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REVIEW

Blood pressure targets in type 2 diabetes. Evidence against or in favour of an aggressive approach

Giuseppe Mancia [1,2] · Guido Grassi [3,4]

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Abstract

When associated with high blood pressure, type 2 diabetes mellitus is characterised by a high risk of adverse cardiovascular (CV) and renal outcomes. However, both can be effectively reduced by antihypertensive treatment. Current guidelines on the treatment of hypertension emphasize the need to effectively treat high blood pressure in diabetic individuals, but their recommendations differ in terms of the optimal target blood pressure value to aim for in order to maximise CV and renal protection. In some guidelines the recommended target blood pressure values are <140/90 mmHg (systolic/diastolic), whereas in others, blood pressure values close or even less than 130/80 mmHg are recommended. This paper will discuss the evidence for and against a conservative or more aggressive blood pressure target for treated diabetic hypertensive individuals based on the evidence provided by randomised trials, trial meta-analyses and large observational studies. Based on the available evidence, it appears that blood pressure targets will probably have to be lower than <140/90 mmHg, and that values approaching 130/80 mmHg should be recommended. However, evidence in favour of even lower systolic values, i.e. <130 mmHg, is limited and is definitively against a reduction to <120 mmHg.

Keywords Antihypertensive treatment · Blood pressure targets · Cardiovascular events · Cardiovascular morbidity · Cardiovascular mortality · Diabetes mellitus · Review

Abbreviations

ABCD	Appropriate Blood Pressure Control in Diabetes
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
CV	Cardiovascular
DBP	Diastolic blood pressure
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HOT	Hypertension Optimal Treatment
INVEST	International Verapamil SR-Trandolapril
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
SBP	Systolic blood pressure
UKPDS	UK Prospective Diabetes Study
VALUE	Valsartan Antihypertensive Long term Use Evaluation

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-017-4537-3) contains a slideset of the figures for download, which is available to authorised users.

✉ Giuseppe Mancia
Giuseppe.mancia@unimib.it

[1] University of Milano-Bicocca, Milano and Policlinico di Monza, Monza, Italy

[2] Present address: p.za dei Daini, 4, 20126 Milano, Italy

[3] Clinica Medica, University of Milano-Bicocca, Milan, Italy

[4] IRCCS Multimedica, Sesto San Giovanni, Milan, Italy

Introduction

There is overwhelming evidence that [1] antihypertensive drugs protect individuals with type 2 diabetes with an elevated blood pressure against diabetes-associated cardiovascular (CV) diseases [1–5] and [2] the protective effect is largely due to blood pressure lowering per se, i.e. regardless of how it is attained [6]. On the other hand, the blood pressure level

that needs to be achieved in order to maximise the CV protection of hypertensive individuals with diabetes is uncertain. This is reflected by the discrepant recommendations of the most popular guidelines, some of which advise that a systolic blood pressure (SBP) and a diastolic blood pressure (DBP) of <130 and <80 mmHg, respectively should be achieved, while others support the more conservative target of <140/90 mmHg [7–11].

This paper will review the evidence on the blood pressure targets to pursue in type 2 diabetic patients, based on the results of randomised outcome trials, trial meta-analyses and, to a limited extent, post hoc analyses of large trials and, thus, data of an observational nature. It will be argued that at present the evidence favours more conservative blood pressure targets, but also that not all results are in line with this view. Therefore the possibility that at least some individuals with diabetes are more effectively protected by lower 'on-treatment' blood pressure values should not be excluded. The review will largely focus on SBP targets, because reducing SBP, rather than DBP, represents the major difficulty faced by physicians when pursuing blood pressure control in hypertensive people, even more so in diabetic individuals in whom a major determinant of the SBP elevation, such as arterial stiffening, is impaired at an earlier stage, more frequently and more markedly [12, 13].

Evidence in favour of a more conservative blood pressure target

Results of randomised outcome trials In 2009 the European Society of Hypertension (ESH) revisited the evidence that had led to the 2007 hypertension guidelines the society had issued with the European Society of Cardiology (ESC) [14], to recommend a reduction in blood pressure to <130/80 mmHg in hypertensive individuals with type 2 diabetes. As shown in Fig. 1 [15, 16], the available randomised outcome trials reported a reduction in SBP of several mmHg in the actively (or more intensively) treated individuals compared with the control group, usually accompanied by a reduction in CV outcomes. However, among the trials that reported a reduction in CV outcomes, the achieved SBP was always confined to values >130 mmHg. The only exception was the Appropriate Blood Pressure Control in Diabetes (ABCD) trial on normotensive individuals with diabetes, which reported a reduction in CV outcomes at an SBP of 128 mmHg, although this was a very small trial with few events and GFR as the primary endpoint [17]. This justified the conclusion that in people with type 2 diabetes, the evidence was largely in favour of an SBP target <140 mmHg but >130 mmHg, which for this reason was recommended as the target range in the 2013 ESH/ESC hypertension guidelines [8]. Indeed, in these guidelines it was more precisely advised that type 2 diabetic individuals with hypertension should have SBP values at the lower end of the 130–139 mmHg range, based on the results of outcome trials such as the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial [18]. In this trial, 11,140 participants with type 2 diabetes and a baseline SBP of about 145 mmHg were randomised to a combination of perindopril and indapamide or a placebo. Over a follow-up of about 5 years, patients in the active treatment arm exhibited an average 'on-treatment' SBP of approximately 134 mmHg compared with a value of approximately 140 mmHg in the placebo group. This was associated with 18% and 14% reductions in CV and all-cause mortality, respectively, beneficial effects that extended to renal outcomes, which were reduced by 21% in the treatment group [18].

Meta-analyses of randomised trials A conservative rather than an aggressive blood pressure target is also supported by the results of several meta-analyses of randomised outcome trials on populations comprising of or including a large subgroup of individuals with diabetes [2–5]. In a meta-analysis of 13 studies on people with type 2 diabetes or impaired fasting glucose [3], compared with standard treatment and higher SBP targets, an SBP reduction to 131–135 mmHg reduced the risk of all-cause mortality by 13%, whereas a reduction to <130 mmHg was associated with a 4% non-significant increase in all fatal events. In a meta-analysis of 49 trials (approximately 73,000 individuals with type 2 diabetes) [4], all-cause mortality, CV outcomes and renal events all decreased if, from a baseline value of >150 mmHg, SBP was reduced to slightly below 140 mmHg, but the benefits decreased or disappeared as, from lower baseline values, SBP approached or went below 130 mmHg. Similar observations have been made in even larger meta-analyses, namely those by Emdin et al (40 trials and more than 100,000 individuals) [2] and Thomopoulos et al (72 trials and more than 260,000 individuals) [5]. In the former [2], antihypertensive treatment significantly reduced mortality, overall CV events, coronary heart disease, heart failure and stroke in type 2 diabetic individuals with an on-treatment SBP of 137–139 mmHg (Fig. 2a), whereas no event, except stroke, showed a statistically significant reduction with an on-treatment SBP of 121–123 mmHg (Fig. 2b). Similarly, in the meta-analysis of Thomopoulos et al [5], antihypertensive treatment reduced CV outcomes and mortality when SBP was lowered to >140 mmHg. Albeit attenuated, the benefits remained visible when on-treatment SBP was reduced to between 130 and 139 mmHg, but they disappeared as values <130 mmHg were reached. Interestingly, this was in contrast with what was

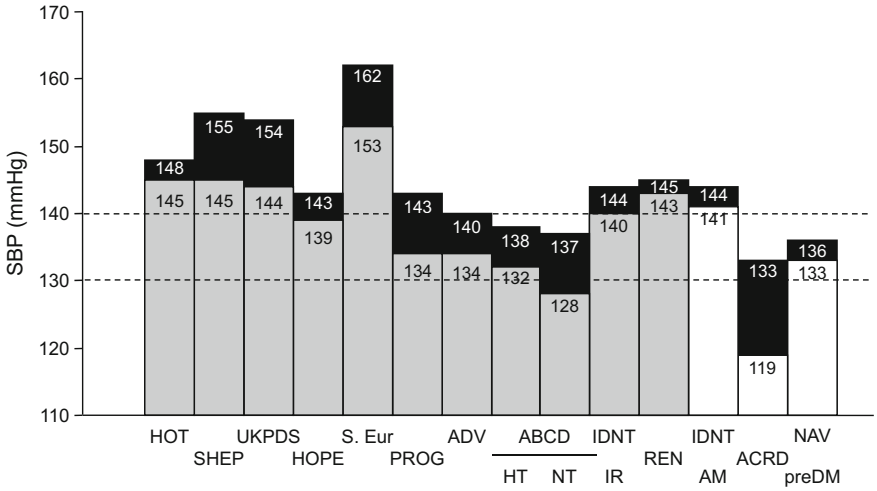

Fig. 1 Achieved SBP in randomised trials on type 2 diabetic individuals receiving antihypertensive treatment. In each histogram the lower and upper values refer to the on-treatment SBP in the actively (or more intensively) treated and control groups of patients, respectively. The grey colour indicates trials in which the SBP reduction was accompanied by CV benefits (reduction of the primary or a major secondary endpoint), whereas the white colour refers to trials in which the blood pressure reduction was associated with no benefit. The black colour refers to the difference in on-treatment SBP between groups. Trial acronyms are indicated at the bottom of each histogram. SHEP, Systolic Hypertension in the Elderly Program; HOPE, Heart Outcomes Prevention Evaluation; S. Eur, Systolic Hypertension in Europe Trial; PROG, Perindopril Protection against Recurrent Stroke; ADV, ADVANCE; ABCD HT, Appropriate Blood Pressure Control in Diabetes Study – hypertensive patients; ABCD NT, Appropriate Blood Pressure Control in Diabetes Study – normotensive patients; IDNT IR, Irbesartan Diabetes Nephropathy Trial-irbesartan versus placebo; REN, Reduction of endpoint in non-insulin dependent diabetes mellitus with AngiotensinII Antagonist Losartan Study; IDNT AM, Irbesartan Diabetes Nephropathy Trial – amlodipine versus placebo; ACRD, Action to Control Cardiovascular Risk in Diabetes Trial; NAV preDM, Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research – pre-diabetic patients. Figure adapted from [15] with permission. This figure is available as part of a downloadable slideset

observed in non-diabetic individuals, in whom antihypertensive treatment reduced all or most outcomes through the range of achieved SBP values, from >140 to <130 mmHg, in a progressive manner.

Post hoc analysis of trial data Because they involve comparison of non-randomised groups of people, observational studies can never completely ensure that the results are dependent on treatment differences rather than on between-group differences at baseline. The evidence obtained is thus weaker than that provided by randomised trials. It is nevertheless interesting to note that observational data such as those generated by post hoc analysis of outcome trials involving individuals with diabetes seem to reach conclusions similar to those generated by randomised trials, namely, that in type 2 diabetes, macrovascular complications can be effectively reduced by lowering SBP to <140 mmHg, with no additional benefit observed for SBP reductions to <130 mmHg, which, at these lower on-treatment values, have usually been found to be attenuated or disappear. For example, in a post hoc analysis of a large number of participants recruited for the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), individuals with diabetes showed a reduction in all CV outcomes when the SBP was

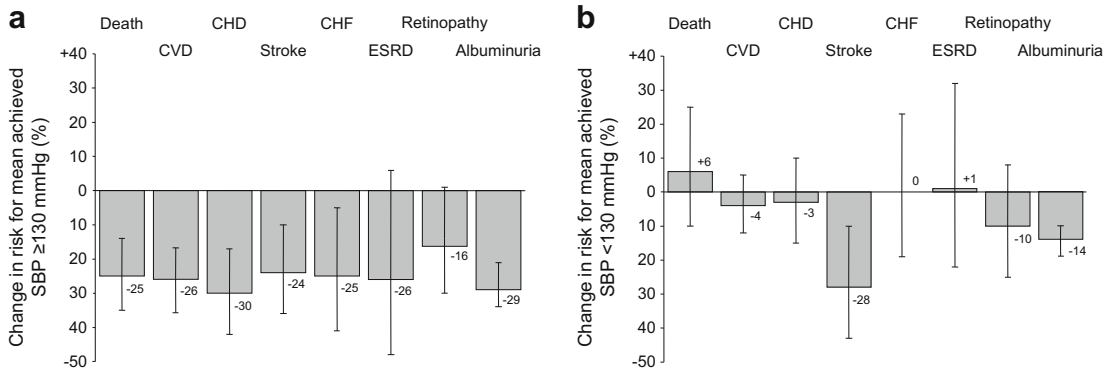

Fig. 2 Effect of 10 mmHg reduction of SBP on outcomes in 40 trials on 100,354 diabetic individuals [2]. Data are stratified for an achieved on-treatment SBP of ≥130 mmHg (mean 138 mmHg) (**a**) or <130 mmHg (mean 122 mmHg) (**b**). Histograms show the risk change and the 95% CIs. CVD, CV disease; CHF, congestive heart failure; ESRD, end-stage renal disease. This figure is available as part of a downloadable slideset

reduced to <140 mmHg but, with the exception of stroke, in both groups benefits were attenuated (and for coronary events disappeared) when SBP went below 130 mmHg [19]. Similar observations were made in post hoc analyses of the hypertensive participants in the Valsartan Antihypertensive Long term Use Evaluation (VALUE) trial, which included a large number of people with type 2 diabetes [20], in the almost 23,000 hypertensive individuals with coronary disease included in the International Verapamil SR-Trandolapril (INVEST) trial [21] and in the hypertensive diabetic patients of the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [22]. In INVEST [21], participants with diabetes were divided according to the average SBP achieved during the treatment period: ≥140 mmHg, 130–139 mmHg and <130 mmHg. Compared with the ≥140 mmHg group, those in the 130–139 mmHg group exhibited a marked reduction in the incidence of overall CV outcomes. There was, however, no further reduction in outcomes in those in the <130 mmHg group, in whom the risk was slightly, albeit not significantly, greater than that for those in the 130–139 mmHg SBP group. In addition, there was a tendency for the increased risk to become significant as SBP decreased to <120 mmHg—a 'J curve' phenomenon compatible with the possibility for too aggressive blood pressure targets to be dangerously close to the blood pressure value at which perfusion of vital organs is compromised [23].

Evidence in favour of a lower blood pressure target

Lower SBP target and stroke Randomised outcome trials, trial meta-analyses and post hoc trial analyses all concur that reducing SBP to <130 mmHg may offer further protection against stroke compared with reducing SBP to within the 130–139 mmHg range. This was found in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in which more than 10,000 individuals with type 2 diabetes were randomised to one of two target SBP groups: <140 mmHg or <120 mmHg [24]. Compared with the higher SBP target group (mean achieved SBP 134 mmHg at 1 year), the lower target group (mean achieved SBP 119 mmHg) did not show a reduction in all fatal and non-fatal CV outcomes, but it did show a 41% lower risk of stroke. Although this result was open to the criticism that the number of strokes was small, this finding has since been reported by meta-analyses of the randomised outcome trials [2–5], as shown in the example of Fig. 2b [2]. Furthermore, similar observations have been made by post hoc analyses of the individuals at high CV risk, largely or exclusively with diabetes, in the ONTARGET, INVEST and VALUE trials [19–21]. Finally, reducing SBP to <130 mmHg has been shown to much more effectively protect against haemorrhagic stroke (a cerebrovascular event that is much rarer than ischaemic stroke but often with more serious clinical sequelae) than reducing SBP to <140 mmHg [25]. In the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, people with documented lacunar strokes exhibited a 63% reduction in the risk of intracerebral haemorrhage, although not of other vascular outcomes, if SBP was reduced to 127 mmHg rather than to 138 mmHg [26]. Similar marked benefits were reported years ago in the patients with a history of cerebrovascular events in the Perindopril Protection Against Recurrent Stroke (PROGRESS) trial [27]. In the group randomised to antihypertensive treatment, the blood pressure reduction was accompanied by a reduction in the risk of stroke recurrence that was significant in both diabetic and in non-diabetic individuals. The benefit in terms of reduction of haemorrhagic stroke was striking (a reduction of 60–80%), and a benefit was also seen for initial SBPs of 120–139 mmHg and achieved SBPs of <120 mmHg [28].

Re-analysis of the ACCORD trial Recently, the ACCORD trial has been reanalysed by separately considering the subgroup of individuals with diabetes ($n = 4733$) randomised to intense vs standard SBP reduction (achieved values 119 and 136 mmHg, respectively) after initial randomisation to intense vs standard reduction of HbA_{1c}, which had been implemented for all trial participants ($n = 10,251$) [29]. As shown in Fig. 3, in the SBP subgroup, intense SBP reduction after standard reduction of HbA_{1c} was accompanied by a marked reduction not just of the risk of stroke (−39%), but also of the risk of CVD outcomes combined (−33%) and myocardial infarction (−37%). The intense reduction of HbA_{1c} also had substantial CV protective effects, whereas no further CV protection was observed for the two intense interventions together. These results support the interesting hypothesis that intense interventions targeting multiple risk factors do not substantially increase the benefit of a single intense intervention, possibly because of the reciprocal adverse consequence of their side effects. In the setting of the ACCORD trial, a greater protective effect of a more intense blood pressure reduction might have been offset by the increased incidence of hypoglycaemic episodes that accompanied intense glucose-lowering treatment, given the documented CV risks associated with serious blood glucose falls [30]. These findings also suggest that, in individuals with diabetes, aggressive SBP reductions protect the CV system beyond the cerebrovascular region, although the absence of any favourable effect on CV death, all cause death and diabetes-related microvascular complications (Fig. 3) [29] suggests a limited extracerebral-protective role for SBP lowering. What does appear to be clear, on the other hand, is that in individuals with diabetes, SBP values <120 mmHg should probably be avoided. In the above-mentioned SBP subgroup of the ACCORD trial, patients randomised to the standard or aggressive SBP target in whom the achieved SBP was <120 mmHg

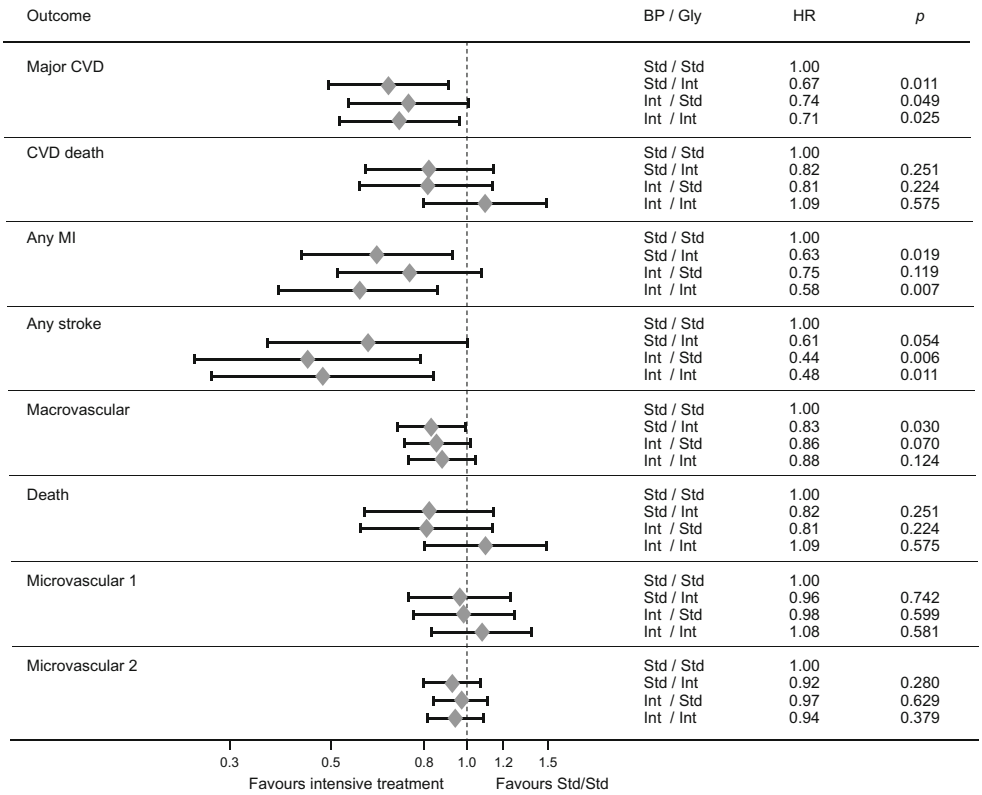

Fig. 3 Risk (HR) and related level of statistical significance (*p* value) of outcomes in the subgroup of diabetic participants in the ACCORD trial who were randomised to intense (Int) or standard (Std) SBP reduction, following randomisation to intense or standard blood glucose reduction (which all trial participants underwent). BP, blood pressure; CVD, CV disease; MI, myocardial infarction; Gly, blood glucose (glycaemia). Adapted from [29]. Copyright 2014 by the ADA. Reprinted with permission from the ADA. This figure is available as part of a downloadable slideset

exhibited a significant increase in CV risk compared with those in whom the on-treatment SBP remained within 120–140 mmHg [31].

Blood pressure target and diabetic nephropathy Neither individual randomised trials nor meta-analyses have consistently documented that the appearance or progression of diabetic nephropathy is more effectively opposed by aggressively reducing SBP to targets lower than the conventional one, i.e. <140 mmHg [32]. However, some guidelines on diabetes recommend SBP to be reduced to <130 mmHg in patients with diabetic nephropathy and an increased urinary protein excretion (microalbuminuria or proteinuria), based on the observation, made many years ago by the Modification of Diet in Renal Disease (MDRD) trial, that in a subgroup of patients in whom diabetic nephropathy was accompanied by marked proteinuria (>1 g/day) reducing blood pressure more aggressively (on-treatment mean arterial pressure 92 vs 107 mmHg) delayed the rate of decline of GFR to renal failure [33]. This has been further supported by: (1) the experimental evidence that filtered proteins may have a damaging effect on the anatomical integrity of the glomerulus, and (2) reducing SBP to <120 mmHg is accompanied by a progressively greater antiproteinuric effect. However, the MDRD study-derived data on the protective effect of treatment in patients with proteinuria were observational in nature. Furthermore, the prognostic importance of urinary protein excretion is still under debate because, although it is well established that absolute urinary protein values represent a risk factor for either renal or CV outcomes [34, 35], it has not been established whether this is also the case for treatment-induced changes in these values. In a number of studies on diabetic or non-diabetic individuals, increased levels of proteinuria during treatment were accompanied by a significantly greater risk of CV events and renal deterioration than were stable or decreased levels [36–38]. However, in other studies, modification of proteinuria by treatment did not bear any relationship with the risk of end-stage renal disease or CV outcomes [39–41]. Further studies are needed to determine whether, in diabetic nephropathy, treatment-induced changes in proteinuria represent a reliable marker of renal and CV outcomes, reductions in proteinuria by an intensive blood pressure-lowering strategy reflecting an enhanced protective effect of treatment.

DBP target

Although some guidelines set the DBP target in type 2 diabetes at <90 mmHg, at least two randomised outcome trials clearly document that lower DBP targets may offer a greater degree of CV protection. In one trial (Hypertension Optimal Treatment; HOT) type 2 diabetic individuals with hypertension showed a 51% reduction in CV events when the DBP target was set at <80 mmHg (achieved value 81 mmHg) rather than at <85 mmHg or <90 mmHg [42]. In the other trial (UK

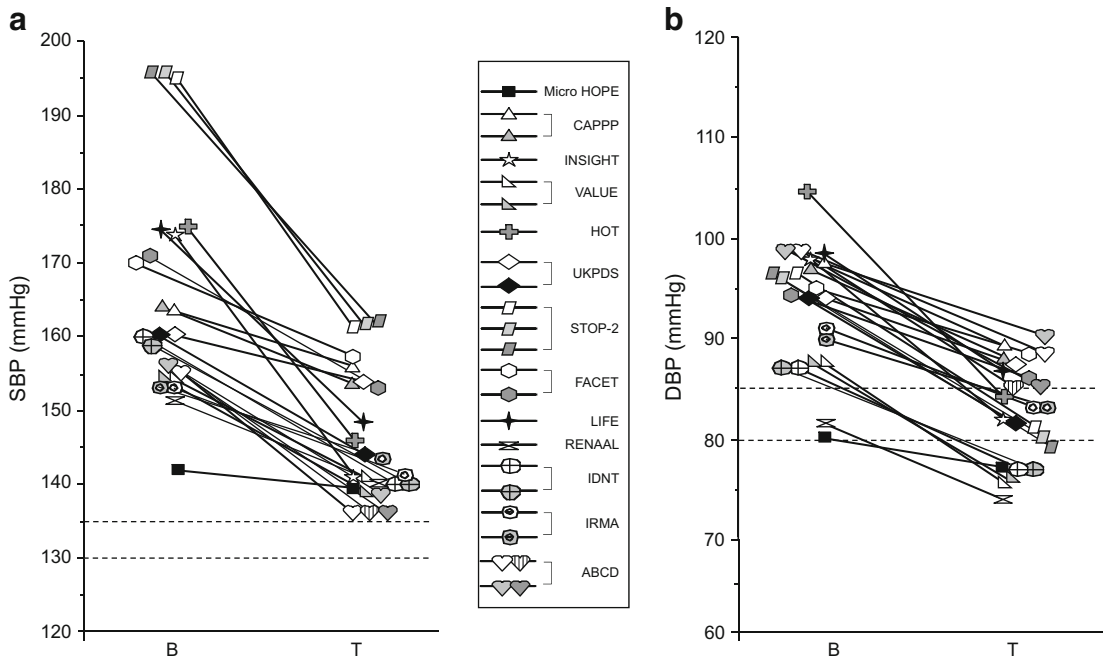

Fig. 4 (**a**) SBP (**a**) and DBP (**b**) values in randomised clinical trials that have included exclusively, or a large number of type 2 diabetic patients. The horizontal dashed lines indicate the SBP/DBP targets in the diabetic population recommended by guidelines. B, blood pressure values at the trial entry phase; T, on-treatment blood pressure values. Trial acronyms are indicated in the central panel. In CAPPP, VALUE; UKPDS; STOP-2, FACET, IDNT, IRMA and ABCD trials the different symbols refer to conventional treatment and treatment with the specific drug tested in the trial (see below for the definition for each trial acronym). CAPPP, Captopril Prevention Project in Hypertension; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; IDNT, Irbesartan Diabetes Nephropathy Trial; INSIGHT, International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment; IRMA, Irbesartan in the Treatment of Microalbuminuria and Proteinuria in Patients with Type 2 Diabetes and Hypertension-Prospective Observational Study; LIFE, Losartan Intervention For Endpoint reduction; Micro-HOPE, Heart Outcome Prevention Evaluation microvascualr study; RENAAL, Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan Study; STOP-2, second Swedish Trial in Old patients with Hypertension. Figure adapted from [49] with permission. This figure is available as part of a downloadable slideset

Prospective Diabetes Study [UKPDS]), type 2 diabetic individuals with hypertension who had an on-treatment DBP of 83 mmHg showed a lower incidence of CV events (myocardial infarction −21%, stroke −44%, all diabetes-related endpoints −24% and microvascular endpoints −37%) vs patients with an on-treatment DBP of 87 mmHg [1]. As mentioned in the Introduction, however, in type 2 diabetes, antihypertensive treatment is largely dominated by the difficulty of effectively reducing SBP, the control of which within the 130–139 mmHg range is almost invariably accompanied by DBP values <90 or <85 mmHg. Indeed, values <80 mmHg are also common, with no evidence that the benefits of SBP control are offset, as exemplified by the reduction in CV and all-cause mortality seen in the ADVANCE trial for on-treatment blood pressure values of 134/75 mmHg [18]. This has recently been confirmed in a randomised trial-based meta-analysis, which reported that in diabetes the risk of most outcomes is similarly reduced at on-treatment DBP values above or below 80 mmHg, similar to what occurs in non-diabetic individuals [5]. Thus, in diabetes, lowering DBP to 80 mmHg, or even to the 70–79 mmHg range, does not seem to pose safety problems in patients achieving SBP control. On the other hand, there is little or no evidence available on the effects of DBP reduction to <70 mmHg. Based on post hoc data on non-diabetic patients, a possibility exists that in the general hypertensive population these lower values lead to a 'J curve' phenomenon [23], particularly in individuals with long-standing diabetes, in whom local and integrated mechanisms of blood pressure control may be more clearly impaired [23, 43].

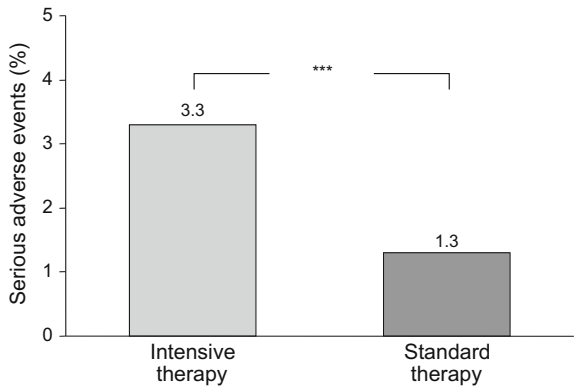

Fig. 5 Serious adverse events attributed to antihypertensive treatment in the ACCORD study [24]. Data are shown for the intensively treated (SBP goal <120 mmHg) and standard-treated (SBP goal <140 mmHg) patients. ***$p < 0.001$. This figure is available as part of a downloadable slideset

Conclusions

Data from randomised outcome trials, trial meta-analyses and observational studies provide solid evidence that in diabetic individuals with hypertension, an SBP reduction to 130–139 mmHg effectively protects against CV and renal blood pressure-related complications, and that, within this range, values closer to 130 mmHg are preferable. There is also solid evidence that in diabetic individuals, DBP can be reduced to 70–79 mmHg without compromising the individual's protection and safety. In contrast, there are no conclusive data that lowering SBP to <130 mmHg leads to a further increase in CV and renal protection, and that thus in diabetes a lower SBP target should be recommended. Although, evidence strongly suggests that SBP values <120 mmHg should be avoided. Considering the present stage of knowledge, it may thus be appropriate that in individuals with type 2 diabetes, guidelines recommend an SBP target close to but not less than 130 mmHg, with a DBP <80 mmHg and >70 mmHg. It should be emphasised, however, that data on the optimal blood pressure target for patients with diabetes do not cover the entire diabetic population and are sometimes inconsistent [44], explaining the different interpretations of data and conclusions drawn. Moreover, the database on which conclusions have been drawn is not scientifically impeccable [1] since, in most trials, antihypertensive agents were used for purposes different from those of determining the benefit of blood pressure-lowering interventions, an approach that may generate confounding. Second, because optimal blood pressure targets may vary between patients (and perhaps also within patients according to age and organ damage), the most protective on-treatment blood pressure is probably described by several, rather than a single or few, values. Third, no data are available in patients with recent-onset diabetes with or without diabetic- or blood pressure-related complications, and thus a relatively low CV risk. In these individuals, the blood pressure treatment target may reflect the epidemiological evidence that in diabetes the lower the blood pressure, the lower the patient's CV risk. Fourth, there is evidence that, in diabetic individuals, lower blood pressure targets provide extra protection against stroke and, therefore, that an on-treatment SBP of <130 mmHg may benefit individuals with a particularly high risk of a cerebrovascular event, such as in individuals [1] with a history of stroke, in which the risk of a stroke recurrence exceeds that of a cardiac or any other vascular event [45]; or [2] receiving anticoagulant treatment, because the associated risk of intracranial bleeding is closely related to low SBP [46]. Fifth, because an aggressive blood pressure reduction has a pronounced antiproteinuric effect, this may also be the case in patients with diabetic nephropathy and a marked proteinuria, albeit under this circumstance the prognostic significance of treatment-dependent changes in this variable will need to be more consistently documented. Fifth, recent large meta-analyses of randomised outcome trials, suggest that in the general hypertensive population, an SBP reduction <130 mmHg is associated with a protective effect that extends beyond stroke and includes CV events and mortality [47, 48]. It is not immediately evident why this should not apply also to diabetic individuals, although an earlier and greater impairment of mechanisms preserving blood pressure homeostasis and vital organ perfusion might be a reasonable pathophysiological explanation [43].

A final consideration is that when setting lower blood pressure targets for diabetic individuals, with the aim of enhancing protection, practitioners should be aware that achieving blood pressure control in these individuals is more difficult than it is in non-diabetic individuals. Indeed, in many diabetes-based trials, participants have failed to reach even the conventional SBP target of <140 mmHg (Fig. 4) [49]. Furthermore, as shown in ACCORD [24], pursuing a lower SBP target implies a much larger use of antihypertensive drugs and a marked increase in serious side effects (Fig. 5). In trials as well as in real life this represents the major cause of treatment discontinuation [50, 51], leading to a marked increase in the risk of fatal and non-fatal events, and rebalancing, or perhaps even offsetting, whatever benefit a lower on-treatment blood pressure target might provide. In diabetes this may be particularly relevant because in the ADVANCE trial, treatment discontinuation was associated with an almost ten times greater risk of all-cause death compared with treatment continuation [52].

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement Both authors were responsible for drafting the article and revising it critically for important intellectual content. Both authors approved the version to be published.

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