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U-shaped Relationship of Blood Pressure to CVD Risk and Relevance to Treatment Goals in Diabetes

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Abstract A heated debate has developed on the blood pressure goal for treatment of hypertension in patients with type 2 diabetes. The evidence for going below 130 mmHg systolic blood pressure has been found to be weak and that is why new guidelines have advocated a somewhat more conservative view, aiming for a blood pressure goal <140/85 mmHg in European guidelines and <140/80 mmHg in American guidelines from 2013. One important argument has been the description of a J-shaped curve for associations between achieved blood pressure levels in the trials and risk of cardiovascular events. These observational data have contributed to the change in attitudes for defining blood pressure goals in patients with type 2 diabetes, and will be briefly summarised here. Not only *post hoc* observational data from clinical trials will be discussed but also observational data from a National Diabetes Register, covering 2/3 of all diabetes patients in Sweden.

Keywords Cardiovascular · Diabetes · Drugs · Epidemiology · Hypertension · Risk · Treatment

Introduction

Hypertension in diabetes is a well-recognised cardiovascular risk factor, as documented in numerous epidemiological studies and in the UK Prospective Diabetes Study (UKPDS) [1]. This is due to the impact of elevated blood pressure itself on the development of target organ damage and cardiovascular events, but also due to the clustering of hypertension with other cardiovascular risk factors linked to insulin resistance [2], for example dyslipidaemia and impaired fibrinolysis. A common root has been suggested to be found in the influence of early life factors, for example intrauterine growth retardation (IUGR) causing small for gestational age phenotypes of new-born babies [3]. This risk for programming of future hypertension, type 2 diabetes and cardiovascular risk is further increased if a rapid post-natal catch-up growth pattern is present [4]. In the end these influences linked to hypertension in diabetes will all converge to cause an increased cardiovascular risk and a higher incidence of coronary and cardiovascular events as compared with the risk in corresponding normoglycaemic subjects [5].

Over the last 15 years, a number of randomised controlled intervention studies have contributed to the evidence for benefits linked to blood pressure control in type 2 diabetes. These studies include some larger ones (UKPDS, ADVANCE, ACCORD, ALTITUDE) but also some smaller ones (ABCD, FACET), and in addition a number of sub-studies of patients with diabetes within larger intervention studies with mixed patients according to diabetes status (HOT, LIFE, ASCOT, ACCOMPLISH, INVEST, ONTARGET). The accumulated evidence has been used to influence various guidelines for recommendations on blood pressure goals for treatment as well as composition of drug treatment, the most recent guidelines presented in 2013 from both sides of the Atlantic are in [6••, 7••, 8•].

Blood Pressure Goals Set in Guidelines

Previous guidelines have recommended a tight blood pressure goal <130/80 mmHg, but following a long debate within the scientific community this has now changed. The current goal based on the joint new European guidelines is <140/85 mmHg from the European Society of Hypertension (ESH), European

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Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) [6••, 7••], while the American Diabetes Association (ADA) recommends a goal <140/80 mmHg for most patients with diabetes, but <130/80 mmHg in younger and newly detected patients [8•]. A common attitude is to apply more flexible goals according to patients´ characteristics. Similar to the treatment of hyperglycaemia it is now recommended to use less strict goals for the elderly and frail patient with co-morbidities and prone to have adverse reactions. National guidelines in individual countries may still vary, but there is a trend to have a more uniform view on the blood pressure goals as influenced by the current international guidelines [6••, 7••, 8•]. However, in the UK the NICE organisation advocates a blood pressure goal below 140/90 mmHg for all patients treated for hypertension without any specific mentioning about goals for patients with diabetes [9].

The Problem with Increased Risk at Lower Treatment Blood Pressure Levels

A worrying fact is that a number of observational studies have now indicated the existence of an increased cardiovascular risk associated with achieved low blood pressure in treated patients with diabetes, the so called J-shaped curve (Table 1). On the one hand there are observational studies from a large register of patients with diabetes, such as the Swedish National Diabetes Register (NDR) [10, 11•], but on the other hand there also exist a number of *post hoc* analyses based on observations within randomised controlled studies. Some examples come from the INVEST [12] and ONTARGET [13•] trials. In addition, recommendations from meta-analyses exist based on observational data from the large trials [14].

Observational Data from a National Diabetes Register in Sweden

The NDR has been active in Sweden since 1996 and currently includes register data on about 300,000 patients with diabetes registered for treatment and risk factor control on an annual basis, corresponding to 2/3 of all patients with diabetes in Sweden. These subjects can be followed over a period of years to analyse the risk of cardiovascular events, with outcome data originating from register linkage analyses with national registers on morbidity and mortality, as provided by the National Board of Health and Welfare in Sweden. This enables researchers to do analyses not only on the association between achieved blood pressure levels in patients on antihypertensive drug treatment and future cardiovascular risk, but also to adjust for a number of confounding factors obtained during the annual registration of personal data, e.g. on-going drug treatment and risk factor levels in general.

In the first publication from the NDR the aim was to estimate risks of fatal/nonfatal coronary heart disease (CHD), stroke and cardiovascular disease (CVD) with systolic blood pressure (SBP) in an observational study of 12,677 patients with diabetes aged 30-75 years, treated with antihypertensive drugs, without previous congestive heart failure, followed for 5 years [10]. The results showed that risk curves of CHD and stroke increased progressively with higher baseline or updated mean SBP in a Cox model, in all participants, and in two sub-groups without (n=10 304) or with (n=2373) a previous history of CVD, with no J-shaped risk curves at low SBP levels below 130 mmHg. However, no clinical benefits were found in patients with a treated blood pressure below this level. Hazard ratios (HR) for CHD and stroke per 10 mmHg increase in updated mean SBP in all participants, adjusting for clinical characteristics and traditional risk factors, were HR 1.08 (95 % confidence interval: 1.04-1.13) and HR 1.20 (1.13-1.27), p<0.001. With updated mean SBP of 110-129 mmHg used as reference, SBP of at least 140 mmHg showed risk increases of 37 % for CHD, 86 % for stroke and 44 % for CVD (p=0.001), whereas SBP of 130-139 mmHg showed non-significant risk increases for these outcomes. With baseline SBP of 110-129 mmHg, CHD and CVD risks increased with further SBP reduction during follow-up, HRs were 1.77 and 1.73 (p=0.002), but decreased considerably for CHD, stroke and CVD with higher baseline SBP. It was concluded that risks of CHD and stroke increased progressively with higher SBP, with no J-shaped curves, although a risk increase was significant only for SBP of at least 140 mmHg, but not comparing 130-139 and 110-129 mmHg [10]. Additionally, a baseline SBP of 110-129 mmHg showed increased CHD and CVD risk associated with further SBP reduction during follow-up of 5 years, whereas baseline SBP of at least 130 showed benefits. Thus the take home message of this observational study was that patients with a treated blood pressure already well controlled at baseline were at increased risk during the follow-up. This is why a further SBP reduction is not of benefit to these well controlled patients. One of the strengths of this study is that all patients with a diagnosis of congestive heart failure (CHF) had on purpose been excluded

Table 1 Factors explaining the J-shaped curve found between achieved systolic blood pressure during antihypertensive treatment and risk of cardiovascular events

True finding based on increased risk linked to the blood pressure lowering itself
Confounding caused by reversed causality associated with certain comorbidities such as congestive heart failure with impaired myocardial pumping function
Confounding by influence of specific antihypertensive drugs used
Insufficient registration of cardiovascular endpoints
Publication bias

to avoid confounding by reverse causation as many of these patients may have a low SBP just because of impaired myocardial function, and therefore be at increased risk.

In the second publication from the NDR, the objective was to estimate risks of CHD, stroke and CVD with updated mean SBP and diastolic (DBP) blood pressure in an observational study of 35,041patients with type 2 diabetes treated with antihypertensive drugs, and 18, 512 untreated patients, aged 30-75 years, without previous CHF, followed for 6 years [11•]. We found that in treated patients, non-linear splines for 6-year risk of fatal/nonfatal CHD, stroke and CVD by blood pressure as a continuous variable showed a progressive increase with higher SBP from 140 mmHg and higher, and with DBP from 80 mmHg, with a J-shaped risk curve at lowest SBP levels, but not obviously at lowest DBP levels. Analysing intervals of SBP with 130-134 mmHg used as reference at Cox regression, adjusted HRs for fatal/nonfatal CHD, stroke and CVD with at least 140 mmHg were 1.22 (1.08-1.39), 1.43 (1.18-1.72), 1.26 (1.13-1.41), all $p<0.001$. HRs with 115-129 and 135-139 mmHg were non-significant, whereas increased with 100-114 mmHg, 1.96 ($p<0.001$), 1.75 ($p=0.02$), and 2.08 ($p<0.001$), respectively. With DBP 75-79 mmHg as reference, adjusted HR for fatal/nonfatal CHD, stroke and CVD with DBP 80-84 mmHg were 1.42 (1.26-1.59), 1.46 (1.24-1.72), 1.39 (1.26-1.53), all $p<0.001$. Corresponding HR with DBP 60-69 and 70-74 mmHg were non-significant. The findings were similar in 7059 patients with previous CVD and in untreated patients with diabetes. It was concluded that an achieved blood pressure around 130-135/75-79 mmHg during antihypertensive treatment showed lower risks of CVD in these patients with type 2 diabetes. It could be argued that patients were often included in treatment programmes with scheduled follow-up appointments within the Swedish diabetes team care model, which is why results could eventually not be extrapolated to other populations or health care settings.

Findings in Post-hoc Analyses from Randomised Trials

In the International Verapamil SR-Trandolapril Study (INVEST) study patients with hypertension and established coronary artery disease (CAD) were recruited for antihypertensive treatment. In an observational subgroup analysis of 6400 of the 22,576 participants, these participants were at least 50 years old and had both diabetes and CAD [12]. Patients received first-line treatment of either a calcium antagonist or beta-blocker followed by angiotensin-converting enzyme inhibitor, a diuretic, or both, to achieve SBP of less than 130 and DBP of less than 85 mmHg. Patients were further categorised as having attained a tight control if they could maintain their systolic BP at less than 130 mmHg; usual control if it ranged from 130 mmHg to less than 140 mmHg; and uncontrolled if it was 140 mmHg or higher. During 16,893 patient-years of follow-up, 286 patients (12.7 %) who maintained tight control, 249 (12.6 %) who had usual control, and 431 (19.8 %) who had uncontrolled systolic BP experienced a primary cardiovascular event. Patients in the usual-control group had a cardiovascular event rate of 12.6 % vs. a 19.8 % event rate for those in the uncontrolled group, with adjusted HR: 1.46 (1.25-1.71; $p<0.001$). However, little difference existed between those with usual control and those with tight control. Their respective event rates were 12.6 % vs. 12.7 %, with non-significant adjusted HR 1.11 (0.93-1.32). The all-cause mortality rate was 11.0 % in the tight-control group vs. 10.2 % in the usual-control group with adjusted HR, 1.20 (0.99-1.45). However, when extended follow-up was included, risk of all-cause mortality was 22.8 % in the tight control vs. 21.8 % in the usual control group, adjusted HR 1.15 (1.01-1.32; $p=0.04$). The authors concluded that a tight control of systolic BP among patients with diabetes and established CAD was not associated with improved cardiovascular outcomes compared with usual control and even at higher risk at low levels of achieved SBP [12]. It should be remembered that many of these patients with established CAD might be susceptible to a fall in blood pressure with resulting hypoperfusion of coronary arteries leading to myocardial ischaemia.

J-shaped Curve in the ONTARGET Trial for Patients with Diabetes

In one of the largest intervention trials ever conducted in hypertension, high-risk patients were treated either by ramipril, telmisartan or the combination of these two antihypertensive drugs in the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) [13•]. In a *post-hoc* analysis the authors aimed to determine whether the blood pressure levels at which cardiovascular (CV) protection is achieved differ between diabetic and non-diabetic patients from this trial. A total of 25,584 patients (9603 diabetic), older than 55 years, at high CV risk were randomised to ramipril, telmisartan, or both and observed for 4.6 years. In observational analyses the treatment arms were pooled to examine the relationships between blood pressure and the primary composite cardiovascular outcome (CV death, nonfatal myocardial infarction or stroke, or hospitalised heart failure) and its components. The primary outcome occurred in 1938 (20.2 %) patients with diabetes and in 2276 (14.2 %) non-diabetic patients. Compared with non-diabetic patients, diabetic patients had a significantly higher risk for the primary endpoint with HR 1.48 (1.38-1.57) and CV death HR 1.56 (1.42-1.71); myocardial infarction HR 1.30 (1.17-1.46); stroke HR 1.39 (1.23-1.56); and CHF hospitalisation HR 2.06 (1.82-2.32). The CV risk was

significantly higher in diabetic than in non-diabetic patients regardless of the systolic BP changes during treatment. In both diabetic and non-diabetic patients, progressively greater systolic BP reductions were accompanied by reduced risk for the primary outcome only if baseline SBP levels ranged from 143 to 155 mmHg. Except for stroke, there was no benefit in fatal or nonfatal CV outcomes by reducing systolic BP below 130 mmHg. Thus, the relationship between blood pressure and overall CV risk showed a similar pattern in diabetic and non-diabetic patients over a wide range of baseline and in-treatment BP values although, for the same systolic BP, a higher risk was observed in patients with diabetes. A J-shaped curve for increased cardiovascular mortality in patients with diabetes was observed at lower attained mean SBP.

Results from Meta-analysis

Another approach is to use meta-analyses in order to analyse the optimal blood pressure level for lowest cardiovascular risk. In one meta-analysis by Bangalore et al. [14] all randomised clinical trials were sought from 1965 through 2010 of antihypertensive therapy in patients with type 2 diabetes mellitus or impaired fasting glucose/impaired glucose tolerance that enrolled at least 100 patients with achieved systolic BP of ≤135 mmHg in the intensive BP control group and ≤140 mmHg in the standard BP control group, had a follow-up of at least 1 year, and evaluated macrovascular or microvascular events. This also included the ACCORD study, the only randomised trial with a group of patients treated to a very ambitious SBP goal <120 mmHg [15]. In total 13 randomised clinical trials enrolling 37,736 participants were selected. Intensive BP control was associated with a 10 % reduction in all-cause mortality with 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 BP control. The results were similar in a sensitivity analysis using a Bayesian random-effects model. More intensive BP control (≤130 mmHg) was associated with a greater reduction in stroke, but did not reduce other cardiovascular events. Meta-regression analysis showed continued risk reduction for stroke to a systolic BP of <120 mmHg. However, at levels <130 mmHg, there was a 40 % increase in serious adverse events with no benefit for other outcomes. The meta-analysis concluded that in patients with type 2 diabetes mellitus/impaired fasting glucose/impaired glucose tolerance, a systolic BP treatment goal of between 130 to 135 mmHg is acceptable based on observational outcomes [15]. However, with more aggressive goals (<130 mmHg), target organ heterogeneity was observed 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 serious adverse events even increased.

Treatment Strategies of Hypertension in Diabetes

In general, lifestyle modification should be tried initially for a few months or so, but if severe (grade 3) hypertension (systolic >180 and/or diastolic >110 mmHg) or signs of hypertensive target organ damage are present drug therapy should be started immediately. Initially, mono-therapy with one of the first-line drugs suggested below should be used, the choice being influenced by other factors such as coexistence of angina, left ventricular hypertrophy (LVH), CHF, or nephropathy, but not primarily by age and sex of the patient [6••].

Choice of Antihypertensive Drugs

Blood pressure control is generally more important than the choice of individual drugs [16].

First-line antihypertensive drugs suitable for use in patients with diabetes are ACE inhibitors and angiotension-II (AT_1) receptor antagonist (ARB) to block the renin-angiotensin system (RAS), but also low-dose diuretics (e.g. in combination with agents that block the RAS), calcium-channel antagonists, and cardioselective β-blockers [6••, 7••, 8•]. Drugs can be selected for their beneficial effects on coexistent problems, e.g. angina or arrhythmia (β-blockers, calcium antagonists), heart failure (ACE inhibitors, ARB, certain β-blockers), previous myocardial infarction (ACE inhibitors, β-blockers), impaired lung function (calcium antagonists) or nephropathy (ACE inhibitors, ARB).

The ACE-inhibitor ramipril has strong evidence-based support for its use in type-2 diabetic patients because of their high cardiovascular risk [17]. ß-receptor blockers (in combination with low-dose aspirin) are indicated as secondary prevention for patients who have suffered a myocardial infarct, as long as no serious contraindications are present. Diuretics, often used at low dosage, are useful in elderly diabetic patient, as this class of drugs has proven efficacy in preventing stroke and all-cause mortality in elderly hypertensives, also with diabetes [18]. Indapamide is well-tolerated and with no metabolic side effects. Spironolactone may also be of value, especially for elderly, obese female patients with hypertension and hypervolaemia characterised by a low-renin profile. α_1-receptor blockers may be used as part of combination therapy, especially in patients with dyslipidaemia (high triglycerides, and low HDL-cholesterol levels) or prostatic hyperplasia.

Drug Combination Therapy

Combination therapy is needed in most patients with type 2 diabetes to achieve satisfactory blood pressure control [6••, 7••,

8•]. It is often better to use low-dose combinations than to increase dosages of single agents, as side effects are commonly dose-dependent. Potassium-sparing agents (spironolactone and amiloride) should not be combined with an ACE inhibitor because of the increased risk for hyperkalaemia. Another combination that is not recommended is to combine two RAS blockers, for example an ACE-inhibitor with an ARB, or either of these drugs combined with a direct renin inhibitor (DRI) [6••].

Certain combinations of antihypertensive drugs have proved to be very safe and effective in low to moderate doses, e.g. ACE inhibitor/ARB + low-dose thiazide diuretic; calcium antagonist + ACE inhibitor; selective $ß_1$-blocker + calcium antagonist; or β-blocker + α_1-blocker. It is often possible to achieve a positive synergistic effect based on one of these combinations, either prescribed one by one or used as fixed combinations.

Conclusion

The updated European guidelines for treatment of hypertension in type 2 diabetes has recently redefined the blood pressure goal to be <140/85 mmHg [6••, 7••], because of lack of evidence for benefits to go lower. This treatment most often requires use of drug combinations, and some useful examples have been provided in the new guidelines [6••]. The treatment of hypertension should be part of an overall risk factor control, also addressing smoking, dyslipidaemia and hyperglycaemia, as used in the Danish Steno-2 study [19]. Treatment with an ACE inhibitor (ramipril) has been shown effective in preventing macro- and microvascular events in high-risk diabetics with controlled hypertension [17].

Based on evidence, the following updated conclusions can therefore be made:

1. Patients with type 2 diabetes should be aggressively treated for hypertension when blood pressure is above 140 and/or 90 mmHg, aiming at blood pressure <140/85 mmHg [6••, 7••]. Based on observational data from intervention trials an achieved SBP goal of around 135 mmHg is associated with benefits [14]. However, evidence is lacking for benefits with SBP <130 mmHg except for stroke reduction.
2. These patients usually need two or more drugs in combination therapy to reach the blood pressure target, especially for SBP. However, the combination of two agents that block RAS should be avoided due to increased risk of adverse effects.
3. Although ACE inhibitors have been proven cardiovascular protective and some angiotensin-II receptor blockers nephroprotective, there is still no consensus on the "drug of choice" for all hypertensive patients with type 2 diabetes.
4. Most studies support the notion that blood pressure reduction *per se* is more important than individual properties of specific drugs in most cases.
5. Blockade of RAS seems to be an appropriate choice for being one of the partner drugs in offering combination therapy to hypertensive patients with diabetes or glucose intolerance.

As no large-scale intervention trials are on-going in patients with diabetes for reduction of blood pressure, we will have to live with existing evidence for a considerable time, now summarised in updated current guidelines [6••, 7••, 8•].

In the future, the application of cardiovascular genomics and stratified medicine may substantially change the approach to treating hypertension in diabetes, with the possibility of tailoring antihypertensive treatment according to the genotype of the individual patient. This will greatly reinforce the evidence-based approach to the treatment of this high-risk group. Finally, new clinical and experimental investigations can hopefully shed new light on hypertension in diabetes being one example of early vascular ageing, EVA [20], as shown by, for example telomeric attrition [21], and how to prevent this process.

Compliance with Ethics Guidelines

Conflict of Interest Peter Nilsson declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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