno-2 study (35). The fact that reductions of both SBP and HbA<sub>1c</sub> seem to have additive effects on these end points highlights the need to obtain an HbA<sub>1c</sub> target of  $< 7\%$  generally, although this should be individualized based on, for example, comorbid conditions, adults with limited life expectancy, and severe hypoglycemia in patients with advanced disease (36). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications observational study (37) and a recent observational NDR study (38) of patients with type 1 diabetes have demonstrated significant risk reductions of 40% for fatal/nonfatal CVD and CHD, when groups of baseline HbA<sub>1c</sub> mean  $\sim 7\%$  were compared with groups of HbA<sub>1c</sub> 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 both type 1 and type 2 diabetes. Even if a previous study by the ACCORD investigators (39) reported that intensified glycemic control in patients with type 2 diabetes was associated with an increased risk of mortality, recent meta-analyses of several trials (40–43) have demonstrated significant risk reductions of 10–15% for CHD and of 10%

for CVD with an HbA<sub>1c</sub> difference of average 0.9% and tight HbA<sub>1c</sub> control of 6.5–7%, as well as no risk increase regarding fatal CVD or total mortality. This was also verified in a recent observational NDR study, showing no increased risk of CVD or total mortality at low HbA<sub>1c</sub> levels, also in subgroups with longer diabetes duration or a history of previous CVD (44,45).

Antihypertensive drug treatment has been reevaluated in recent American Diabetes Association (36) and ESH (13) guidelines. A large meta-analysis in 2005 of available trials (8) showed that in diabetes all major antihypertensive drug classes protect against cardiovascular complications, probably because of the protective effect of blood pressure lowering per se. Combination treatment is commonly needed to effectively lower blood pressure. A renin-angiotensin receptor blocker or an angiotensin II receptor blocker should always be included because of the evidence of its superior protective effect against initiation or progression of nephropathy. American Diabetes Association guidelines underline that if needed a diuretic can be added in those with an estimated glomerular filtration rate (GFR) of  $\geq 30$  mL/min/1.73 m<sup>2</sup>, or a loop diuretic for those with GFR  $< 30$  mL/min/1.73 m<sup>2</sup>. The recent ADVANCE trial underlines this, using a fixed combination of an ACE inhibitor and a diuretic often on top of preexisting antihypertensive drugs to produce some further blood pressure reduction, with benefits on the combined major macro- and microvascular end point and mortality. However, ACCOMPLISH (46), including 60% of diabetic patients among 11 000 individuals, has reported superiority of an ACE inhibitor combined with a calcium antagonist, compared with the combination of an ACE inhibitor and a diuretic, with a relative risk reduction of 20% ( $P < 0.001$ ) for the primary end point fatal/nonfatal CVD.

Additionally, because aging is a common denominator to diabetes, hypertension, and CVD, clinical investigations of patients with diabetes and hypertension may benefit from development of the concept of early vascular aging, with estimation of arterial “tissue biomarkers” such as arterial stiffness and carotid intima thickness, except for circulating classic risk factors such as blood pressure, glycemia, and blood lipids, which are fluctuating during follow-up of patients (47,48). Treatment of hypertension in diabetes may also benefit from development of clinical practice, as demonstrated in a

recent study that group sessions with active individualized treatment by a care team improved mean SBP, compared with usual primary care (49).

**CONCLUSION**—The results in the recent randomized clinical trials and observational studies support an SBP goal in type 2 diabetes well below 140 mmHg and most probably below 135 mmHg based on data from ADVANCE (24). In populations at high risk for stroke, the blood pressure goal could be even lower, although the increased risks of CHD and total mortality seen with very tight SBP control <110 mmHg should be taken into account. In addition, there are benefits recorded with combined blood pressure and glycemic control strategy.

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