



# How useful are hypertension guidelines for diabetes?

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### Practice Points

- Hypertension in diabetes is a major and treatable cardiovascular risk factor in patients with diabetes, well documented in many observational epidemiological studies.
- In the post-UKPDS era since 1998, several large-scale clinical trials have added to our understanding of how hypertension should be treated based on drug combinations, but the evidence for the appropriate blood pressure goal in these patients has been scarce.
- Most guidelines during the last decade have stated progressively lower blood pressure goals for patients with hypertension and diabetes, from less than 140/90 to 130/80 mmHg, or to even lower goals in patients with nephropathy.
- This view has been challenged since the end of 2009 because the evidence base to define the blood pressure goals has been too weak.
- European organizations now recommend a blood pressure goal below 140/90 (NICE) or below 140/80 mmHg (European Society of Cardiology [ESC]) as also recently accepted by the American Diabetes Association (ADA). In 2013, new guidelines will be issued both in Europe and the USA.

**SUMMARY** Millions of patients all over the world suffer from a combination of hypertension and diabetes mellitus. During the last decade, national and international guidelines have advocated a blood pressure goal of less than 130/80 mmHg in these patients, even if the evidence has largely been lacking from randomized trials. This has led to critical discussion and the proposal from European scientific organizations to return to a somewhat higher blood pressure goal, less than 140/80–90 mmHg, in order to avoid potential side effects in susceptible patients who may not tolerate extensive blood pressure lowering due to, for example, coronary heart disease. My own interpretation of the data is that a systolic blood pressure goal of 130–135 mmHg is based on the totality of evidence right now. However, more than half of all patients with diabetes do not have a systolic blood pressure of less than 140 mmHg despite treatment.

### Hypertension in diabetes as a global challenge

Hypertension constitutes a major cardiovascular risk factor in patients with diabetes mellitus,

both Type 1 and 2. This is well documented in numerous observational studies from various populations [1]. For Type 1 diabetes, important predictors of this risk are, most notably, diabetes

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duration and the degree of albuminuria, while obesity, insulin resistance and nephropathy contribute to the elevated blood pressure in Type 2 diabetes [2]. Interestingly, there seems to be no overlap between the genetic architecture of Type 2 diabetes [3] and the genes regulating blood pressure [4]. This means that the two conditions, even if they overlap from a clinical perspective, have different genetic backgrounds.

Over the years, a number of important intervention studies have added to our knowledge regarding the benefits of blood pressure lowering in patients with Type 2 diabetes. Either these studies have compared different antihypertensive drugs or different blood pressure goals. In most studies, only subgroups of diabetes patients have been analyzed, for example in the HOT [5], ALLHAT [6] and ONTARGET [7] studies, to name just a few, whereas in other studies, only patients with diabetes were recruited, for example in UKPDS [8], ABCD [9], ADVANCE [10] and ACCORD [11].

A number of guidelines have tried to summarize the evidence for blood pressure control in diabetes over the last 10 years of the post-UKPDS era, ever since the publication of the results from the blood pressure arm of UKPDS in 1998 [8]. These guidelines have been published in Europe by several national organizations, but most importantly by the European Society of Cardiology (ESC) [12], the European Society of Hypertension (ESH) [13] and the European Association for the Study of Diabetes (EASD) [14]. NICE has published reports on the evidence behind clinical decision-making, as well as recommendations on hypertension management together with the British Hypertension Society (BHS) [15]. In North America, guidelines have been published by the Joint National Committee 7 (JNC-7) [16], the American Diabetes Association (ADA) [17] and the National Kidney Foundation (NKF) [18]. In Canada, important guidelines have been published over the years by scientific organizations [19].

In Asia, hypertension guidelines have been published in Japan [20] and China [21]. Finally, in the international arena, the International Diabetes Federation (IDF) has published its own recommendations for diabetes management and hypertension control [22].

In all these guidelines, recommendations and statements, the existence of hypertension in patients with diabetes has been considered to be an important risk factor for macro- and

micro-vascular diabetes complications. Based mainly on observational data, and not from randomized controlled trials, a blood pressure goal below 130/80 mmHg has been proposed in most of these guidelines over the last 10 years with few exceptions. In fact, there has been a trend to lower the blood pressure goal gradually from 140/90 mmHg through to 140/85 mmHg and 135/85 mmHg, to a goal of less than 130/80 mmHg in recent years. In patients with nephropathy, an even lower goal of less than 120/75 mmHg was once proposed. In essence, the concept of ‘the lower the better’ was advocated, very much influenced by the almost linear risk curves shown from the UKPDS observations [23].

### New data challenged previous guidelines

In 2009, this view was challenged by the ESH when a document was published entitled ‘A reappraisal of European Guidelines’ in the *Journal of Hypertension* by a group of authors from the Council of the ESH [24]. The document stated that the lack of evidence from randomized controlled studies called for a re-evaluation of the blood pressure goal in high-risk patients; for example, in diabetes. It was concluded in this document, as well as in an editorial in the *European Heart Journal* by Zanchetti, that in a wide range of randomized studies, patients did not achieve the systolic blood pressure goal of less than 130 mmHg in the intensive arm of the trial [25]. This goal was achieved in only one study (ABCD) in a small group of patients with diabetes, but with normotension [9]. In conclusion, as the evidence is lacking, it is not appropriate to continue with the recommendation of a blood pressure goal of less than 130/80 mmHg, as set in most other contemporary guidelines.

This started an international debate that is still ongoing. The publication of the ACCORD-BP trial in 2010 fueled the debate even more, as the finding of this trial was that a randomization to the two systolic blood pressure goals of less than 140 or 120 mmHg in patients with Type 2 diabetes and medium-to-high cardiovascular risk did not translate into a significant reduction of the composite cardiovascular end point, even if the achieved mean systolic blood pressures were well separated – 119 versus 134 mmHg in the two arms, respectively [11]. However, a secondary end point, stroke, was significantly reduced in the intensive blood pressure control arm, but this was achieved at the price of an increased risk of serious adverse events in the intensive arm. The

costs for the use of more drugs and the need for more clinical visits to manage side effects should also be taken into account.

In the ADVANCE study, on the other hand, benefits were seen with more intensive blood pressure lowering with a mean systolic blood pressure of 134 mmHg achieved in the intensively treated group [10], similar to what was achieved in the control group of the ACCORD-BP trial [11].

Later on, a number of observational studies reported that patients at high cardiovascular risk and who had attained a low systolic blood pressure of less than 130 mmHg, had an unchanged or even increased risk of coronary heart disease (CHD) events. This was shown in observational analyses from the INVEST [26] and ONTARGET [7] studies in patients with diabetes, and also in a lipid-lowering trial, the TNT [27].

### Experience from a national diabetes register in Sweden

In Sweden, the existence of the National Diabetes Register (NDR) made it possible to follow a large number of treated patients with a combination of diabetes and drug-treated hypertension over a number of years. As Sweden is a country with high-quality diabetes care, owing to diabetes teams both at the hospital and the primary care level, the data are of interest. The finding in general was that no further benefits were noticed for total cardiovascular events in patients who had achieved a systolic blood pressure of 130 mmHg, when 35,000 patients were followed for more than 5 years, and after controlling for a number of covariates, including diabetes duration and other risk factors [28]. Stroke was reduced in a linear manner at lower systolic blood pressure levels, but CHD increased at systolic blood pressure of below 115 mmHg. However, side effects and number of clinical visits were not recorded. The conclusion based on this analysis, and two previous ones from NDR, is that clinical benefits are largely offset in patients with diabetes and treated hypertension if the blood pressure goal is too ambitious, except for stroke prevention [29,30]. In ACCORD-BP, it was also shown that adverse effects may increase to a worrying degree [11].

### Blood pressure goal in new guidelines

How have these publications influenced the more recent set of guidelines that have been published over the last 1–2 years? In 2011, NICE set the blood pressure goal at less than 140/90 mmHg in all patients with hypertension irrespective of

diabetes status, and at an even higher level in the old [31]. This was followed by a recommendation in the Joint European Guidelines in May 2012 to use the goal of less than 140/80 mmHg in patients with diabetes, supported by ESC, ESH and EASD, as well as a number of other scientific organizations within Europe [12]. The systolic blood pressure goal of 140 mmHg was suggested to avoid harm as there might exist some hazards of intensive blood pressure lowering in patients with established CHD due to hypoperfusion, and a decrease in stroke volume of the heart. It should, however, be remembered that a more ambitious attitude towards aggressive risk factor control can be applied in the younger or middle-aged patients with diabetes of shorter duration compared with elderly and frail patients with diabetes of longer duration, comorbidities, or clinical or subclinical CHD. The diastolic goal of less than 80 mmHg was defended based on data from a subgroup of diabetes patients in the HOT study [5], despite the attained diastolic blood pressure in this randomized group being 81–82 mmHg [ZANCHETTI A, PERS. COMM.]. In the UKPDS, benefits were shown with a target diastolic blood pressure below 85 mmHg [8]. On the other hand, data from a *post hoc* analysis of the VADT study indicated that the risk increases at a diastolic blood pressure of less than 70 mmHg [32]. This was, however, based on limited *post hoc* analyses and it should, thus, be acknowledged that we lack data on the appropriate lower limit of a diastolic blood pressure goal in patients with diabetes. Furthermore, it might be difficult to reduce systolic blood pressure below 140 mmHg without causing the diastolic blood pressure to drop close to or even below 70 mmHg, especially in patients with stiff arteries. It should also be emphasized that most researchers today agree on the prime importance of systolic blood pressure control for reducing cardiovascular risk. Therefore, the diastolic blood pressure issue is of secondary importance in my opinion, at least in the middle-aged and elderly populations, and also in patients with diabetes.

Finally, a task force set up by the ESH and ESC is currently reviewing all of the evidence to write the next version of the European Guidelines on Hypertension, to be expected in June 2013. It is reasonable to believe that the blood pressure goal in diabetes will somehow reflect what has already been proposed in 2012, as these organizations were also partners behind the Joint European guidelines on prevention of cardiovascular disease [12].

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### American view on treatment goals

What about the view in North America? To date, the ADA has kept the 'old' blood pressure goal in diabetes of less than 130/80 mmHg, but the organization recently changed its view in the 2013 edition of 'Standards of diabetes care', in which the new goal of less than 140/80 mmHg was introduced for the first time [17]. This is probably a reflection of the internal debate within the ADA, but is also related to the influence of European views. The evidence is the same on both sides of the Atlantic and this should support convergence of guidelines on treatment targets. In the USA, the long awaited JNC-8 guidelines are expected during 2013. This document is planned to provide answers to a few well-defined clinical questions and will probably not represent a full set of guidelines. The blood pressure goal in diabetes will most certainly be commented upon, as this is part of the clinical questions asked. In Canada, new guidelines are also awaited. In China and Japan, new guidelines have already been launched [20,21].

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### Antihypertensive drugs in patients with diabetes

What about the recommended drugs to be used in these patients with hypertension and diabetes? The European view is that all antihypertensive drugs are useful, especially in combinations. However, the combination of two drugs that both block the renin-angiotensin system is contraindicated based on data from ONTARGET [7] and the ALTITUDE [33] studies because of side effects, with a nonsignificant increase of stroke in the actively treated arm as well as hypotension. Similarly, the combination of a renin-angiotensin system-blocking agent and an aldosterone antagonist is not recommended because of the risk of hyperkalemia, especially in patients with nephropathy and impaired renal function. Otherwise, the use of renin-angiotensin system blockers is recommended as one part of the many possible drug combinations that can be used. The evidence supporting the use of ACE inhibitors (ACE-I) and ARBs is more or less comparable and, in one study with a randomized design, the ONTARGET trial [7], there was no clinical difference according to major end points between the ACE-I (ramipril) and ARB (telmisartan). There may, however, exist some differences between certain subgroups of patients, or according to side effects or pricing. Calcium antagonists are widely used, as well

as low-dose thiazide diuretics or other newer diuretic drugs such as indapamide. The most controversial drugs during the last few years are the  $\beta$ -receptor blockers, as some evidence suggest that they are less effective for stroke prevention, perhaps because of reduced control of central blood pressure, and they might increase weight and worsen insulin resistance and dyslipidemia. On the other hand,  $\beta$ -receptor blockers are successful for secondary prevention following a myocardial infarction and are often useful in drug combinations. The more modern versions, with vasodilating properties, should not be regarded as similar to the old nonspecific  $\beta$ -receptor blockers [24]. These newer vasodilating  $\beta$ -receptor blockers have less influence on bodyweight, and may even improve the metabolic profile, as well as both glucose and lipid metabolism. One combination that should be avoided is the use of a high dosage of  $\beta$ -receptor blockers and corresponding dosages of thiazide diuretics, as this might further impair metabolism in subjects with hypertension and impaired glucose tolerance or fasting glucose as part of the metabolic syndrome. In addition, lower dosages in combination may prove to be detrimental in susceptible patients. It is, therefore, recommended to follow changes in metabolic variables between clinical visits in these patients.

In the USA, there has been a strong focus on the thiazide-like diuretics such as chlorothalidone based on data from the ALLHAT [6] and SHEP [34] studies, and this has influenced the recommendations in, for example, the JNC-7 document. Metabolic side effects have been downplayed and not taken as seriously as in some European documents. Interestingly, the BHS has advocated a wider use of chlorothalidone, despite the fact that this drug was withdrawn from most European countries many years ago. Other experts think that the low-dose thiazide diuretics should stay in the therapeutic armamentarium and not be replaced by chlorothalidone, but complemented by newer diuretic drugs with good evidence for clinical effects with or without the combination of an ACE-I, such as indapamide in the ADVANCE [10], PROFESS [35] and HYVET [36] studies.

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### Conclusion

In conclusion, the case for treatment of hypertension in diabetes is a clinical example of when guidelines have changed based on the combination of critical arguments and the

limitations of the available evidence. The most well-documented blood pressure goal based on the totality of evidence available today, both from randomized and observational studies, is that the systolic blood pressure should be constantly kept under 140 mmHg [37], probably in the range of 130–135 mmHg, in my opinion, as supported by a meta-analysis [38]. This is based on a balanced judgment of the available evidence of associations between achieved blood pressure in studies that include patients with diabetes and prospective cardiovascular risk, as shown in meta-analyses, and not on solid evidence, as there is currently no randomized controlled study available to define the exact systolic blood pressure goal.

The diastolic blood pressure should be constantly kept lower than 90 mmHg, and probably in the range of 80–85 mmHg, despite the fact that one study (HOT) provides some evidence to use the goal of below 80 mmHg [5]. The diastolic blood pressure should not be below 70 mmHg based on observational data [32]. It seems that all antihypertensive agents can be used, often in combination and with few exceptions, but tolerability, costs and clinical effects should be taken into consideration.

Finally, it has to be remembered that the majority of patients with hypertension and diabetes still do not have a systolic blood pressure below 140 mmHg [39]. This is why I personally think that efforts should be directed towards bringing these patients at least to this target before clinicians worry about even tighter blood pressure goals.

In the future, new drugs might be developed for vascular protection in diabetes and for lowering of arterial stiffness, not just for control of

brachial blood pressure *per se*. However, most likely, there is a long road to go before such drugs will enter clinical practice [40].

### Future perspective

As it is unlikely that new large-scale intervention trials will be started to define blood pressure goals in patients with diabetes, at least in the next few years, we have to live with the evidence available today. Guidelines reflect the current level of scientific understanding, and it is likely that they will become more uniform on a global scale as the evidence is very similar and freely available. Therefore, I believe that within a multiple risk factor approach and treatment strategy in patients with diabetes, a systolic blood pressure goal of less than 140 mmHg, and possibly in the range of 130–135 mmHg, is what we are going to see in most, if not all, guidelines. This is simply because this is supported by available evidence. The diastolic blood pressure goal is only of secondary importance.

### Financial & competing interests disclosure

*The author has been a member of Advisory Boards for pharmaceutical companies with products used for diabetes patients (Novo Nordisk, Merck, Astrazeneca, Boehringer-Ingelheim, Pfizer and Servier), and has received honoraria for lectures and presentations at various meetings. He has been serving as the current Secretary of the European Society of Hypertension (ESH) since 2009. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

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