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VIEWPOINT

The ideal blood pressure target to prevent cardiovascular disease in type 2 diabetes: A neutral viewpoint

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Abstract Type 2 diabetes mellitus (T2DM) and essential hypertension are often associated, and retrospective data analyses suggest an association between lower blood pressure (BP) values and lower cardiovascular (CV) risk in patients with T2DM. However, the most recent intervention trials fail to demonstrate a further CV risk reduction, for BP levels <130/80 mm Hg, when compared to levels <140/90 mm Hg. Moreover, a J-shaped, rather than a linear, relationship of BP reduction with incident CV events has been strongly suggested. We here debate the main available evidences for and against the concept of 'the lower the better', in the light of the main intervention trials and meta-analyses, with a particular emphasis on the targets to be pursued in elderly patients. Finally, the most recent guidelines of the scientific societies are critically discussed.

Type 2 diabetes mellitus (T2DM) and essential hypertension, two major risk factors for cardiovascular (CV) morbidity and mortality, often co-exist. European surveys report the presence of hypertension in over two-thirds of T2DM patients [1] with the diagnosis of the former often overlapping the development of hyperglycaemia [2]. Prospective longitudinal studies, such as the Framingham Heart Study and the Multiple Risk Factor Intervention Trial (MRFIT) [3,4], documented that T2DM patients have a greater risk of CV disease for a given blood pressure (BP) level, being a relevant percent of the excess CV risk in T2DM patients attributable to the presence of hypertension itself, even after controlling for other CV risk factors [5]. While diabetes magnifies CV risk, the relationship between BP and overall CV risk had a similar pattern in diabetic and non-diabetic subjects over the whole range of baseline and on-treatment BP values.

Retrospective data analyses suggest an association between lower BP values and lower CV risk in patients with T2DM. Such observation, however, is hampered by the consideration that most of the intervention trials failed to achieve mean systolic BP values <130 mm Hg. Moreover, appropriately powered prospective outcome trials show a lack of further CV risk reduction for BP levels <130/80 mm Hg when compared to levels <140/90 mm Hg. On the other hand, accumulating evidences strongly support the

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possibility of a J-shaped, rather than linear, relationship of BP reduction with incident CV events, that is, a new increase of the rate of CV events when a more pronounced reduction of BP is induced [6]. The present viewpoint summarises the most significant points of a consensus statement on BP targets in diabetes, recently endorsed by the Italian Society of Diabetology (SID), Italian Society of Nephrology (SIN) and Italian Society of Arterial Hypertension (SIIA), trying to discuss the main available evidences for and against the concept of 'the lower the better', in the light of a neutral evaluation of the main intervention trials and meta-analyses, also summarising the suggestions of the major guidelines with regard to BP targets to be pursued in T2DM patients to reduce their CV risk.

Pros: the concept of 'the lower the better'

It is a matter of fact that a careful BP control is beneficial in improving the CV prognosis in hypertensive T2DM patients, and this has been proven in several large studies. In the HOT (Hypertension Optimal Treatment) study [7], a reduction of diastolic BP $\leq$ 80 mm Hg reduces major CV events by 51% and 24% with respect to less stringent targets ($\leq$90 mm Hg and $\leq$85 mm Hg, respectively). To our knowledge, the HOT study is the only one that compares the effects of different achieved BP values in three randomised groups suggesting no evidence of a J-shaped relationship between diastolic BP and incidence of major CV events in the diabetic subgroup (as well as in the entire low-CV-risk population). These results are consistent with those of the United Kingdom Prospective Diabetes Study (UKPDS) [8], where a tight BP control is associated with a 32% reduction in deaths and 44% reduction in stroke. However, in the UKPDS trial, the BP values achieved in the 'aggressively' treated group (144/82 mm Hg) were well above the levels that are more likely to be associated to an increased CV risk by an impairment of organ perfusion, so portraying a J-shaped curve. This observation might be extended to almost all intervention trials that included subgroups of T2DM subjects. Nevertheless, the positive relationship between BP and the incidence of major CV events described in observational studies has strengthened the conviction of the need for an aggressive reduction of BP in T2DM patients over the years. An epidemiological analysis of the UKPDS has shown a 12% reduction in the risk of any complication related to diabetes, 15% for deaths related to diabetes and 11% for myocardial infarction for every 10-mm Hg decrease of systolic BP, in the absence of a threshold effect [9]. The ADVANCE (Action in Diabetes and Vascular disease, PreterAx and DiamicroN MR Controlled Evaluation) study [10], performed in >11,000 T2DM patients, has shown that the addition of a fixed combination of perindopril and indapamide to standard anti-hypertensive therapy decreases the risk of macro- or microvascular events by 8% and 9%, respectively and the risk of CV death by 18%. However, it should be stressed that in such trial, a difference of 5.6 mm Hg for systolic and of 2.2 mm Hg for diastolic BP between perindopril–indapamide and placebo arm was observed during the follow-up.

The ABCD (Appropriate Blood Pressure Control in Diabetes) study, where lower systolic BP goals were achieved, documented a lack of effect of the intensive BP control on the primary end point, but an improvement in secondary outcomes. In particular, a systolic BP of 132 mm Hg reduced the total mortality in the hypertensive ABCD study [11], and a systolic BP of 128 mm Hg reduced the incidence of stroke in the normotensive ABCD study [12]. Furthermore, the normotensive ABCD study also demonstrated an association between intensive BP control and a significant slowing of incipient and overt nephropathy progression. The Syst-Eur (Systolic Hypertension in Europe) study, showing a greater reduction in all CV events, overall mortality and mortality from CV disease for the same differences in BP in T2DM as compared to non-diabetics, has strengthened the importance of a tight BP in these individuals [13].

The relatively small SANDS (Stop Atherosclerosis in Native Diabetics Study) study, comparing the efficacy, tolerability and safety of achieving tighter BP and LDL cholesterol targets with respect to standard targets, reported a greater reduction in carotid intima-media thickness and a decrease in the left ventricular mass in the aggressively treated group, even though no difference emerged in the rate of CV events [14].

It should be emphasised that the recommendation of a more stringent BP goal in T2DM proteinuric patients seems to be supported by the strong benefits in terms of CV and renal prognosis [15]; however, the complex issue of treating hypertension in a patient with chronic kidney disease (CKD) is beyond the scope of this viewpoint.

According to the results of the above-reported trials, in 2003, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7 report) [16], recommended a BP $<$ 130/80 mm Hg in patients with T2DM and hypertension and a BP $<$ 125/75 mm Hg in those with proteinuria. The American Diabetes Association (ADA), in the 'Standards of Medical Care in Diabetes' published yearly up to 2012 [17] and other scientific associations [18,19], acknowledged this recommendation.

Contra: the concept of 'the lower the better'

In the past 5 years [20], a critical reappraisal of the stringent target BP values to be achieved in hypertensive T2DM, clearly stated by the international scientific societies, has been made mainly in the light of the fact that a target systolic BP $<$ 130 mm Hg was truly reached only in the normotensive ABCD study [12] in association with an uncertain reduction in CV events. Evidence supporting the clinical indication for an anti-hypertensive treatment in T2DM patients with high-normal BP values is even scantier [21]. Recent evidence from large intervention trials show that, in T2DM, the lowest BP values are associated with an increased rate of CV events and mortality, and this is particularly true in the elderly [22–25].

However, a recent study conducted on a very large prospective cohort of African-American and Caucasian T2DM patients has documented the presence of a J-shaped curve in the group of younger patients (below 50 years) also at a systolic BP < 130 mm Hg and at a diastolic BP < 80 mm Hg for coronary heart disease [26] and at a systolic BP < 120 mm Hg and at a diastolic BP < 70 mm Hg for stroke [27].

Even trials specifically designed to answer this crucial question does not support the recommendation of reducing systolic BP < 130 mm Hg in patients with T2DM and hypertension. In fact, in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study [28], patients randomised to intensive therapy (average achieved: 119/64 mm Hg) or standard therapy (133/70 mm Hg) [29,30], despite a difference of 14.2 mm Hg in systolic BP, did not show a reduction in the incidence of the primary end point. Intensive therapy was actually associated with a lower incidence of stroke (pre-specified secondary outcome), but with a higher rate of serious adverse events like hypotension, bradycardia, hyperkalemia and renal function impairment. In an additional analysis, it was also shown that intensive BP control did not reduce the progression of diabetic retinopathy [31]. Interestingly, although in the ACCORD study the CV event rate was similar at the achieved systolic BP of 133 and 119 mm Hg, this large difference in systolic BP values cannot exclude the possibility of a lower risk of event (and thus of a J-curve) in a third group of T2DM with on-treatment intermediate BP values.

An observational analysis of the INVEST (International Verapamil SR − Trandolapril) study, performed in T2DM patients with hypertension and CV disease, is particularly interesting because it evaluates the effect of quite low levels of systolic BP (<115 mm Hg) in 6400 patients [25]. During follow-up, the primary composite CV outcome was reached in 19.8% of the patients in the 'not-controlled' (systolic BP ≥ 140 mm Hg) group and in 12.6% and 12.7% of patients in the 'usual control' (130–139 mm Hg) and 'tight control' groups (<130 mm Hg), respectively. However, it is worth considering that mortality from all causes was marginally higher in the tight BP control group compared to the 'usual control' group, and systolic BP < 110 mm Hg was associated with significantly increased risk (hazard ratio (HR) 2.18; $p = 0.02$) of all-cause mortality. Some limitations of the study (observational analysis of a randomised controlled trial, inclusion of only patients with coronary disease and division of the groups on the basis of the BP values reached) suggest caution in the interpretation of these data. In the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study, a *post hoc* analysis of the incidence of CV events in relation to the levels of BP reached with treatment was performed in the T2DM patients subgroup [24]. A clear-cut CV benefit of BP reduction was observed only when the baseline systolic BP was >140 mm Hg, while in patients whose baseline systolic BP was about 130 mm Hg or lower, the advantage was less marked and became evident only for stroke. Moreover, the risk of stroke showed a clear-cut relationship with systolic BP over a wide range of in-treatment values, continuing to go down to achieved systolic BP of 115 mm Hg, with no evidence of an upward J-curve inflection. On the other hand, the relationship of systolic BP with myocardial infarction and CV death was flat over a wide range of on-treatment values with untoward cardiac effects with the more aggressive BP reductions.

Similar observations, even though supported by less clinical evidence, can be performed for diastolic BP also. In the ONTARGET study, regardless of the in-treatment systolic BP, low achieved diastolic BP levels were associated with lower risk of stroke and higher risk for the primary outcome and myocardial infarction [24]. Similarly, the VADT (Veterans Affairs Diabetes Trial) study has shown an increased risk of CV events in patients with T2DM and a diastolic BP < 70 mm Hg, even in the presence of a target systolic BP value of 130 mm Hg [22].

This debated and hot topic has been evaluated in the past years even through several meta-analyses. Bangalore et al. [32] included 13 randomised clinical trials comparing levels of systolic BP < 130, 135 and 140 mm Hg in 37,736 patients with T2DM or impaired fasting glucose/impaired glucose tolerance. They showed that systolic BP values <130 mm Hg were associated with a greater reduction in the incidence of stroke, but not of other major CV events, in the face of a 40% increased frequency of adverse events. By contrast, systolic BP levels <135 mm Hg were associated with a reduced mortality, acknowledging a therapeutic systolic BP target of 130–135 mm Hg. The meta-analysis by Reboldi et al. [33], which includes 73,913 patients with diabetes randomised in 31 intervention trials, confirmed that decreasing BP levels are associated with an increased benefit in terms of incidence of stroke (reduction by 13% for each 5-mm Hg reduction in systolic BP and by 11.5% for each 2-mm Hg reduction in diastolic BP), but not of myocardial infarction. Similarly, a more recent meta-analysis of randomised clinical trials performed in patients with T2DM and comparing pre-specified BP targets (intensive, <130/80 vs. standard <140–160/85–100 mm Hg) did not show any significant reduction in mortality or incidence of non-fatal myocardial infarction, but only with a small reduction in the relative risk of stroke in subjects with lower BP values [34].

Indeed, in high-risk patients, therapeutic regimens that reduce systolic BP to values close to or <120–125 mm Hg and diastolic BP < 70–75 mm Hg could induce an increase (rather than a further reduction) in the incidence of major CV events, likely as a result of the hypoperfusion of vital organs (J-shaped curve phenomenon) [20]. An alteration of the mechanisms that ensure the autoregulation of the blood flow could increase the BP threshold at which hypoperfusion occurs in high-risk patients [35,36]. Furthermore, the relationship between BP levels and rate of CV events is linear when CV events are quantified on a logarithmic scale [37], implying lower absolute differences for gradients in the low-BP range. However, the apparently opposed effects of intensive BP controls on the risk of myocardial infarction and stroke are interesting and not entirely unexpected. In fact, while the excessive reduction

of systolic BP in patients with prior coronary disease may be associated with an increased risk of myocardial infarction secondary to hypoperfusion [38], the most efficient cerebral autoregulation allows an adequate perfusion even in the presence of the lowest BP values [39]. This hypothesis is confirmed by the results of PROGRESS (Perindopril Protection Against Recurrent Stroke Study) showing, in stroke survivors, a progressive reduction of recurrent ischaemic strokes and haemorrhages due to systolic BP $<$ 115 mm Hg, with no evidence of a 'J-shaped curve phenomenon' [40].

A point recently deserving attention and still needing to be clarified concerns the role of an early, rather than too stringent, BP control on the occurrence of major CV events in T2DM patients at relatively low CV risk, that is, those with newly diagnosed arterial hypertension with no coronary or cerebrovascular disease. A cluster-randomised Danish trial treated all the CV risk factors, including hypertension, intensively or conventionally by a multifactorial approach co-existing in a group of screening-diagnosed T2DM patients; such early intensive management was associated with a small, non-significant reduction in the incidence of CV events and all-cause mortality [2]. More recently, an interesting, although retrospective, study examined whether a proper control of BP within 1 year from the onset of hypertension would predict the subsequent onset of CV disease. Baseline BP was 136.8/80.8 mm Hg, and after 1 year it decreased to 131.4/78.0 mm Hg ($<$130/80 mm Hg in 32.9% of patients and $<$140/90 mm Hg in 80.2%). During the 3.2-year-follow-up, the age-adjusted rate of major CV events was significantly higher in patients with mean 1-year BP $\geq$ 140/90 mm Hg after the onset of hypertension, underlining the likelihood of patients with inadequate BP control within 1 year from hypertension onset to have major CV events within a relatively short time [41].

Desirable BP values in the elderly T2DM patients to reduce CV risk

In discussing the ideal BP targets in elderly T2DM patients, it should be noted that diagnosis of hypertension itself can be problematic in these subjects, and the use of the common criteria to define a patient as hypertensive may not be appropriate in all ageing individuals. Data from the Framingham study suggest that the threshold systolic BP which marks an increase of mortality rises with increasing age [42]: in men aged 45–54 years, this threshold is approximately 140 mm Hg, whereas in those between 65 and 74 years it is about 160 mm Hg; according to these data, a safe threshold for men aged over 75 years could be even higher. These considerations are supported by the results of some observational studies, such as the ZODIAC-12 (Zwolle Outpatient Diabetes project Integrating Available Care) and the Botnia Study [43,44], where an inverse relationship was found between mortality and systolic and diastolic BP in elderly T2DM patients, probably because of co-morbidity and/or an excessive BP reduction in a particularly frail category of patients, mainly those with previous CV disease.

No randomised controlled studies investigating the effects of anti-hypertensive treatment in T2DM patients older than 75 years are so far available, making the evidence of the opportunity to reach a target systolic BP $<$ 140 mm Hg in the elderly inconsistent. Some information comes from the analysis of the small subsets of T2DM participants in large trials. The HYVET (Hypertension in the Very Elderly Trial) trial (7% of the enrolled individuals affected by T2DM) investigated the effect of BP reduction on CV events in people aged over 80 years [45]. After the 2-year-follow-up, 48% of actively treated patients achieved an average systolic BP of 143 mm Hg, showing a 21% reduction in mortality from all causes as well as CV morbidity and mortality; in particular, fatal or non-fatal stroke was reduced by 30%, death from stroke by 39%, CV death by 23% and heart failure by 64%. In the SHEP (Systolic Hypertension in the Elderly Program) study carried out in patients aged 60–90 years (10% of the study population had T2DM), subjects achieving a systolic BP $<$ 160 mm Hg had a 33% reduction in stroke; a further 5% reduction was achieved in patients with systolic BP $<$ 150 mm Hg with no additional benefits for further BP reduction [46]. The Japanese, prospective and randomised JATOS (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients) study (65–85 years old, 8% had T2DM) has shown that reducing systolic BP $<$ 140 mm Hg does not determine any benefit in terms of mortality and CV and renal events compared to a systolic BP $<$ 160 mm Hg [47].

The results of the ADVANCE trial [48] appear to be at odds with the above-reported studies, given the very low mortality rate reported in the ageing population in ADVANCE. It has been emphasised, however, that clinical characteristics of such cohorts are not representative of the real-life elderly T2DM population [49], and the same authors concluded that, until convincing evidence are not available, a cautious approach is required in setting a target BP for elderly T2DM patients; a more conservative strategy in such peculiar patients may be appropriate [49].

Which is the present position of the scientific societies?

In the light of the available data of clinical trials aiming at achieving progressively lower BP targets, which suggest a flattening of the BP–CV risk curve, several scientific associations in the most recent guidelines suggest less ambitious BP targets in T2DM patients, especially in the elderly.

The International Diabetes Federation (IDF), in the 'Global Guideline for Type 2 Diabetes' of 2012, recommended to start an anti-hypertensive treatment when BP is constantly $>$130/80 mm Hg, with the objective of maintaining the BP values $\leq$130/80 mm Hg if the therapy is well tolerated. The IDF emphasises the need to make the goals less stringent if there is a significant risk of postural hypotension and falls. Furthermore, caution is advised in the administration of aggressive therapeutic strategies for reducing BP in the elderly: in patients between 70 and 80 years, the treatment should be started when the BP is consistently $\geq$140/90 mm Hg, pursuing a target BP $<$ 140/

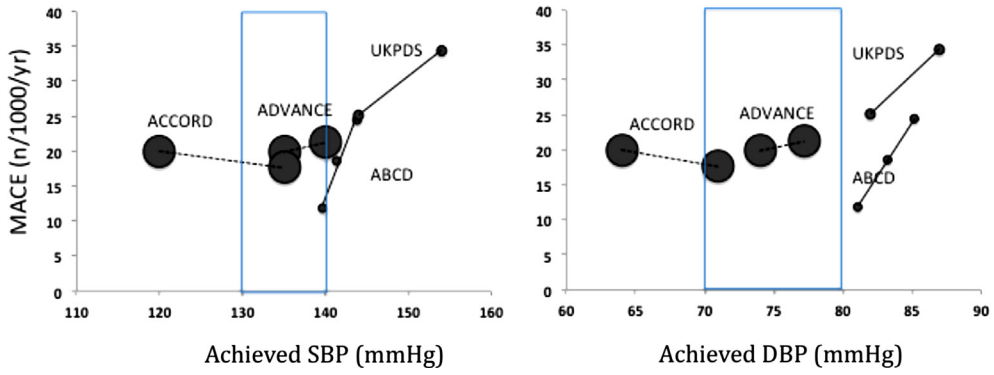

Figure 1 Upper and lower limits of achieved systolic and diastolic blood pressure (SBP, DBP) in intervention trials, and Major Adverse Cardiac Events (MACE).

90 mm Hg. In patients over 80 years of age, the treatment must be started if the BP is consistently ≥150/90 mm Hg and the target BP should be < 150/90 mm Hg [50].

Interestingly, in 2011, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published a consensus document on hypertension in the elderly [51] that, extending the same target recommended for all diabetic individuals to the elderly T2DM patients, recommends a BP target of 140/90 mm Hg in T2DM patients with uncomplicated hypertension and suggests a target of 130/80 mm Hg only if well tolerated. However, such indications were rather based on expert opinions than on data from randomised clinical trials; in addition, it is unclear whether the target systolic BP should be the same in patients aged 65–79 years compared to older patients.

Very recently, the IDF has published the 'Managing Older People with Type 2 Diabetes' global guidelines [52] that essentially followed the launch of the IDF 2012 document [50]. This guideline was developed to address treatment decisions in older people. A diagnosis of hypertension is established by reporting a systolic BP ≥ 140 mm Hg and/or a diastolic BP ≥ 90 mm Hg on at least two occasions. Functionally independent individuals (category 1) should be managed to achieve a target BP of <140/90 mm Hg. In functionally dependent subjects (category 2), caregivers have to arrange a safe administration of a BP-lowering therapy with a target BP of up to 150/90 mm Hg in frail individuals (sub-category A), while a target of 140/90 mm Hg should be pursued in individuals with cognitive impairment or dementia (sub-category B). Finally, unless BP readings are immediately life-threatening, strict BP control may not be necessary at the end-of-life care (category 3) and withdrawal of BP-lowering agents may be appropriate [52].

The ADA, in the 'Standards of Medical Care in Diabetes – 2013' [53], changed the target BP from <130/80 mm Hg[8] to <140 mm Hg for systolic BP, indicating that a lower target (<130 mm Hg) may be appropriate for some individuals (younger patients), if this can be achieved without additional charges. The objective of diastolic BP < 80 mm Hg was unchanged. No specific different objectives were recommended in the elderly, and writers of the recommendations stated that "there is strong evidence from clinical trials of the value of treating hypertension in the elderly."

The Italian Standards for Diabetes Mellitus 2009–2010 recommended a BP goal <130/80 mm Hg and agree on a target BP < 140/80 mm Hg to be pursued if well tolerated in elderly patients, specifying that a further BP decrease (<130/80 mm Hg) could imply an additional benefit. However, as elderly subjects may show a low tolerance to a very rapid BP reduction, the anti-hypertensive treatment should be gradually initiated and carefully titrated [18].

The NICE (UK National Institute for Health and Clinical Excellence) guidelines suggest a target BP < 140/90 mm Hg for T2DM patients and also for those aged under 80 years, and a target <150/90 mm Hg for those aged over 80 [54]. The American Association of Clinical Endocrinologists (AACE) in its 'Comprehensive Diabetes Management Algorithm 2013 Consensus Statement' recommends a BP target of approximately 130/80 mm Hg, largely based on results of the ACCORD-BP trial [28] and the Bangalore meta-analysis [32]; however, patients at high risk of stroke may benefit from a lower target [55].

Such a relatively more conservative approach is also mostly shared by the guidelines from the main societies of cardiology.

The 2009 reappraisal of guidelines of the European Society of Hypertension (ESH), considering the difficulties in reaching systolic BP values of <130 mm Hg in T2DM patients, recommended to start an anti-hypertensive treatment when BP values are confirmed ≥140/90 mm Hg. The beginning of treatment with high-normal BP values (systolic BP 130–139 mm Hg or diastolic BP 85–89 mm Hg), although currently not sufficiently supported by evidence, can be recommended in cases of microalbuminuria/proteinuria [20]. The new guidelines of the ESH/ESC (European Society of Cardiology), published a few months ago, confirm the ADA recommendation of a systolic BP target <140 mm Hg in patients with T2DM, however, suggesting a different target for diastolic BP, that is, <85 mm Hg [56]. The recent 'ESC Guidelines on diabetes, pre-diabetes, and CV diseases developed in collaboration with the EASD' (European Association for the Study of Diabetes) stated that evidences make it

reasonable to reduce BP in patients with T2DM to <140/85 mm Hg, while noting that further reduction in BP might be associated with an increased risk of serious adverse events, especially in the presence of advanced age or long duration of diabetes. The risks and benefits of a more intensive BP management need to be carefully considered on an individual basis [57]. The 2013 Canadian Guidelines on Hypertension recommend, in people with diabetes mellitus, targets of systolic BP < 130 mm Hg and diastolic BP < 80 mm Hg, advising caution in patients in whom a marked reduction in BP is more likely to be poorly tolerated (e.g., elderly individuals and patients with autonomic neuropathy) [58].

The JNC 7[16] recommended <140/90 mm Hg overall and <130/80 mm Hg in the presence of diabetes, heart failure or CKD. The JNC 8 has finally released its new guidelines on the management of adult hypertension [59]. The expert writing group recommends a relaxing of the more aggressive JNC 7 target BP, with higher thresholds for treatment initiation in the elderly and in patients under the age of 60 years with diabetes and kidney disease. Thus, very simply, in patients ≥60 years, treatment has to be started if systolic BP ≥ 150 mm Hg or diastolic BP ≥ 90 mm Hg, trying to keep BP values below these thresholds. In patients <60 years, treatment initiation and goals should be 140/90 mm Hg; the same threshold should be used in patients ≥18 years with either CKD or diabetes.

Conclusions

The analysis of the most recent data of the literature suggests that, in order to reduce CV morbidity and mortality in patients with T2DM, the benefits of the BP reduction to particularly low values are few and unconvincing; by contrast, a rapid reduction of BP may be dangerous to the frailest patients. International guidelines acknowledge a more prudent approach in suggesting BP targets, even though the BP values that should not be overcome are not always clearly indicated. As illustrated in Fig. 1, these limits could be empirically identified as 130/70 mm Hg. In addition, although the upper diastolic BP target remains a matter of debate, the balance of evidence supports the value of 80 mm Hg. BP levels <130/70 mm Hg may be appropriate in selected T2DM patients at an increased risk of stroke, considering, however, the difficult identification of this 'high risk' category. Despite not determining a univocal target BP, the results of the studies on elderly patients with T2DM and hypertension imply some important considerations: mainly, the need to adapt the therapeutic strategy to the vast heterogeneity of the patients and their co-morbidities, and the possible different impact on CV outcomes of a same pressure value, achieved without the administration of pharmacological interventions that do not always entail beneficial effects [38]. Therefore, in vulnerable individuals, such as elderly T2DM patients, either with coronary artery disease, orthostatic hypotension and/or at risk of dehydration and acute renal failure, where appropriate, randomised clinical trials are lacking, a less aggressive, higher BP target (<140/90) should be considered. It is a matter of fact that in T2DM hypertensive patients, it is still currently necessary to collect further data from randomised prospective and controlled trials to possibly recommend more ambitious BP targets than those proposed by existing guidelines. Likely these highly hoped studies might allow future guidelines to take into due account the target organ heterogeneity emerging from meta-analyses in balance against the increased risk of serious adverse events. Furthermore, the most recent literature suggests shifting the attention from the 'target pressure' to the 'point in time' in which this target BP should be reached: beyond the therapeutic objective, a timely diagnosis of hypertension aimed at an equally timely achievement of BP recommended targets seems to gain particular importance.

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