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E-mail: jzus@zju.edu.cn

Review:

Target blood pressure in diabetes patients with hypertension —What is the accumulated evidence in 2011?*

Peter M. NILSSON

(*Department of Clinical Sciences, Lund University, University Hospital, S-205 02 Malmö, Sweden*)

E-mail: Peter.Nilsson@med.lu.se

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Abstract: There is overwhelming evidence that hypertension is an important risk factor for both macrovascular and microvascular complications in patients with diabetes, but the problem remains to identify appropriate goals for preventive therapies. A number of guidelines (the European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) 2007, the Joint National Committee (JNC)-VII 2003, the American Diabetes Association (ADA) 2011) have for example advocated a blood pressure goal of less than 130/80 mmHg, but this suggestion has been challenged by findings in recent trials and meta-analyses (2011). The European Society of Hypertension (ESH) therefore recommends a systolic blood pressure goal of "well below" 140 mmHg. Based on evidence from both randomized controlled trials (hypertension optimal treatment (HOT), action in diabetes and vascular disease: preterax and diamicron MR controlled evaluation (ADVANCE), action to control cardiovascular risk in diabetes (ACCORD)) and observational studies (ongoing telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET), international verapamil-trandolapril study (INVEST), treat to new targets (TNT), and the National Diabetes Register (NDR)), it has been shown that the benefit for stroke reduction remains even at lower achieved blood pressure levels, but the risk of coronary events may be uninfluenced or even increased at lower systolic blood pressure levels. In a recent meta-analysis, it was therefore concluded that the new recommended goal should be 130–135 mmHg systolic blood pressure for most patients with type 2 diabetes. Other risk factors should also be controlled with a more ambitious strategy applied in the younger patients with shorter diabetes duration, but a more cautious approach in the elderly and frail patients with a number of vascular or non-vascular co-morbidities. In patients from East Asia, such as China, the stroke risk is relatively higher than the risk of coronary events. This must also be taken into consideration for individualized goal setting in relation to total risk, for example in patients from stroke-prone families. In conclusion, the current strategy is to have a more individualized approach to risk factor control in patients with type 2 diabetes, also relevant for blood pressure control.

Key words: Blood pressure, Cardiovascular, Diabetes, Goal, Hypertension, Treatment
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1 Introduction

On a global scale, hypertension is a leading risk factor for mortality in both developing and developed countries (Yach *et al*., 2004), and a well-established risk factor for cardiovascular disease (CVD) in patients with diabetes (Stamler *et al*., 1993). An observational analysis from the UK Prospective Diabetes Study Group (UKPDS) has demonstrated a linear relationship between mean in-study systolic blood pressure (SBP) and the risk of macrovascular and microvascular complications (Adler *et al*., 2000). Tighter blood pressure control in hypertensive patients with type 2 diabetes, by use of several antihypertensive drug classes, has been documented to reduce the risk of both microvascular and macrovascular diseases, in the UKPDS (Turner *et al*., 1998; UK Prospective Diabetes Study Group, 1998) as well as in a number of other intervention studies

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(Hansson *et al*., 1998; Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, 2000; Turnbull *et al*., 2005; Patel *et al*., 2007). Guidelines have thus far advocated a treatment target of blood pressure <130/80 mmHg for most patients with type 2 diabetes (Buse *et al*., 2007; Mancia *et al*., 2007; Rydén *et al*., 2007). This recommendation was mostly based on data from observational studies, as the evidence from intervention trials was largely lacking.

However, the recent European recommendations from the European Society of Hypertension ("Reappraisal of European Guidelines", ESH 2009) included that patients with diabetes should have a SBP "well below" 140 mmHg, without mentioning a specific lowest target (Mancia *et al*., 2009). This is despite the fact that the lower blood pressure goals (<130/80 mmHg) recommended for patients with diabetes had not been the subject of any large trial by 2009, and is seldom attained in practice. This ESH recommendation was partly based on the results of some trials (Telmisartan Randomised Assessment Study in ACE intolerant Subjects with Cardiovascular Disease (TRANSCEND) Investigators, 2008; Yusuf *et al*., 2008) and post-hoc analyses of high-risk hypertensive patients (Messerli *et al*., 2006; Bangalore *et al*., 2009), as in the ONTARGET (ongoing telmisartan alone and in combination with ramipril global endpoint trial) post-hoc study (Redon *et al*., 2009; Sleight *et al*., 2009) 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. From this perspective, it is therefore of interest to take a closer look at some more recent trials and two meta-analyses regarding blood pressure control in patients with diabetes, published in 2011.

2 ACCORD-BP—a landmark study

The action to control cardiovascular risk in diabetes (ACCORD)-BP trial was published in April 2010 (The ACCORD Study Group, 2010) and included 4733 high-risk patients with type 2 diabetes (34% had previous CVD). Two randomly selected groups were analyzed, one group assigned to intensive therapy targeting SBP of less than 120 mmHg, and another group on standard therapy targeting SBP of less than 140 mmHg. The mean SBP after one year was 119 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 terms of risk for the primary outcome or risk for total mortality, with hazard ratios (HRs) for intensive therapy of 0.88 (95% confidence interval (CI): 0.73–1.06; P=0.2) and 1.07 (95% CI: 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 (95% CI: 0.39–0.89; P=0.01). One drawback was, however, that serious adverse events (SAEs) 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%)). The findings question the rational for very intense blood pressure lowering in these patients. However, it should be kept in mind that the ACCORD-BP study included a mixed group of patients in the US, and the interpretation of data could perhaps be different in another setting, for example, in East Asian populations, where the stroke risk is relatively high.

There have also been published some interesting observational studies. For example, the international verapamil-trandolapril study (INVEST) was a randomized controlled trial of 22500 patients with hypertension and CHD, with the objective to compare the effects of treatment with verapamil-trandolapril or atenolol-hydrochlorothiazide on the risk for CVD (Pepine *et al*., 2003). The primary outcomes were first occurrence of all-cause mortality and nonfatal myocardial infarction or stroke. The mean follow-up was 2.7 years. A post-hoc observational subgroup follow-up analysis of 6400 hypertensive patients with diabetes and CHD was presented in 2010 (Cooper-Dehoff *et al*., 2010), showing a higher risk for the primary endpoint with SBP >140 mmHg (outcome rate 19.8%), adjusted HR 1.46 (95% CI: 1.25–1.71; P<0.001), while similar risk with SBP <130 mmHg (outcome rate 12.7%), adjusted HR 1.11 (95% CI: 0.93–1.32; P=0.2), compared to usual control blood pressure range of 130–139 mmHg as reference (outcome rate 12.6%). This is an indication that some

at-risk patients with established CHD are vulnerable to a tight blood pressure control. The results held even after full adjustment for previous myocardial infarction, congestive heart failure, and a number of potential confounders. The risk was especially pronounced at the low SBP levels below 115 mmHg.

3 Data from the National Diabetes Register in Sweden

In Sweden, the National Diabetes Register (NDR) has been on-going since 1996, collecting data on risk factor burden and control in patients with diabetes. In total around 2/3 of all patients with diabetes are currently registered within the NDR on an annual basis because the coverage rate is relatively high. A recently published observational study from the NDR of 12677 patients with type 2 diabetes treated with antihypertensive drugs (Cederholm *et al*., 2010) analyzed the effect of SBP levels on risks for fatal/nonfatal CHD, stroke, and CVD, when followed for five years from 2002 to 2007 after exclusion of patients with a history of heart failure (the NDR-BP study).

Risk curves of CHD and stroke increased progressively with higher baseline or updated mean SBP across 110–180 mmHg in a Cox regression model using continuous data, and no J-shaped risk curves were seen at low SBP levels in all patients, or in two subgroups without (n=10304) or with (n=2373) a history of CVD. With the updated SBP 110–129 mmHg (mean 123 mmHg) as reference, SBP >140 mmHg (mean 152 mmHg) showed adjusted HR 1.37 (95% CI: 1.12–1.68, P=0.003) for CHD, 1.86 (95% CI: 1.34–2.59, P<0.001) for stroke, and 1.44 (95% CI: 1.21–1.72, P<0.001) for CVD, while SBP 130–139 mmHg (mean 135 mmHg) showed a non-significant risk increase for cardiovascular outcomes. In an additional analysis with baseline SBP 110–129 mmHg, further SBP reduction from baseline to follow-up after five years was associated with 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, where only benefits were registered irrespective of baseline blood pressure category. However, with a baseline SBP of 130 mmHg or more, considerable 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 to P<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 (Sleight *et al*., 2009), in which cardiovascular mortality was increased with further SBP reduction from baseline to follow-up (P<0.001).

The NDR-BP results are well in accordance with both ACCORD-BP (The ACCORD Study Group, 2010) and the post-hoc INVEST (Pepine *et al*., 2003) studies showing benefits in CVD risk with an SBP below 140 mmHg, although no obvious difference in benefits between lower intervals in the SBP range 110–139 mmHg, bearing in mind that NDR-BP is an observational study. Thus, these recent studies in general support the reappraisal of the European guidelines aiming for SBP well below 140 mmHg (Mancia *et al*., 2009).

At the ESH XXI meeting on hypertension and cardiovascular protection, held in Milan on 17th–20th June 2011, additional data from the NDR-BP observational study was presented (Figs. 1–4) (Nilsson *et al*., 2011a). Interestingly it was shown that different methods of presenting the same data lead to different graphical expressions based on shifting statistical methods (spline models). This has to be taken more seriously into account when debating the outcomes of observational studies, as data can be graphically misleading. One example of this is the treat to new targets (TNT) study with statin treatment in patients with established coronary artery disease where certain statistical spline models have been used for graphical illustration of results (Bangalore *et al*., 2010).

4 ADVANCE and the combined treatment of hypertension and hyperglycaemia

One study of special importance also for Asian patients is the action in diabetes and vascular disease: preterax and diamicron MR controlled evaluation (ADVANCE) trial (ADVANCE Collaborative Group, 2007). This was a randomized controlled trial in 11140 patients (38% Asians, mostly Chinese 30%) with type 2 diabetes that analyzed the effect of treatment with a fixed combination of an angiotensin-converting enzyme (ACE) inhibitor (perindopril)

versus a thiazide-like diuretic (indapamide) compared to placebo, for the effect on microvascular and macrovascular complications. The mean follow-up time was 4.3 years. SBP was reduced to less than 135 mmHg in the drug-treated patients, compared with patients on placebo in whom SBP remained at approximately 140 mmHg. The primary endpoint was a composite of major macrovascular 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 endpoint was reduced by 9%, HR 0.91 (95% CI: 0.83–1.00; *P*=0.04). The separate reductions in macrovascular and microvascular events were similar, but not independently significant, while HRs for fatal CVD and total mortality were significant,

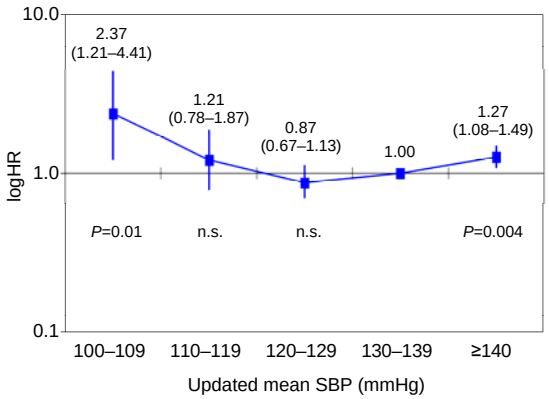

Fig. 1 Adjusted hazard ratios for fatal/nonfatal CHD by intervals of updated mean SBP

Data are from the National Diabetes Register (NDR) of Sweden including 12751 patients with type 2 diabetes treated with antihypertensive drugs (Nilsson *et al*., 2011a)

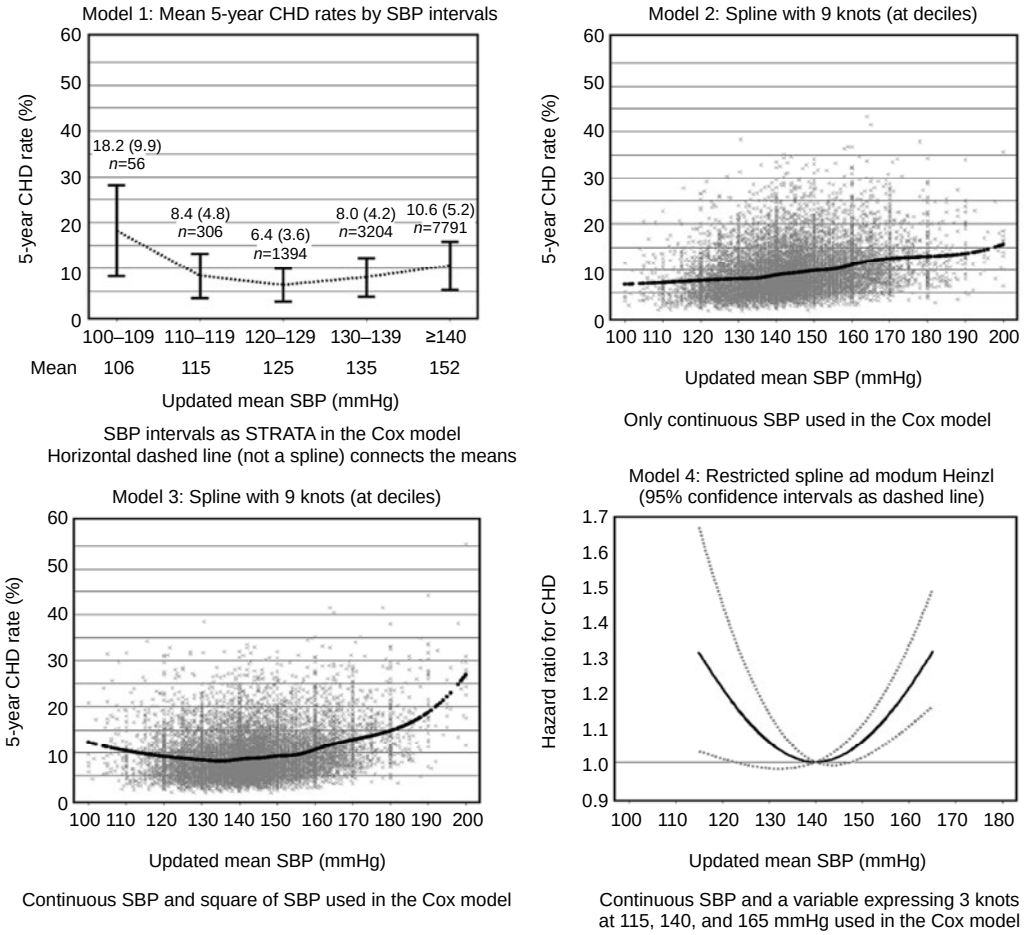

Fig. 2 Different ways to graphically present the same data for CHD risk by use of varying spline models

Adjustment for age, sex, diabetes duration, HbA1c, body mass index (BMI), smoker, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, albuminuria, atrial fibrillation, a history of CVD, and hypoglycemic treatment (Nilsson *et al*., 2011a)

0.82 (95% CI: 0.68–0.98; *P*=0.03) and 0.86 (95% CI: 0.75–0.98; *P*=0.03), respectively.

The ADVANCE trial also demonstrated a reduced risk of 18% (95% CI: 0.01–0.32; *P*=0.04) for total mortality with a combination of antihypertensive drug treatment and intensive glucose control compared to placebo blood pressure treatment and standard glucose control. In the post-hoc analysis, SBP was reduced below 140 mmHg in the combined treatment group, with a difference in SBP of 7 mmHg and in HbA1c of 0.6%. Combination treatment reduced the risks of several outcomes, for example new or worsening nephropathy by 33%, new onset of macroalbuminuria by 54%, and new onset of microalbuminuria by 26%.

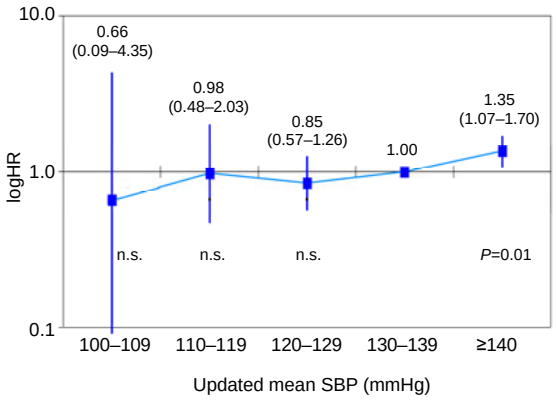

Fig. 3 Adjusted hazard ratios for fatal/nonfatal stroke by intervals of updated mean SBP (Nilsson *et al*., 2011a)

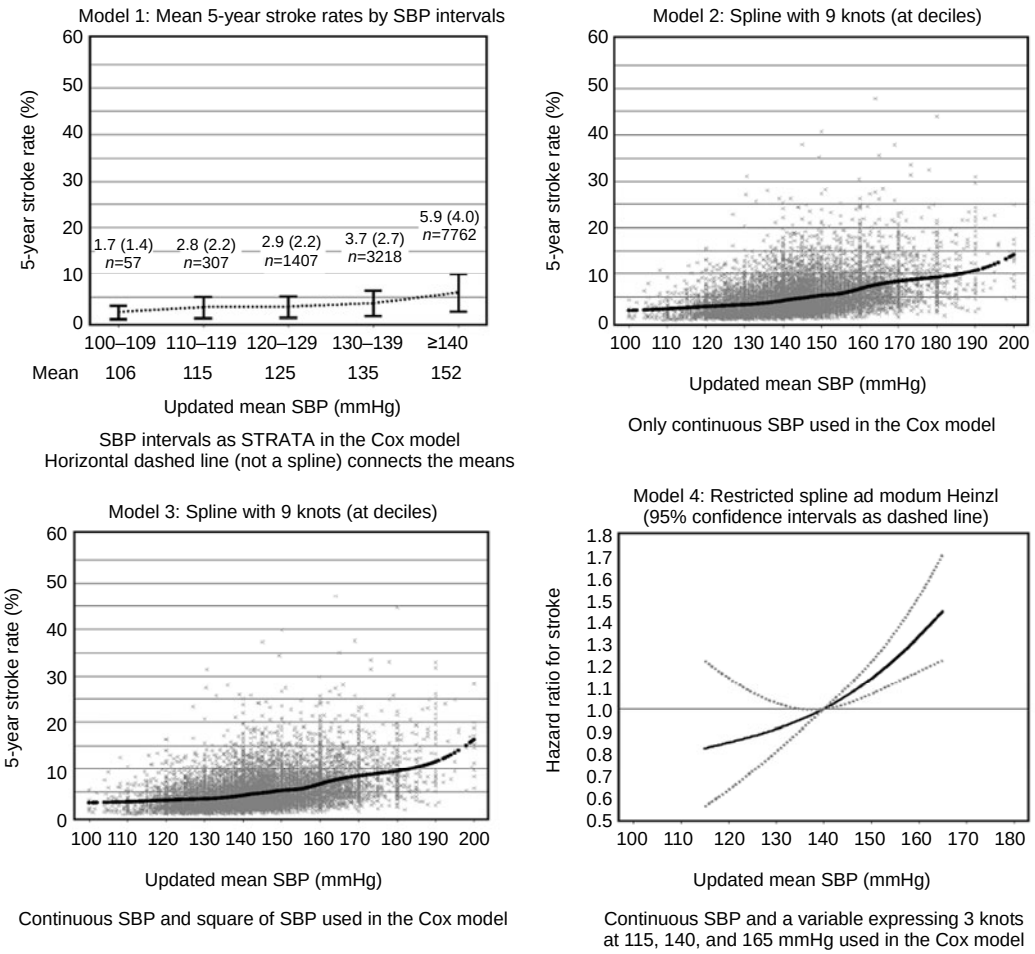

Fig. 4 Different ways to graphically present the same data for stroke risk by use of varying spline models
Adjustment for age, sex, diabetes duration, HbA1c, body mass index (BMI), smoker, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, albuminuria, atrial fibrillation, a history of CVD, and hypoglycemic treatment (Nilsson *et al*., 2011a)

The effects of blood pressure and glucose were found to be additive in the ADVANCE trial, without formal statistical interaction between them. A similar finding of this additive combined effect has also been reported in observational data from UKPDS, the Swedish NDR, the multiple risk factor intervention trial (Stamler *et al*., 1993), and the Diabetes Intervention Study (Hanefeld *et al*., 1996). In the UKPDS 75 study (Stratton e*t al*., 2006), outcome incidence was analyzed by use of an adjusted Poisson model in 4320 newly detected patients with type 2 diabetes followed for 10 years. It was found that those in the highest HbA1c and SBP category (>8% and >150 mmHg), compared to 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). Correspondingly, the NDR study (Cederholm *et al*., 2009b) found that 2593 patients with type 2 diabetes on tight combined control (median HbA1c and blood pressure 6.5% and 130/80 mmHg), compared with 2160 patients on adverse control (median HbA1c and blood pressure 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 (0.55–0.86; $P<0.001$) and 0.62 (0.45–0.84; $P<0.001$), respectively. The variables associated with tight blood pressure control were baseline lower body mass index (BMI) and absence of microalbuminuria. The summary of the findings in ADVANCE, UKPDS, and NDR-BP jointly supports a multi-factorial strategy to improve HbA1c, blood pressure, and other risk factors. This is especially relevant in younger patients with shorter diabetes duration, who should be able to tolerate intensive risk factor control, whereas in the elderly and more fragile patients with diabetes, there should be a more cautious approach to tight risk factor control.

5 Benefit with 130–135 mmHg goal shown by new meta-analysis

Just recently, 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 (Bangalore *et al*., 2011). Studies were included with patients with type 2 diabetes mellitus or impaired fasting glucose/impaired glucose tolerance that enrolled at least 100 patients with 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 macrovascular or microvascular events. Finally the authors were able to identify thirteen randomized clinical trials enrolling 37736 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 macrovascular 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. Meta-regression analysis showed continued risk reduction for stroke to an SBP of <120 mmHg. However, at levels of <130 mmHg, there was also a 40% increase in SAEs with no benefit for other outcomes. The authors concluded that in patients with type 2 diabetes mellitus/impaired fasting glucose/impaired glucose tolerance, an SBP treatment goal of 130 to 135 mmHg is acceptable (Bangalore *et al*., 2011). 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 macrovascular 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, as many other authors also advocate (Grossman and Messerli, 2011).

This view is also reflected in the 2011 edition of the American Diabetes Association (ADA) statement on standards of diabetes care, even if a blood pressure goal of less than 130/80 mmHg is kept for most patients (American Diabetes Association, 2011). The position of ADA is reflected in the following citation from their 2011 document: “The absence of significant harm, the trends toward benefit in stroke, and the

potential heterogeneity with respect to intensive glycaemia management suggest that previously recommended targets are reasonable pending further analyses and results. Systolic blood pressure targets more or less stringent than <130 mmHg may be appropriate for individual patients, based on response to therapy, medication tolerance, and individual characteristics, keeping in mind that most analyses have suggested that outcomes are worse if the systolic blood pressure is >140 mmHg." On balance this is, however, a less strict wording than found in the corresponding ADA document from 2010, and reflects the international debate on the topic. This may be half-a-step towards the more conservative European view, as expressed by the ESH.

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 (Reboldi *et al*., 2011). A number of 73913 patients with diabetes (295652 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 31%, relative risk (RR) 0.61 (95% CI: 0.48–0.79), whereas the reduction in the risk of myocardial infarction approached, but did not achieve, significance, odds ratio (OR) 0.87, (95% CI: 0.74–1.02). In a meta-regression analysis, the risk of stroke decreased by 13% (95% CI: 0.05–0.20, P=0.002) for each 5-mmHg reduction in SBP, and by 11.5% (95% CI: 0.05–0.17, P<0.001) for each 2-mmHg reduction in diastolic blood pressure (DBP). In contrast, the risk of myocardial infarction did not show any association with the extent of blood pressure reduction (P>0.20). It was concluded by Reboldi *et al*. (2011) that in patients with diabetes, protection from stroke increases with the magnitude of blood pressure reduction, but this relation was not seen for myocardial infarction.

6 Discussion

It is of great importance that the evidence for risk factor control, in general, and blood pressure control, in particular, should undergo a critical review when new evidence is being accumulated. The important aspect is that tight risk factor control should always be balanced against medical risks, adverse effects, and the cost of treatment. Findings in recent studies of the effect of various SBP levels on risk for CVD and mortality, and the recent ESH statement from 2009, should be considered against the background of the importance of treatment of hypertension in clinical practice. Hypertension is up to three times more common in patients with type 2 diabetes than in non-diabetic subjects, and is frequent in patients with type 1 diabetes as well (Rydén *et al*., 2007).

The frequency of hypertension (untreated blood pressure >140/90 mmHg or treated) was recently reported to be 45% in patients with type 1 diabetes in 2004 in the NDR of Sweden in a national sample (Eeg-Olofsson *et al*., 2007). A high blood pressure >140/90 mmHg was reported in 29% of patients with type 1 diabetes, and in 46% of patients with type 2 diabetes, in the same register (Eeg-Olofsson *et al*., 2007; Cederholm *et al*., 2009a). The frequency of hypertension was 40% in a representative sample of patients with diabetes (mean age 59 years) in the American NHANES 1999–2000 (Saydah *et al*., 2004). This supports the argument that substantial efforts should be carried out in order to reduce the number of patients with diabetes still with elevated SBP levels above 140 mmHg. All the observational studies INVEST, NDR-BP, and ONTARGET have provided strong arguments that substantial benefits of reduced risks for CHD, stroke, and CVD can be obtained with a treated SBP below 140 mmHg.

The ESH statement in the "Reappraisal of European Guidelines" (Mancia *et al*., 2009) of an SBP treatment target in patients with type 2 diabetes "well below" 140 mmHg points is currently widely debated. The more recent ACCORD-BP had a mean SBP of 119 mmHg in those on intensive treatment targeting SBP below 120 mmHg, while the lowest SBP interval in NDR-BP was 110–129 mmHg (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 below 110 mmHg had an increased risk of total mortality, HR 2.18 (95% CI: 1.17–4.09, P=0.02), compared to SBP 125–129 mmHg, adjusting for the

influence of congestive heart failure (Cooper-Dehoff *et al*., 2010). NDR-BP found increased risk of CHD, but not of stroke, with further SBP reduction during follow-up below baseline SBP of 110–129 mmHg, while excluding previous heart failure. Increased risks of myocardial infarction, CVD, total mortality, but not of stroke, with very tight SBP control <110 to 120 mmHg were recently reported in the post-hoc observational analysis of the treating to new targets (TNT) trial of 10001 patients with a history of CHD in the general population (Bangalore *et al*., 2010). This could have been influenced by reversed causality as previous heart failure was adjusted for, but was only excluded with ejection fraction <30% (Franklin, 2010).

In addition, a post-hoc analysis from the veterans administration diabetes trial (VADT) showed that there is an increased risk for CVD events with an attained DBP <70 mmHg, even when combined with SBP in guideline-recommended target ranges (Anderson *et al*., 2011). The results emphasize that DBP <70 mmHg in these patients with long diabetes duration and increased risk status was associated with elevated CVD risk and should be avoided.

A useful clinical approach may thus be to apply an individualized target well below 140 mmHg, taking into account individual clinical factors of importance, such as comorbidities and diabetes duration, as well as advanced age of the patient (Nilsson, 2010). A history of CVD might be one of these factors, even if the NDR-BP study 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 when blood pressure was used as a continuous variable, but an increased risk when blood pressure was stratified for categories (Figs. 1–4). It can also be argued that a lower SBP target might be of value in some patients expected to run 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 below 120 mmHg. This could apply to some populations at high risk for stroke, e.g., in many parts of eastern Asia.

6.1 Combined goals for hypertension and hyperglycaemia control

In summary, ADVANCE, UKPDS 75, and NDR data on combined intensified treatments of both SBP and HbA1c support a multifactorial approach in order to reduce risks of macrovascular and microvascular complications, as also demonstrated in the STENO 2 study (Gæde *et al*., 2003). The fact that reductions of both SBP and HbA1c seem to have additive effects on these endpoints affirms that the effort to obtain a HbA1c target of <7% is important; however, this must be individualised, based on comorbid conditions, advanced age, and the risk of severe hypoglycemia in patients with advanced disease (Edelman *et al*., 2010). The diabetes control and complications trial/epidemiology of diabetes interventions and complications (DCCT/EDIC) observational study (Nathan *et al*., 2005) and a recent observational NDR study (Eeg-Olofsson *et al*., 2010a) of patients with type 1 diabetes have both demonstrated significant risk reductions of 40% for fatal/nonfatal 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 both type 1 and type 2 diabetes. Even if the ACCORD study (Gerstein *et al*., 2008) 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 (Kelly *et al*., 2009; Mannucci *et al*., 2009; Ray *et al*., 2009; Turnbull *et al*., 2009) have demonstrated significant risk reductions of 10%–15% for CHD and of 10% for CVD with an HbA1c difference of average 0.9% and tight HbA1c control of 6.5%–7.0%, and no risk increase for fatal CVD or total mortality. Similar findings were obtained in another NDR study, showing no increased risk of CVD or total mortality at low HbA1c levels (Eeg-Olofsson *et al*., 2010b).

6.2 Choice of antihypertensive drug therapy

Antihypertensive drug treatment has been re-evaluated in recent ADA (American Diabetes Association, 2011) and ESH (Mancia *et al*., 2009) guidelines. A large meta-analysis of available trials (Turnbull *et al*., 2005) showed that in patients with 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, and many combinations are now available. A renin-angiotensin receptor blocker (ACE-inhibitor or angiotensin II receptor blocker) should always be included because of the evidence of its superior protective effect against initiation or progression of nephropathy. ADA guidelines underscore that, if needed, a diuretic can be added in those with an estimated glomerular filtration rate (GFR) of >30 ml·min/1.73 m^2, or a loop diuretic for those with GFR of <30 ml·min/1.73 m^2. Recommendations based on the ADVANCE trial suggest using a fixed combination of an ACE inhibitor and a diuretic often on top of pre-existing antihypertensive drugs to achieve further blood pressure reduction, for cardiovascular benefits. It should be noted that avoiding cardiovascular events through combination therapy in patients living with systolic hypertension (ACCOMPLISH) (Jamerson *et al*., 2008), including 60% of diabetic patients among 11000 individuals from an American population, has reported on the 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/nonfatal CVD. In the end, the drug of choice should be based both on evidence from trials and on the tolerability of individual patients, as Chinese patients might be somewhat more susceptible to some adverse effects, e.g., non-productive cough following treatment with an ACE-inhibitor (Tseng *et al*., 2010).

Treatment of hypertension in diabetes may also benefit from developments in clinical practice, as demonstrated in a recent study showing that group sessions with active individualized treatment by a care team improved mean SBP, compared to usual primary care (Edelman *et al*., 2010).

6.3 Current trends in blood pressure control in a national study

How have guidelines impacted on clinical practice for blood pressure treatment in the post-UKPDS era since more than 10 years? In a recent study, the trends for blood pressure control in Sweden were analyzed in view of the debate regarding blood pressure goals (Nilsson *et al*., 2011b). We therefore assessed blood pressure trends in patients with type 2 diabetes from the NDR using three cross-sectional samples (aged 30–85 years) in 2005, 2007 and 2009, and in patients from 2005 followed individually until 2009. The prevalence of hypertension was 87% among all 180369 patients in 2009, although lower in subgroups with ages 30–39, 40–49 and 50–59 years: 40%, 60%, and 77%. In the three cross-sectional surveys, mean blood pressure decreased (141/77 to 136/76 mmHg), uncontrolled blood pressure ≥140/90 mmHg decreased (58% to 46%), and antihypertensive drug treatment increased (73% to 81%). Comparatively in 79185 patients followed individually for five years, mean blood pressure decreased (141/77 to 137/75 mmHg), uncontrolled blood pressure ≥140/90 mmHg decreased (58% to 47%) and antihypertensive drug treatment increased (73% to 82%). Independent predictors of blood pressure decrease were BMI decrease (stronger) and increase in use of antihypertensive drug treatment. This treatment occurred among 81% of all patients in 2009. In 57645 patients on drug treatment for hypertension followed individually, mean blood pressure decreased (143/77 to 138/75 mmHg) and uncontrolled blood pressure ≥140/90 mmHg decreased (63% to 50%), as shown in Fig. 5 (Nilsson *et al*., 2011b). Among 5164 patients with nephropathy on drug treatment followed individually, blood pressure <130/80 mmHg increased (12% to 21%). The interpretation of this observational study based on national data was that blood pressure control improved from 2005 to 2009, relative to BMI

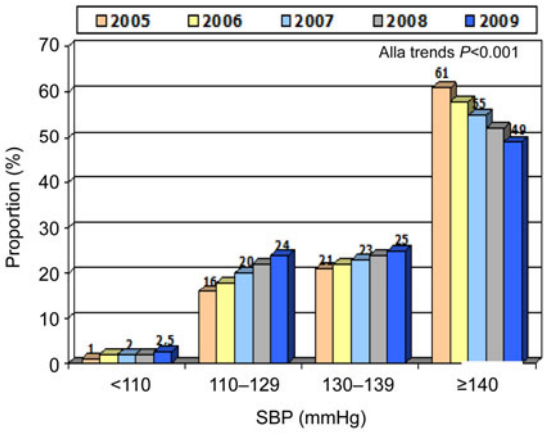

Fig. 5 SBP levels in 57645 patients with type 2 diabetes and treatment with antihypertensive drug therapy followed individually 2005 to 2009 in the NDR
Adapted from data presented in (Nilsson *et al*., 2011b)

decrease and increase of antihypertensive drug treatment, although about half of the patients had blood pressure ≥140/90 mmHg. This means that the greater problem is still that so many patients are not at goal (below 140 mmHg) and the lesser problem, on the other hand, is that some patients may be too tightly controlled.

7 Conclusions

There is no doubt that hypertension should be taken seriously in patients with diabetes, and should be integrated in a more general strategy to address risk factors (Nilsson and Cederholm, 2011). The results obtained in recent randomized clinical trials, observational studies and two meta-analyses, as reviewed here (Table 1), support an SBP goal in type 2 diabetes well below 140 mmHg, and below 135 mmHg based on data from ADVANCE (Bangalore *et al*., 2010). This is supported by findings in a new meta-analysis suggesting an SBP target of 130–135 mmHg in patients with diabetes. 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 with very tight SBP control <110 mmHg. In addition, there are benefits with combined blood pressure and glycemic control, as well as lipid control. It has to be recognized that the stroke risk is generally high in East Asian patients from China (O′Donnell *et al*., 2010). This should therefore also be taken into consideration when an individual blood pressure goal is determined for risk patients in this country. A positive family history of an early stroke event in several family members, but lack of coronary heart events, could support the ambition of a tight blood pressure control, even below 130 mmHg SBP, especially if varying degrees of albuminuria is also present.

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Table 1 Summary of recent intervention or observational studies in patients with type 2 diabetes and hypertension

Study	*n*	Design	Major outcomes	Ref.
ADVANCE-BP	11140	RCT	Reduced major microvascular and macrovascular events and mortality with SBP <135 mmHg vs. ~140 mmHg	Patel *et al.*, 2007
ACCORD-BP	4733	RCT	No difference in risk of fatal/nonfatal CVD between SBP <120 mmHg and <140 mmHg	The ACCORD Study Group, 2010
INVEST	6400	Post-hoc observational analysis of RCT	No difference in risk of nonfatal myocardial infarction or stroke between SBP <130 mmHg and 130–139 mmHg, but increased risk of total mortality with SBP <115 mmHg vs. 125–129 mmHg after full adjustments	Cooper-Dehoff *et al*., 2010
ONTARGET-DM	9300	Post-hoc observational analysis of RCT	Increased cardiovascular mortality with SBP less than 125 mmHg compared to SBP less than 130 mmHg	Redon *et al.*, 2009; 2011*
VADT	1791	Post-hoc observational analysis of RCT	Increased risk with DBP <70 mmHg even if SBP was within range recommended in guidelines	Anderson *et al.*, 2011
NDR-BP	12677	Observational, national study	No difference in risk of fatal/nonfatal CVD between SBP 110–129 mmHg and 130–139 mmHg, but increased risk with baseline SBP 110–129 mmHg and further SBP reduction from baseline to follow-up	Cederholm *et al*., 2010

Adapted from the study of Nilsson and Cederholm (2011). *n*: participant number; RCT: randomized controlled trial; SBP: systolic blood pressure; CVD: cardiovascular disease. * Abstracts presented at European Society of Hypertension Meeting in Milan, 2009 and 2011

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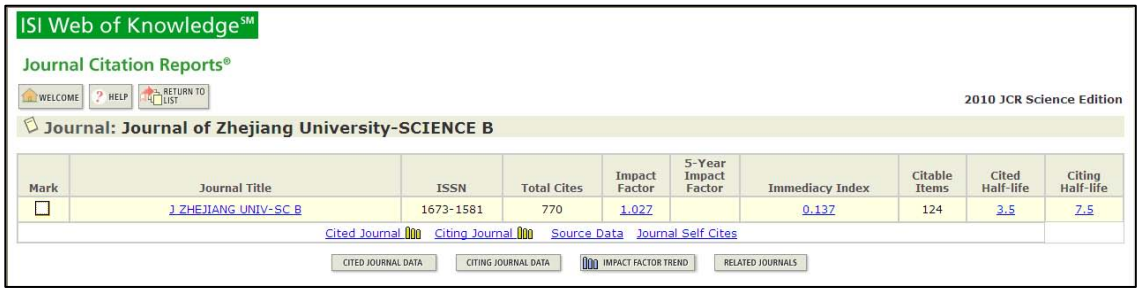
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