Optimal blood pressure targets in 2014 – Does the guideline recommendation match the evidence base?

C.L. Alviar\textsuperscript{a}, S. Bangalore\textsuperscript{a}, F.H. Messerli\textsuperscript{b,}\textsuperscript{*}

\textsuperscript{a} New York University Langone Medical Center, New York, NY, United States
\textsuperscript{b} Mount Sinai Health System, New York, NY, United States

Received 2 March 2015; accepted 2 March 2015
Available online 25 March 2015

Abstract Various scientific societies have recently published practice guidelines for the diagnosis and management of arterial hypertension with no clear consensus on a blood pressure target. This article reviews those recommendations and critically examines if they are based on sound evidence.

© 2015 SEHLELHA. Published by Elsevier España, S.L.U. All rights reserved.

Introduction

In the recent years, various scientific societies have published practice guidelines for the diagnosis and management of arterial hypertension.\textsuperscript{1-3} However, there appears to be no clear consensus on a BP target, highlighting that the “one size fits all” approach is probably not appropriate. Our aim is to review the recommendation regarding blood pressure targets by various national and international hypertension societies and to critically examine whether these recommendations are based on sound evidence.

Guideline recommendations for specific blood pressure targets

Blood pressure targets by major national and international societies are summarized in Table 1.
American guidelines

2014 evidence-based guideline for the management of high blood pressure in adults (from the panel members of the Joint National Committee 8)

Historically, the Joint National Committee (JNC) has had a more aggressive approach for BP targets. The JNC 7, published in 2003, introduced the concept of pre-hypertension as a new subset of patients in whom lifestyle modification and close follow-up may be beneficial. The next iteration of the JNC-7 termed the 2014 Evidence-Based Guideline for the Management of High Blood Pressure recommends systolic blood pressure (SBP) ≥150 mmHg or diastolic blood pressure (DBP) ≥90 mmHg to start pharmacologic treatment in the general population 60 years or older, a departure from prior JNC and other major guideline society recommendations. In addition, the guidelines recommend a target of <150/90 mmHg for this age group, which is a departure from prior JNC as well as other guideline society recommendations. For subjects between 30–59 years of age, the recommended target is <140/90 mmHg. The target of <140/90 mmHg is also recommended for patients with CKD or diabetes.

Despite the above, the 2014 guidelines are controversial since there is no unanimity among members of the group especially with regards to the target SBP of <150 mmHg in patients 60 years or older. The reasons for such disagreement were based on several factors. First, the fact that setting a higher target might reduce the intensity of treatment in a significant group of patients at risk of cardiovascular disease. Second, the evidence to support the target of <150 mmHg is weak at best. Finally, the potential of reversing the decade-long progress in reducing cardiovascular disease mortality, in particular stroke mortality, raised concerns among these members of the panel who did not endorse this goal.

Scientific advisory from the American Heart Association/American College of Cardiology/Centers for Disease Control

The purpose of the scientific advisory was to describe the value of treatment algorithm and its utility in approaching hypertensive patients based on the current guidelines, more than exploring the available evidence in diagnostic and therapeutic targets. However, they recommend a target BP >140/90 mmHg to start treatment for hypertensive adults while at the same time recognizing that different targets might be appropriate for certain populations, including African-Americans, elderly subjects or patients with systolic/diastolic dysfunction, diabetes or CKD, but without providing evidence nor specific targets for these subgroups.

American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on lifestyle management

Another US guideline that discusses hypertension management is the AHA/ACC Guidelines on Lifestyle Management to reduce cardiovascular risk published in 2013. This provides a more general recommendation, without specific BP targets. The guideline recommends specific dietary measures if SBP ranges between 120 to 159 and DBP between 80 and 95 mmHg in adults with hypertension.
American Society of Hypertension (ASH)/International Society of Hypertension (ISH)

The ASH/ISH guidelines for the management of hypertension in the community that was published in 2013 have set similar BP targets as that of other societies with a general BP target of <140/90 mmHg while acknowledging the lack of evidence to support lower BP targets. For subjects 80 and older a target of <150/90 for stroke protection is recommended. On the other hand the guidelines state that there is significant lack of evidence about BP targets in subjects younger than 50 years, but state that it would be reasonable to achieve a DBP < 90 mmHg as diastolic BP is considered important in this group but no specific evidence is cited for this particular recommendation. Of note they state that some experts recommend a goal of <130/80 mmHg for patients with chronic kidney disease and microalbuminuria.

European guidelines

European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines

The 2013 ESC/ESH guidelines have published their recommendations for hypertensive patients according to the risk profile. For the low to moderate risk category their recommendations are based on three trials that demonstrated that a target SBP of <140 mmHg was associated with a reduction in cardiovascular events. For elderly hypertensive patients the ESC guidelines recommend a SBP between 140 and 150 mmHg. However, the level of evidence supporting this recommendation varies according to the age. For instance, for elderly hypertensives who are <80 years this is a class 1 recommendation, level of evidence A, whereas for >80 years this is a class 1 recommendation, level of evidence B. The ESC/ESH guidelines state that if the patient is considered fit and is able to tolerate medications a SBP <140 mmHg might be considered, however, this recommendation is not based on randomized evidence (Class Ib, level of evidence C). For DBP, the guideline committee recommends a target of <90 mmHg for all patients, except in diabetics where the target DBP is <85 mmHg, while <80 mmHg might be advisable if the patient can tolerate it (Class I, level of evidence A). No recommendation is made about DBP target for patients with chronic kidney disease. Of note, the recently published European Guidelines for Cardiovascular Prevention recommend a target BP of 140/80 mmHg for patients with diabetes.

Spanish society of hypertension

The Spanish society of hypertension in conjunction with other societies including the Spanish League Against Hypertension, the Argentinean society of hypertension, the Spanish Geriatrics and Gerontology association and the Spanish society of Nephrology, published their guidelines for the management of hypertension in the elderly in 2007. These guidelines support the recommendations of the ESC 2007 with a target of 140/90 mmHg for non-diabetic patients and 130/80 mmHg for diabetics, with the later not being supported by the most recent ESC guidelines (2013) as discussed above.

In regards to elderly patients the guidelines recommend a target of 140/90 mm. Of note no age threshold is discussed to define “elderly individuals” in these guidelines. Notably, the Spanish Society of Hypertension has not updated their guidelines since 2007.

National Institute for Health and Care Excellence (NICE) guidelines

Similar to the ESC guidelines, the NICE guidelines from the United Kingdom published in 2011 classify hypertensive patients into grade 1 and grade 2 hypertension. Their approach for selection of target BP values was based on a rigorous examination of the available literature.

A remarkable aspect, of the NICE guidelines that was introduced in their latest recommendations in 2011, is the inclusion of separate targets for office and ambulatory or home blood pressure monitoring. They recommend an office target BP below 140/90 mmHg for patients younger than 80 years and a target of 150/90 mmHg for those older than 80 years. For ambulatory or home blood pressure monitoring the recommended average target while being awake was 135/85 for people under 80 years of age and 145/85 for people older than 80 years. There are no separate recommendations for patients with diabetes, established cardiovascular disease or patients with chronic kidney disease, a departure from prior recommendations.

International guidelines

World Health Organization/International Society of Hypertension

The World Health Organization/International Society of Hypertension (WHO/ISH) published their last guidelines in 2003. In that report from 2003 they recommend a target BP of <140/90 for the general population and <130/80 mmHg for high-risk individuals, including patients with diabetes, CKD and history of cardiovascular disease. However, they do not provide specific recommendations for elderly patients, other than recommending not withholding antihypertensive therapies in patients older than 80 years. Of note, the WHO have not updated their guidelines since 2003 nor have joined any other society for this purpose, while the ISH partnered with the American Society of Hypertension and published the latest version of their guidelines in 2013 as detailed in prior sections of this manuscript.

Blood pressure targets for specific populations

Elderly patients

Establishing the optimal blood pressure target for elderly patients has been a challenging issue. First, there is no uniform consensus as to who is elderly (≥60 years, >70 years, >75 years or >85 years). Secondly, up until recently most major hypertension trials excluded the very elderly patients. Fortunately, more recently a number of studies specifically aimed to study blood pressure management and targets in
older subjects have been published, providing support for specific recommendations in this subgroup.

Non-randomized studies have consistently pointed at the hazards of lowering BP in the elderly. In 1988, Mattila et al. reported an inverse relationship between blood pressure levels and mortality in an observational study that included 561 subjects, 83% older than 85 years, in whom the mortality rates at 5 years were higher in patients within the lowest SBP and DBP groups. \(^7\) Similar results were seen in other observational studies. \(^8,9\)

The findings from observational studies have considerable limitations. The landmark Hypertension in the Very Elderly Trial (HYVET). \(^10\) Study included patients older than 80 years with SBP > 160 mmHg who were randomized to the diuretic indapamide with the addition of an angiotensin converting enzyme inhibitor if BP target was not reached or placebo The achieved BP in the diuretic/ACEI group was 143.5/77.9 mmHg while that in the placebo group was 158.5/84 mmHg. There was a significant reduction in fatal stroke, heart failure, all-cause death, and all cardiovascular events, as well as non-significant reductions in non-fatal stroke and cardiovascular death at 1.5 years follow-up (the trial was stopped prematurely by safety monitoring committee). These data suggested a blood pressure target of 150/80 mmHg in the very elderly. Nonetheless, despite these compelling results, HYVET trial included only octogenarians who were in good physical and mental conditions and excluded frail and ill subjects as well as those with orthostatic hypotension, restricting the applicability of these results to only a fraction of the octogenarians commonly seen in clinical practice. \(^10\)

Several studies included patients who were older than the average cohorts traditionally enrolled in hypertension trials. The Systolic Hypertension in the Elderly Program (SHEP) included patients with an average age of 72 years who had SBP > 160 mmHg and compared different treatments to placebo, and demonstrated that a successful reduction of SBP (143/68 mmHg in the treatment group versus 155/72 mmHg in the placebo group) was associated with reductions in non-fatal ischemic stroke and non-fatal myocardial infarction. \(^11\) Similar results were seen in the Swedish Trial in Old Patients With Hypertension (STOP-Hypertension), which included patients between 70 and 84 years of age with SBP 180–230 mmHg, DBP > 90 mmHg or 105–120 mmHg regardless of SBP. \(^12\) In this trial the achieved blood pressure was 186 ± 22/96 ± 10 mmHg in the placebo group and 167 ± 21/87 ± 9 mmHg for the intervention group.

The available evidence to establish BP targets in elderly patients was carefully evaluated by both the ESC/ESH and by the JNC 8. \(^13-16\) Based on this evidence, the JNC-8 panel concludes that for subjects 60 years or older, a treatment target of 150/90 mmHg is associated with reduction in stroke, heart failure, and coronary artery disease rates, while using a SBP target of 140 does not provide additional benefits and might indeed be harmful. Conversely recent data showed a reduction in cardiovascular events when SBP was lowered just below 140 mmHg as opposed to 145 mmHg, \(^15\) with such data coming from subgroup analysis from the FEVER study. In a recent post hoc analysis from the INVEST trial of 8354 who were 60 years or older with coronary artery disease and baseline SBP > 150 mmHg, we showed that lowest rates of cardiovascular outcomes were seen in patients who achieved SBP < 140 mmHg when compared with targets of 140–150 mmHg or > 150 mmHg. \(^17\) This highlights the potential harm of using higher blood pressure targets in elderly patients, especially with history of CAD. Notably it is worth mentioning that both the JNC 8 and the latest ESC/ESH guidelines recommend that if an elderly subject, even if older than 80 years, achieves a BP lower than 140 mmHg, withholding medications or reducing doses is not recommended, as long as the patient has no adverse effects. This recommendation was based on the fact that several patients from the Syst-Eur and the HYVET trial, did achieve a SBP less than 140 mmHg and it was generally well tolerated. \(^18,19\)

The ongoing Systolic Blood Pressure Intervention Trial (SPRINT) will provide additional data about BP targets in the elderly hypertensives. \(^20\) This trial will enroll over 9200 patients with one or more of the following risk factors: age greater than 75 years, presence of cardiovascular disease other than stroke, chronic kidney disease, Framingham Risk Score for 10-year cardiovascular disease risk of 15 percent or more. Patients will be randomized into an intensive BP arm, with a target of SBP < 120 mmHg or a standard with a SBP target <140 mmHg. The primary hypothesis is that the rates of CVD events be lower in the intensive arm, including first myocardial infarction, acute coronary syndrome, stroke, heart failure or cardiovascular death. Secondary outcomes will include all-cause mortality, decline in renal function, development of end stage renal disease, dementia, decline in cognitive function and small vessel cerebral ischemic heart disease. Participants will be recruited at approximately 90 clinics over approximately 2-year period, and will be followed for 4–6 years.

**Diabetic patients**

There is a cumulative body of evidence, including high quality randomized trials, that demonstrated significant reductions in cardiovascular events when blood pressure is lowered in patients with diabetes mellitus (DM). These were derived from subgroup analysis from major trials, \(^21,22-24\) as well as from two trials including only diabetic patients\(^25,26\) and a more recent meta-analysis. \(^27\)

The largest randomized clinical trial to assess the effect of intensive blood pressure control in diabetic patients, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, has provided important information that questioned the rationale of having a lower blood pressure target. Notably, this trial assessed the lowest BP target of any randomized clinical trial in diabetics. \(^28,29\) The ACCORD trial included 4733 patients with diabetes who were high risk for complications due to pre-existing vascular disease or multiple risk factors, who were randomized to target a SBP <140 mmHg (standard therapy group) or <120 mmHg (intensive therapy group). The mean follow-up was 4.7 years and the primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular mortality. This study failed to demonstrate a significant reduction in the primary endpoint in diabetic patients who achieved an average SBP of 119.3/64.4 mmHg (target SBP of 120 mmHg) when compared to those who had an average of 133.5/70.5 mmHg (target BP of 140 mmHg, p = 0.5). In a similar way, the rate of serious adverse events in the intensive-therapy group was significantly higher (P < 0.001),
including hypotension, bradycardia or arrhythmias, hyperkalemia. The results from the ACCORD trial provided a much better understanding of the role of aggressive BP reduction in diabetics and contribute to clarify questions raised by prior studies analyzing this question in smaller cohorts that yielded inconclusive findings.44-56

More recently, the results of the ACCORD trial were confirmed by a meta-analysis that included 13 randomized clinical trials, with a total of 37,736 subjects, of antihypertensive therapy in patients with type 2 diabetes mellitus or impaired fasting glucose/impaired glucose tolerance. Such trials enrolled at least 100 patients, followed for at least one year and who with achieved systolic BP of ≤135 mmHg in the intensive BP control group and ≤140 mmHg in the standard BP control group. Results from this meta-analysis reported that intensive BP control (≤135 mmHg) was associated with a 10% reduction in all-cause mortality (OR 0.90; 95% CI, 0.83–0.98) and a 17% reduction in stroke. However, there was a 20% increase in serious adverse effects, but with similar outcomes for other macrovascular and microvascular outcomes when compared with standard BP control. This suggested that a SBP target of 130–135 mmHg in diabetic patients or glucose intolerance might be acceptable, while lower targets might lead to serious adverse events while providing no additional cardiovascular protection.37

**Chronic kidney disease**
The goal of BP reduction in patients with CKD is 2 folds: first, to prevent or slow down the rate of deterioration of kidney function and second, to prevent the occurrence of cardiovascular events. However, data providing specific targets for this group of patients are limited.38 Studies including patients with CKD that were not diabetics, have failed to demonstrate a reduction in the progression to end-stage renal disease or mortality, when comparing SBP targets of 125–130 mmHg versus 140 mmHg.39–41 This was also true for black individuals, as seen in the AASK trial, where African American patients with hypertensive nephrosclerosis did not demonstrate a decrease in the progression of CKD with lower BP targets (<130/80 mmHg), even when these targets were readily achievable in these subjects.40 On the other hand, non-randomized evidence from observational follow-up from randomized trials suggested lower incidence of events with lower blood pressure levels, particularly in patients with proteinuria.42,43 Unfortunately, two large studies that aimed to study the effect of a SBP target below 130 mmHg in patients with nephropathy could not provide any meaningful data, as the target SBP was not achieved in the aggressive treatment groups.44,45 Similarly, the lack of data suggesting the use of more intensive BP targets in patient with CKD is also supported by the ACCORD trial55 and by recent bimodal analysis.46,47 There are currently ongoing studies to assess the optimal BP targets in elderly patient and in patients with chronic kidney disease that might provide useful additional information. One example is the SPRINT trial mentioned above, which is using as inclusion criteria, for one of the risk factors, patients with a GFR of 20–59 ml/min/1.73 m².28

The J shape curve phenomenon – is such observation being acknowledged by the guidelines?

As discussed above finding the most appropriate BP target has been a challenging task for the different hypertension expert societies. This is complicated even further by the transition of evidence supporting the “lower the better” strategy that mostly came from observational data suggesting a linear relationship between BP and mortality,8–53 to the J-shape curve phenomenon described by prior authors.30,54–58 This refers to the bimodal association seen at high and low blood pressure levels where there is an increase in adverse outcomes. In other words, the J-shape curve hypothesis postulates the existence of a BP threshold below which adverse events, including mortality, will start to increase. This phenomenon has also been coined by some authors as the “U shape phenomenon”, especially when referring to increase mortality with low BP levels, but in practical terms it is similar to J shape/J curve phenomenon.18,59,60

The J-curve phenomenon was first described in the late 1970s, with the report of higher rates of adverse events, such as myocardial infarction, in patients who achieved lower DBP levels,56 and with similar findings published later for those with lower SBP as well.61–63 Several potential mechanisms can explain the J-shape phenomenon. First it is plausible that low BP levels are more commonly found in sick and debilitated patients with chronic illness or systolic heart failure, being more a consequence than a cause of poor health states.54,64,65 In these patients, it is conceivable that severe ventricular dysfunction precludes achieving high SBP levels, acting as a marker of advance cardiovascular disease, which entails worse prognosis overall.

Second, the adverse events with low diastolic pressure may be the result of wide pulse pressure seen in the elderly. Third, low pressure, especially diastolic can compromise coronary circulation more so in patients with CAD, resulting in myocardial ischemia. Finally, the J-curve phenomenon could also be the result of statistical aberration and not necessarily a true clinical entity in some of the studies that have demonstrated such phenomenon. A list of the studies that have shown a J curve phenomenon are summarized in Table 2.

In patients with Coronary Artery Disease, the J-shape phenomenon has been described in several studies for both diastolic and systolic BP. In an analysis from the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial, a J-shape phenomenon was observed for both SBP and DBP and cardiovascular outcomes including all cause mortality, MI, angina requiring hospitalization, need for repeated revascularization at 30 days and stroke. The lowest rates of events were seen at a BP 135/85 mmHg, with an increase when SBP >160 mmHg or <100 mmHg or when DBP was >100 mmHg or <60 mmHg.66 Similarly, in an analysis from the Treating to New Targets (TNT) trial, the lowest rates of adverse cardiovascular events was when BP was close the nadir of 146.3/81 mmHg, increasing when SBP was >140 or <110 mmHg or when DBP was >90 or <70 mmHg.66 In a similar way several studies have demonstrated the J-curve phenomenon, including the
Table 2  Selected studies demonstrating J-shape curve phenomenon according to specific endpoints and by systolic blood pressure (SBP) and diastolic blood pressure (DBP).

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Percentage of patients with CHD</th>
<th>Presence of J-curve phenomenon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total mortality</td>
</tr>
<tr>
<td>Stewart et al. (1979), Lancet55</td>
<td>169</td>
<td>Not reported</td>
<td>SBP: N/A</td>
</tr>
<tr>
<td>Australian Therapeutic Trial in Mild Hypertension (1982), Lancet76</td>
<td>3931</td>
<td>0</td>
<td>DBP: N/A</td>
</tr>
<tr>
<td>IPPP (1985), J Hypertens56</td>
<td>6357</td>
<td>0</td>
<td>DBP: Yes</td>
</tr>
<tr>
<td>Lindholm (1985), Acta Med Scan57</td>
<td>954</td>
<td>Not reported</td>
<td>SBP: N/A</td>
</tr>
<tr>
<td>Cruickshank (1987), Lancet63</td>
<td>597 (no CHD)</td>
<td>0</td>
<td>DBP: No</td>
</tr>
<tr>
<td>Cruickshank (1987), Lancet63</td>
<td>342 (CHD)</td>
<td>100</td>
<td>DBP: Yes</td>
</tr>
<tr>
<td>D’Agostino (1991), BMJ68</td>
<td>5209</td>
<td>4.1</td>
<td>DBP: Yes</td>
</tr>
<tr>
<td>Voko (1999), Hypertension58</td>
<td>6827</td>
<td>13.4</td>
<td>DBP: Yes</td>
</tr>
<tr>
<td>Boutitie (2002), Ann Int Med77</td>
<td>40,233</td>
<td>3.3</td>
<td>SBP: Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DBP: Yes</td>
</tr>
<tr>
<td>Berl (2005), J Am Assoc Nephrol74</td>
<td>1715</td>
<td>Not reported</td>
<td>SBP: Yes</td>
</tr>
<tr>
<td>Derived from: Staessen (1997), Lancet23</td>
<td></td>
<td></td>
<td>DBP: Yes (only for patients with CAD)</td>
</tr>
<tr>
<td>Pepine (2003), J Am Med Assoc80</td>
<td>22,576</td>
<td>100</td>
<td>SPB: No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DBP: Yes</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>BP Target</td>
<td>SBP</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------</td>
<td>-----------</td>
<td>-----</td>
</tr>
<tr>
<td>Poole-Wilson PA (2004), Lancet(^{81})</td>
<td>7665</td>
<td>100 (angina pectoris attributable to CAD)</td>
<td>N/A</td>
</tr>
<tr>
<td>Bangalore (2010), Eur Heart J(^{74}) Derived from Larosa (2005), N Engl J Med(^{82})</td>
<td>10,001</td>
<td>100</td>
<td>SBP: No</td>
</tr>
<tr>
<td>Sleight (2009), J Hypertens(^{69}) Derived from ONTARGET Investigators (2008), NEJM(^{83})</td>
<td>25,588</td>
<td>75</td>
<td>SBP: No</td>
</tr>
<tr>
<td>Julius (2004), Lancet(^{84})</td>
<td>15,245</td>
<td>46</td>
<td>SBP: Yes</td>
</tr>
<tr>
<td>Cannon (2004), N Engl J Med(^{85})</td>
<td>4162</td>
<td>18% (prior MI), 11% (prior CABG), 69% (ACS at enrollment)</td>
<td>SBP: Yes</td>
</tr>
</tbody>
</table>

Yes = evidence supporting presence of J-curve phenomenon; No = evidence against J-curve phenomenon; N/A = no data reported to support for or against J-curve phenomenon.
Figure 1  (A) Relationship between (a) systolic and (b) diastolic BP and the risk of adverse cardiovascular outcomes in the PROVET-IT TIMI 22 trial (left) and in the TNT trial (right). (B) J-shape curve for blood pressure and adverse outcomes (all-cause death, nonfatal stroke, and nonfatal myocardial infarction) in patients with hypertension and coronary artery disease.

INVEST study,\textsuperscript{67} as well as subgroups with CAD from other trials\textsuperscript{65,68-70} with data demonstrating that achieving BP values ≤120/80 mmHg is associated with worse outcomes in patients with CAD. In patients without CAD, several studies have also shown a J-shape phenomenon, especially for diabetic patients or patients with CKD such as the ACCORD trial, the Appropriate Blood Pressure Control in Diabetes normotensive cohort (ABCD-NT) and the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial,\textsuperscript{36} among others\textsuperscript{71} where lower BP targets failed to show a beneficial effect for cardiovascular and renal outcomes.\textsuperscript{72,73}
While the above studies have shown a consistent J-shaped relationship between blood pressure and coronary events, the same is not true for stroke related events. In the analysis from the TNT trial, the rate of stroke was lower when low SBP (110–120 mmHg) levels were achieved, suggesting the lack of a J-curve relationship for stroke outcomes. Similar findings were seen in the ACCORD BP trial where a lower BP target of 120 mmHg was associated with a significant decrease in stroke when compared to a higher BP target (140 mmHg) but not for coronary events. Similar data were reported in a metaanalysis that included 13 randomized clinical trials that enrolled 37,736 participants and that looked into the occurrence of macro and microvascular events in hypertensive diabetics using an intensive BP control strategy (≤135 mmHg). It was found that there was a significant benefit in trials where the SBP was <130 mmHg with a 47% decrease in the odds of stroke compared with the standard control group. The above studies indicate ‘target organ heterogeneity’ in that lower BP targets do not reduce coronary events (Fig. 1) but can potentially reduce stroke related events (Fig. 2). Thus the concept of BP targets has now suddenly become more complex and the target chosen for a particular patient should be based on the patients’ risk of coronary versus stroke events. Interestingly in the Prevention Regimen for Effectively avoiding Second Strokes (PROGRESS) trial that enrolled patients with recent non-cardioembolic ischemic stroke and without history of hypertension, a similar J-curve relationship was seen for SBP and risk of recurrent stroke. Thus the lower the better for stroke prevention may not be applicable to secondary prevention of stroke.

Of note, despite the growing body of evidence on the J-shape phenomenon, most of the international guidelines do not comment on this phenomenon, except for the ESH/ESC guidelines that have specifically designated a section on this in their latest version.

### Conclusions

Determining the optimal blood pressure targets has been a challenging issue with several changes occurring over the last few decades. The evolution of the understanding of hypertension from its ‘essential’ role to an approach based on the ‘lower the better’ principle from observational studies has contributed to such dynamic process. Later, the possible J-curve phenomenon underscored the concept of target organ heterogeneity and has made the identification

**Figure 2** Intensive versus standard blood pressure control and stroke. Results are further stratified by achieved systolic pressure in the intensive group. The size of the data marker represents the weight of each trial. OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; ALLHAT, antihypertensive and lipid-lowering treatment to prevent heart attack trial; PERSUADE, perindopril substudy in coronary artery disease and diabetes; ADVANCE, action in diabetes and vascular disease: Preterax and DiaMitrcon-MR controlled evaluation; NAVIGATOR, Nateglinide and Valsartan in impaired glucose tolerance outcomes research; ABCD, appropriate blood pressure control in diabetes; DREAM, diabetes reduction assessment with Ramipril and Rosiglitazone medication; SANDS, stop atherosclerosis in native diabetics study; ACCORD, action to control cardiovascular risk in diabetes.
of the optimal blood pressure targets even more challenging. The cumulative evidence and major guideline recommendation now seem to support a target of <140/90 mmHg for the general population (except the elderly), including those with diabetes and those with chronic kidney disease. However, this likely is an oversimplification given the concept of target organ heterogeneity. Despite decades of research and treatment of millions of patients with high blood pressure, the answer to the fundamental question of optimal BP targets appears to be not so simple after all!!

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

The authors declare no conflict of interest.

References


