

MANAGEMENT PERSPECTIVE

Should diabetic blood pressure targets be the same in elderly compared with younger patients?



Claudio Borghi*¹ & Alessandra Pavesi²

Practice Points

- This article analyzes the association between the contemporary presence of diabetes mellitus and hypertension, and the increased risk of major cardiovascular and renal complications.
- Blood pressure targets for diabetic patients have been indicated in the European Society of Hypertension (ESH), the European Society of Cardiology (ESC) and NICE guidelines.
- The association of hypertension and diabetes mellitus is a considerable burden in elderly patients.
- Elderly patients have additional characteristics compared with younger people (e.g., frailty and a high number of comorbidities).
- The therapeutic approach and goals should be different in the elderly, as they change according to the different age level reached by the elderly patients and their general health state.

SUMMARY The association between hypertension and diabetes mellitus increases the risk of major cardiovascular and renal complications. The guidelines on hypertension recommend a specific blood pressure (BP) target for diabetic patients as a preventive strategy that favorably affects the burden of cardiovascular diseases in patients with hypertension and diabetes. The prevalence of the association between hypertension and diabetes mellitus increases with age. At present, it is still unclear what should be the optimal BP target for the elderly with diabetes mellitus. In this review we have considered the literature available to date and the particular characteristics of the elderly population. We propose that the BP target for the oldest old should be higher compared with the BP target for younger people.

Diabetes mellitus–hypertension association & the increased risk of major cardiovascular & renal complications

Hypertension and diabetes are two of the most important risk factors for cardiovascular (CV) disease and they are individually responsible for a significant increase in the risk of major CV and renal complications [1,2]. In particular, according to the results of several epidemiological surveys,

the incidence of hypertension is significantly increased in the diabetic population [3,4], while the presence of glucose abnormalities is largely increased in the presence of elevated blood pressure (BP). This clearly supports the importance of the application of effective preventive strategies that favorably affect the burden of CV diseases in patients with hypertension and diabetes. Moreover, hypertension and diabetes prevalence

¹Dipartimento di Scienze Mediche & Chirurgiche, Via Massarenti, n.9 40138, Bologna, Italy

²Via Pelagio Palagi, n.15 40138, Bologna, Italy

*Author for correspondence: Tel.: +39 051 636 2848; Fax: +39 051 391 320; claudio.borghi@unibo.it

increase with aging, and this promotes their role as CV risk factors in elderly patients.

It should also be taken into account that the elderly have peculiar characteristics compared with younger patients, such as frailer health, a higher number of comorbidities and a poorer compliance to treatment. For these reasons, the management and therapeutic targets of the elderly should be different from those of younger patients.

BP targets for diabetic patients indicated in European Society of Hypertension & European Society of Cardiology guidelines

Several studies have demonstrated that intensive control of BP is associated with a reduction of CV events [5–7]. The 2007 European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) guidelines have established a BP target <130/80 mmHg (if tolerated) for patients with diabetes mellitus of either type. Moreover, they suggest starting the antihypertensive treatment when BP values are in the high normal range and in the presence of microalbuminuria, has a protective effect on the appearance and progression of renal damage [8].

However, a reappraisal of European guidelines on hypertension management [9] brings the target indicated in the guidelines into question; they show both that there is little evidence supporting the start of BP-lowering therapy in diabetic patients with high normal BP and that the evidence favoring a systolic BP (SBP) target below 130 mmHg are almost nonexistent [10]. The results of a recent study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) group show that in patients with Type 2 diabetes at high risk for CV events, reaching a SBP target <120 mmHg compared with reaching a <140 mmHg target did not

reduce the rate of a composite outcome of fatal and nonfatal major CV events [11]. Moreover, in the majority of the patients it is very difficult to obtain a BP control <130/80 mmHg, so it would be more realistic to recommend a consistent BP reduction without fixing a target that, in any case, is not supported by evidence [12].

BP targets for diabetic patients indicated in NICE guidelines

The recent NICE guidelines regarding management of Type 1 diabetes in children, young people and adults recommend a BP target of 135/85 mmHg [13]. The target should be lower (130/80 mmHg) in diabetic patients with an abnormal albumin excretion rate or two or more features of the metabolic syndrome.

The NICE clinical guidelines on Type 2 diabetes underline that different studies show that an association between low BP values and a lower incidence of CV events exist, but no clear BP threshold has been indentified as a potential therapeutic target [14]. The BP reduction should not be excessive because it could be correlated to an enhancement of adverse effects.

In fact, in patients with diabetic nephropathy, as those of the IDNT study [15], a tight reduction of SBP (<120 mmHg) was associated with an increase of CV mortality and congestive heart failure; moreover, it was highlighted that a mean diastolic BP (DBP) reduction of 10 mmHg was correlated to an increased risk of myocardial infarction and stroke (Table 1) [14].

In addition, it has been established that, in diabetic patients with high BP values, the decline in renal function is more rapid than in those with lower BP values [16–18].

Assigning BP-lowering targets in patients with Type 2 diabetes may be problematic for different reasons. First, it is not clear how to

Table 1. Post hoc analysis of the IDNT study.

CV outcome	Size effect
CV mortality	A decrease in risk was observed when SBP decreased from >170 to 120–130 mmHg. In this range, a 20-mmHg lower SBP was associated with a 39% reduction in CV mortality; p < 0.002. An SBP ≤120 mmHg showed a significantly greater risk of CV mortality compared with those with an SBP >120 mmHg; RR: 4.06 (95% CI: 2.11–7.80); p<0.0001
CHF	A decrease in risk was observed when SBP decreased from >170 to 120–130 mmHg. In this range, a 20-mmHg lower SBP was associated with a 39% reduction in CHF; p = 0.001. Those with an SBP ≤120 mmHg had a significantly greater risk of CHF than those with an SBP >120 mmHg; RR: 1.80 (95% CI: 1.17–2.86); p = 0.008
MI	A 10-mmHg lower mean DBP was associated with a significantly higher risk of MI; RR: 1.61 (95% CI: 1.28–2.02); p < 0.0001
Stroke	A 10-mmHg lower mean achieved DBP was associated with a significantly lower risk of stroke; RR: 0.65 (95% CI: 0.48–0.88); p = 0.005

CHF: Congestive heart failure; CV: Cardiovascular; DBP: Diastolic blood pressure; MI: Myocardial infarction; RR: Risk ratio; SBP: Systolic blood pressure. Reproduced with permission from [14].

define a cut-off where the benefits of anti-hypertensive therapy exceed the related adverse effects. Second, patients' heterogeneity determines that, in some people, achieving any reasonable target could be difficult. Moreover, the target level should be determined by the individual risk. According to the NICE guidelines, a target level of <140/80 mmHg is recommended for most people with Type 2 diabetes, while patients at a higher risk should achieve a BP threshold <130/80 mmHg [14]. The group of patients at a higher risk include people with a raised albumin excretion rate (micro-albuminuria or worse), estimated glomerular filtration rate <60 ml/min/1.73 m², those with retinopathy, and those with prior stroke or transient ischemic attack.

Prevalence & burden of the association of hypertension & diabetes mellitus in elderly patients

Currently, an interesting discussion topic is defining whether diabetic BP targets should be the same in elderly compared with younger patients.

The most common form of diabetes in the elderly is Type 2, which occurs approximately ten- to 20-times more frequently than insulin-dependent Type 1 diabetes. In elderly diabetic patients, the prevalence of hypertension is up to 70–80%; in fact, hypertension is well recognized as an insulin-resistant state [4]. Elderly patients with hypertension and diabetes mellitus have a higher mortality risk than similarly aged controls without diabetes mellitus [19].

Analysis of previous studies concerning elderly people with diabetes mellitus & hypertension

People over 65 years of age are considered elderly. The elderly classification defines three categories: 'young old' for the subjects younger than 75 years, 'old' for those with an age between 76 and 80 years and 'oldest old' for those over 80 years; therefore, the therapeutic approach and goals change according to the different age levels reached by the old patients. The oldest old can be included in a special category, and the possible positive outcomes obtainable with antihypertensive treatment in people older than 80 years has often been discussed. Data from the HYVET study underline that the reduction of BP values resulting from a pharmacological therapy is associated with a reduction of CV events and a

prolongation of life, even in patients over 80 years [20]. Based on these results, antihypertensive treatment has been extended to hypertensive patients aged 80 years and above, fixing a higher BP target, which includes values up to 150 mmHg. For patients under 80 years, guidelines have established a BP target <140/90 mmHg [8,13]. Furthermore, it is evident that the oldest old hypertensive patients with diabetes mellitus are a subgroup with special features. In the HYVET study, diabetic patients only represent 7% of the entire group. Unfortunately, a separated analysis of the patients with diabetes has not been published.

More specific data concerning elderly patients with diabetes and hypertension can be found in a data analysis of the ADVANCE study [7]. The aim of this analysis was to evaluate the association between age and risk of CV disease, and to compare the efficacy and safety of routine BP lowering through the fixed combination of perindopril and indapamide for the prevention of major clinical outcomes in subgroups of patients aged below 65, 65–74 and 75 years or older with Type 2 diabetes. The results of this analysis show that there are no significant differences in treatment effects of routine BP lowering using a fixed combination of perindopril and indapamide on the relative risk of CV events, renal events and mortality among participants in the ADVANCE trial aged below 65, 65–74 and 75 years or older. The mean SBP or DBP levels achieved over time in the active treatment groups were 133/77, 135/74 and 137/72 mmHg, respectively. The older age group had greater absolute benefits compared with the younger age group, suggesting that routine treatment with perindopril and indapamide can be recommended for older patients with Type 2 diabetes.

In contrast with the ADVANCE study, Botnia and Zodiac studies led to different conclusions.

Botnia is a prospective observational study that investigated the relationship between different BP indices and all-cause and CV mortality in an average follow-up of 9.5 years of a cohort of Type 2 diabetic patients who had a median age of 69.1 years at baseline [21]. The results of this study show that a low BP is associated with poor survival in Type 2 diabetic patients with a history of previous CV diseases. By contrast, the association between lower BP values and an increased mortality is not as evident in the group without previous CV diseases (Figure 1).

The prospective observational Zodiac study underlined the correlation between a lower BP

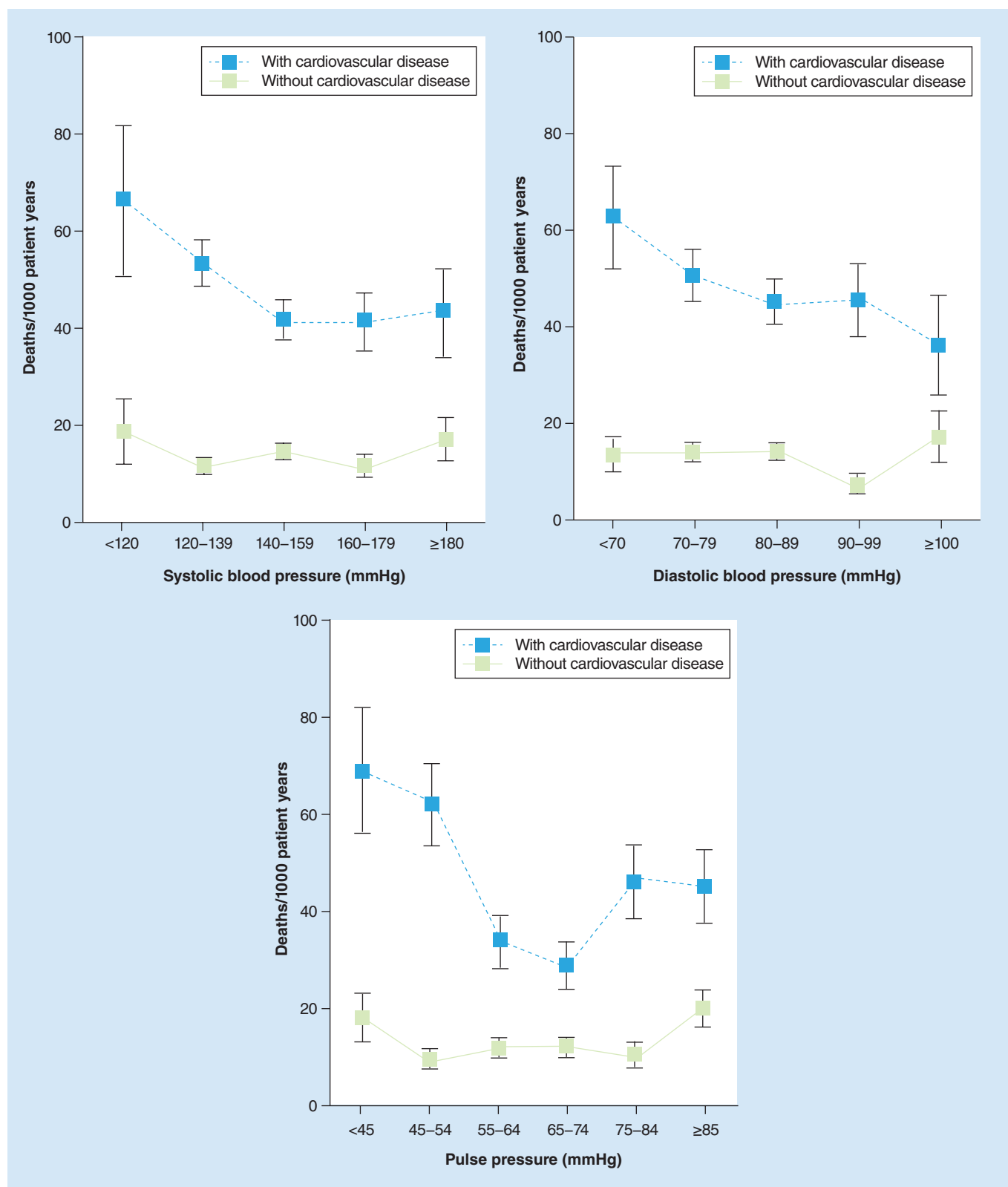


Figure 1. Cardiovascular mortality in patients with and without previous cardiovascular disease in relation to age- and gender-adjusted blood pressure indices. Error bars represent 95% CIs. Reproduced with permission from [21].

and a higher mortality in elderly diabetic patients (>75 years) who were using antihypertensive medication at baseline during an average follow-up of 9.8 years [22]. A 10 mmHg lower level of SBP, DBP and pulse pressure was associated with a higher mortality (20, 26 and 20%, respectively). It is interesting to highlight that these relationships were not present in the elderly patients who did not take antihypertensive drugs at baseline. Another remarkable finding was the absence of a correlation between BP and mortality in the lower age group (60–75 years) (Figure 2).

A recent study compared the clinical characteristics of ADVANCE patients aged more than 75 years with the patients enrolled in the Zodiac study. This analysis suggests that elderly patients included in the ADVANCE study do not represent the general diabetic population; therefore, it is quite difficult to translate the results of this study into daily practice, especially given the heterogeneous status of elderly patients [23].

Unfortunately, to date, there are not enough studies about this topic, and the results are not aligned. Therefore, to better define the treatment and BP target in the hypertensive elderly patients with diabetes, especially the oldest old, more randomized controlled trials or meta-analyses concerning this specific population are necessary.

Conclusion & future perspective

So what is the best treatment approach and BP target in this special category of patients in clinical practice?

First, it is essential to remember that elderly adults have functional and medical heterogeneity: some subjects are physically and cognitively robust, while others are frail, have a reduced functionality or have multiple comorbidities. For this reason, an important bias of the HYVET study [20] has to be underlined; even if it has been very important for the change in the therapeutic approach towards the very elderly patients, this study only considered elderly subjects in good physical condition and without CV disease, while excluding ill and frail individuals who are very frequent among the oldest old. The HYVET patients did not have orthostatic hypotension and this confirms that the individuals enrolled were particularly healthy. Therefore, the results from this study cannot be generalized and, considering the differences in the general health of very elderly patients, the decision to treat should be taken on an individual basis [24].

A recent study has underlined that the association between elevated BP and a higher mortality risk was present only among the subjects

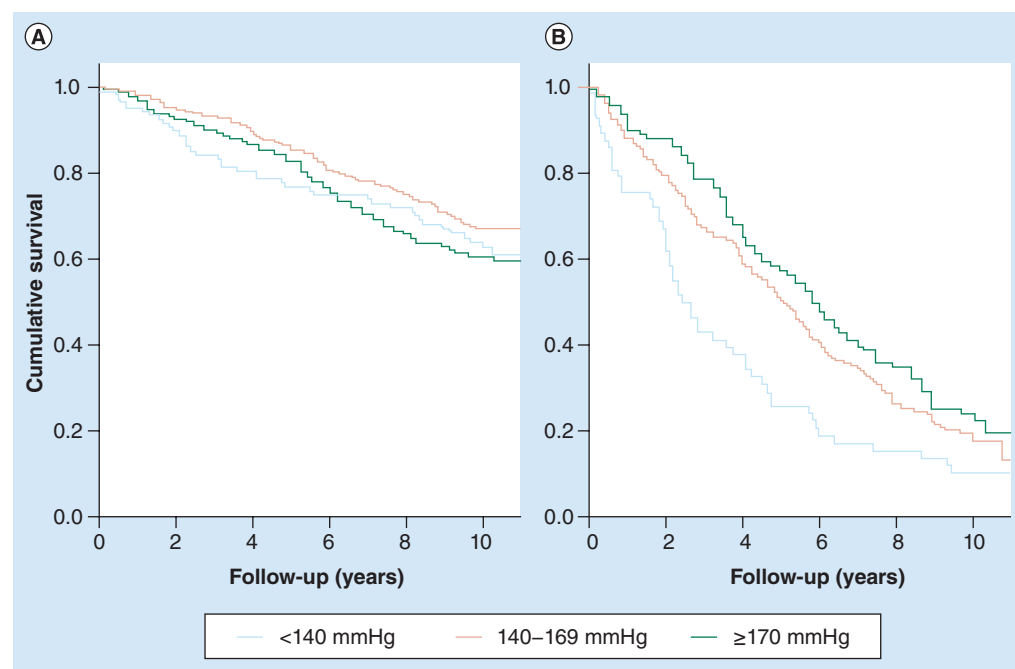


Figure 2. Kaplan–Meier curves for systolic blood pressure and all-cause mortality. Data are presented for the (A) low (60–75 years) and (B) high (>75 years) age groups. Reproduced with permission from [22].

classified as ‘less frail’, and not among those classified as ‘frailer’. The patient’s frailty was based on walking speed. This study suggests that the decision to treat should be influenced by the evaluation of the general health state of the patient [25].

Maintaining a BP control in the diabetic elderly might be useful to reduce the incidence of CV events and organ damage, but it is important to take into account the general health state, eventual comorbidities and the age of the patient [24]. Concerning the patient’s age, a recent study has emphasized that the oldest old with a previous progressive decrease of SBP aged between 85 and 90 years show a higher risk of all-cause mortality [26].

Antihypertensive treatment in elderly people should be gradual and not too aggressive, especially in the oldest old. It is important to keep in mind that obtaining a significant SBP reduction in the elderly could be very difficult since the high SBP values are a consequence of an anatomic alteration, which involves big arterial vessels [27,28].

Some studies of elderly diabetic patients with isolated SBP have shown that antihypertensive therapy reduces the incidence of CV events [29,30]. However, since myocardial perfusion occurs mainly in diastole, in the elderly, low levels of DBP might compromise the coronary flow and myocardial perfusion, especially in patients who have coronary heart disease. Moreover, some studies have shown that DBP values are inversely proportional to the incidence of coronary events [31,32]. For this reason, antihypertensive therapy should not be too aggressive.

Furthermore, with aging, the baroreflex function is reduced and venous insufficiency is increased [33]; for these reasons the prevalence of orthostatic hypotension in the elderly is high, especially for diabetics patients [34]. A BP target that is too low would increase the incidence of orthostatic hypotension, which is a risk for CV events, as well as falls and syncope [35,36].

In conclusion, considering the available literature results, we can suggest that in patients younger than 75 years, with a good general state of health, the BP target could be the same as for the younger subjects. For people aged over 75 years, the BP target should be higher, but more randomized controlled trial or meta-analyses concerning this specific group of patients are needed to define it exactly. Our clinical experience highlights that BP target determination should be influenced by the patient’s clinical conditions, especially in the oldest old. Frail health, a high number of comorbidities, orthostatic hypotension, previous CV events, resistant hypertension and poor compliance with therapy could lead to higher threshold levels; therefore, a 150/90 mmHg BP target could be acceptable.

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