

## Reduction of diastolic blood pressure: Should hypertension guidelines include a lower threshold target?

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### Abstract

Reduction of diastolic blood pressure to less than 60-80 mmHg does not improve mortality and may lead to adverse

cardiovascular events in high risk patient populations. Despite a growing body of evidence supporting the J-curve phenomenon, no major society guidelines on hypertension include a lower threshold target for diastolic blood pressure. Many major society guidelines for hypertension have been updated in the last 5 years. Some guidelines include goals specific to age and co-morbid conditions. The Sixth Joint Task Force of the European Society of Cardiology and the Canadian Hypertension Education Program are the only guidelines to date that have recommended a lower threshold target, with the Canadian guidelines recommending a caution against diastolic blood pressure less than or equal to 60 mmHg in patients with coronary artery disease. While systolic blood pressure has been proven to be the overriding risk factor in hypertensive patients over the age of 50 years, diastolic blood pressure is an important predictor of mortality in younger adults. Post hoc data analysis of previous clinical trials regarding safe lower diastolic blood pressure threshold remains inconsistent. Randomized clinical trials designed to determine the appropriate diastolic blood pressure targets among different age groups and populations with different comorbidities are warranted. Hypertension guideline goals should be based on an individual's age, level of risk, and certain co-morbid conditions, especially coronary artery disease, stroke, chronic kidney disease, and diabetes.

**Key words:** Blood pressure; Guideline; J-curve; Hypertension; Diastolic pressure

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**Core tip:** Reduction of diastolic blood pressure to less than 60-80 mmHg appears to lead to adverse cardiovascular events in high risk patient populations. Currently, only two major society guidelines on hypertension include a minimum threshold for diastolic blood pressure. Available studies demonstrating adverse events at lower diastolic blood pressure vary in their cutoff values and patient populations. Randomized controlled trials comparing outcomes across different diastolic blood pressure targets

are limited. Hypertension guideline goals should be based on an individual's age, level of risk, and certain co-morbid conditions, especially coronary artery disease, stroke, chronic kidney disease, and diabetes.

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## INTRODUCTION

Hypertension remains the most common primary diagnosis for office visits in adult patients<sup>[1]</sup>. Blood pressure (BP) lowering is associated with reduction in cardiovascular morbidity and mortality<sup>[2,3]</sup>. A common practice is to aggressively treat BP as "the lower the better". Generally, guidelines have not cautioned against a lower limit beyond which treatment could be deleterious. A Cochrane review concluded that treating patients to lower than standard BP targets,  $\leq 140$ -160/90-100 mmHg, does not reduce mortality or morbidity<sup>[4]</sup>. Over-treatment of diastolic blood pressure (DBP) has been associated with adverse cardiovascular (CV) events in patients with coronary artery disease (CAD)<sup>[5,6]</sup>. In patients at risk of or with established CAD, adverse events appear when DBP is lowered beyond values of 60 to 80 mmHg<sup>[7-11]</sup>. This J-curve phenomenon, first described by Stewart over 30 years ago<sup>[12]</sup>, continues to be reported in the hypertension literature. Today there is no clear consensus on the ideal range of DBP in various patient groups.

## THE RATIONALE FOR A LOW-END THRESHOLD

Support for a lower threshold of DBP target is found in the rational assertion that at some point BP is too low to perfuse vital organs. The threshold for organ blood flow autoregulation is elevated in the presence of vascular disease, thus elevated BP may be "essential" for preserving organ function<sup>[13]</sup>. Compared to systolic blood pressure (SBP), DBP has a greater contribution to mean arterial pressure, which more closely correlates with organ perfusion. Additionally, since coronary perfusion occurs during diastole, a decrease in DBP would likely reduce perfusion and induce ischemia<sup>[14]</sup>.

## SUMMARY OF THE LITERATURE

Many studies have identified a J-curve relationship between low DBP and adverse events (Tables 1 and 2). Existing data from observational and interventional studies have been reviewed previously<sup>[13,14]</sup>. These represent diverse ages and populations, different cutoff values of

BP targets, varying outcome measures, and inconsistent findings<sup>[15-18]</sup>. Some studies were not appropriately designed to address pre-specified questions, others were underpowered<sup>[19-21]</sup>, and still others lost the beauty of randomization in randomized controlled trials (RCTs) due to re-grouping for post hoc analyses.

More than half of the studies identifying the DBP J-curve are post-hoc analyses<sup>[22-26]</sup>. This finding was most consistent among trials where most patients had underlying CAD compared to patients without CAD. Few RCTs have targeted DBP as an intervention. The average achieved DBP in such trials after intervention was greater than 80 mmHg. In the Hypertension Optimal Treatment (HOT) trial, it is difficult to recognize between-group difference due to the small differences in achieved DBP targets among the three groups (85 mmHg vs 83 mmHg vs 81 mmHg). A non-statistical trend towards increased CV events and mortality was observed at DBP valued  $< 80$  mmHg<sup>[8]</sup>.

Various epidemiological studies have found the J-curve phenomenon for DBP in certain patient subgroups. Increased CV death was seen in patients from the Framingham Heart Study cohort when DBP was reduced below 75-79 mmHg<sup>[27]</sup>. Patients from the National Health and Nutrition Examination Survey (NHANES) I and II both saw an increase in all-cause mortality when DBP was lowered below 70 mmHg<sup>[28,29]</sup>. A recent cohort of Kaiser 398419 patients showed differences in the j-curve nadir based on age and presence of diabetes<sup>[30]</sup>.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial achieved the lowest DBP among diabetic trials at 67.5 mmHg without increasing the risk of MI or CV mortality<sup>[31]</sup>. In a large cohort of 126092 newly diagnosed diabetics with CAD, risk of all-cause mortality increased when DBP was lowered below 75 mmHg<sup>[32]</sup>. Other studies of standard vs lower BP targets in diabetics have produced mixed results<sup>[33-36]</sup>.

Meta-analyses have been conducted to evaluate lower targets compared to standard targets (Table 3). Generally, these analyses have shown no statistical difference in primary outcomes between targets<sup>[4,37-39]</sup>. In patients with chronic kidney disease, two meta-analyses showed conflicting results<sup>[40,41]</sup>. The J-curve effect was seen in one meta-analysis of 49 RCTs. In this study a meta-regression showed the risk of CV mortality increased by 28 percentage points for each 10 mmHg decrease in baseline DBP ( $P = 0.013$ ), with harm being seen at values less than 78 mmHg<sup>[42]</sup>. Certain limitations that are germane to meta-analyses may explain why no J-curve was seen in other reports. First, most of these studies evaluated trials that used a dichotomous comparison of below or above a standard target and were not designed to compare different BP intervals. This is typically not possible without individual patient data. Second, selection bias from the individual trials can highly influence the outcome of the meta-analysis. Finally, outcomes across various studies may not be measured or defined using

**Table 1 Summary of studies evaluating blood pressure thresholds**

Study	Type	n	Age <sup>1</sup>	CAD <sup>2</sup>	DM <sup>2</sup>	CKD <sup>2</sup>	CVA <sup>2</sup>	Baseline DBP <sup>3</sup>	DBP J-curve by outcome	DBP J-curve Nadir <sup>3</sup>
Studies to target DBP										
1967 JAMA	RCT	143	51	22	6			121	CV events and all-cause mortality	Not observed at 92
1970 JAMA	RCT	380	51					104	CV events and all-cause mortality	Not observed at 86
1979 Lancet	Case-Control	169	51					124	MI	90
1998 Lancet (HOT)	RCT	18790	62	6	8		1	105	CV events; CV and all-cause mortality	82-86
Studies in the elderly										
1991 JAMA (SHEP)	RCT	4736	72	5	10		1	77	CVA and other CV events; CV mortality	Not observed at 70
1997 Lancet (Syst-Eur)	RCT	4695	70	30			4	86	CVA and other CV events; all-cause and CV mortality	Not observed at 81
2008 N Engl J Med (HYVET)	RCT	3845	84	12	6.8		7	90	CVA; all-cause mortality; CV mortality; CVA mortality	Not observed at 84
2016 JAMA (SPRINT)	RCT	2636	80	25	0	44	0	71	All CV events; CV mortality; all-cause mortality	Not observed at 65
Studies in CAD										
2005 J Hypertens (ACTION)	Post-Hoc	7661	64	100	15			80	CV mortality; event or procedure; all-cause mortality; CVA	73
2006 Ann Intern Med (INVEST)	Post-Hoc	22576	66	100	29	2	5	87	All-cause mortality; non-fatal MI or CVA	84
2009 J Hypertension (ONTARGET)	Post-Hoc	25588	66	75	37		21	82	CV mortality and all CV events	75-79
2010 Am J Med (INVEST)	Post-Hoc	22576	66	100	29	2	5	87	All-cause mortality; non-fatal MI or CVA	70-75
2010 Eur Heart J (TNT)	Post-Hoc	10001	60	100	15		5	79	All CV events; CV and all-cause mortality	81
2010 Circulation (PROVE IT-TIMI)	Post-Hoc	4162	58	100	18	11	6	75	All-cause mortality and all CV events	84-85
2011 Circulation (ONTARGET)	Post-Hoc	12554	66	75	37		21	82	CV mortality and all CV events	80
2012 Hypertension (SMART)	Post-Hoc	5788	57 vs 65	60	17		28	82	CV events and all-cause mortality	82
2016 Eur Rev Med Pharmacol Sci	RCT	369	67	100	7			105	All CV events	75-80
2016 Eur Heart J (VALUE)	Post-Hoc	15244	67	46	32		20	87	All CV events; all-cause mortality	80
Studies in DM										
1998 BMJ (UKPDS)	RCT	1148	56		100			94	All cause mortality	Not observed at 83
2002 Kidney Int (ABCD)	RCT	480	59		100			84	GFR changes; CV event; retinopathy; neuropathy	Not observed at 75
2005 J Am Soc Nephrol (IDNT)	RCT	1715	59	29	100	100		87	CV events and mortality	85
2010 JAMA (INVEST)	Post-Hoc	6400	66	100	100	4	9	85	All-cause mortality; non-fatal MI or CVA	SBP nadir 115, but no corresponding DBP nadir reported
2010 N Engl J Med (ACCORD)	RCT	4733	62	34	100			76	Non-fatal MI or CVA; CV mortality	Not observed at 68
2012 BMJ	Cohort	126092	67	10	100			83	All-cause mortality	75
Epidemiology studies										
1991 BMJ (Framingham)	Cohort	5209	30-62						CV mortality; non-CV mortality	75-79
2003 Ann Intern Med (NHANES II)	Cohort	7830	54		5			82	All-cause mortality; CV mortality	79
2011 J Gen Intern Med (NHANES I)	Cohort	13792	25-75						All-cause mortality	70-79
2014 J Am Coll Cardiol	Cohort	398419	64	19	30	24	8	73	All-cause mortality; ESRD	60-79

<sup>1</sup>Mean and <sup>2</sup>Units are %; <sup>3</sup>Units are mmHg. ABCD: Appropriate Blood Pressure Control in Diabetes; ACCORD: Action to Control Cardiovascular Risk in Diabetes; CV: Cardiovascular; HOT: Hypertension Optimal Treatment; HYVET: Hypertension in the Very Elderly Trial; IDNT: Irbesartan Diabetic Nephropathy Trial; INVEST: International Verapamil SR Trandolapril Study; MI: Myocardial Infarction; NHANES: National Health and Nutrition Examination Survey; ONTARGET: Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial; PROVE IT-TIMI: Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction; RCT: Randomized Controlled Trial; SHEP: Systolic Hypertension in the Elderly Program; SMART: Secondary Manifestations of Arterial Disease; SPRINT: Systolic Blood Pressure Intervention Trial; Syst-Eur: Systolic Hypertension in Europe; TNT: Treating to New Targets; UKPDS: United Kingdom Prospective Diabetes Study; VALUE: Valsartan Antihypertensive Long-term use Evaluation.

**Table 2** Comments on studies evaluating blood pressure thresholds

Study	Comment
Studies to target DBP	
1967 JAMA	Small sample size
1970 JAMA	Small sample size
1979 Lancet	Small sample size, lacking data on baseline comorbidities
1998 Lancet (HOT)	Event rate lower than expected; difficult to recognize between-group outcomes due to small differences in achieved BP targets among three groups
Studies in the elderly	
1991 JAMA (SHEP)	Stepwise titration of Chlorthalidone and addition of Atenolol <i>vs</i> placebo elderly isolated systolic hypertension; reduced all CV events with Rx
1997 Lancet (Syst-Eur)	Stepwise titration of Nifedipine and addition of enalapril and HCTZ <i>vs</i> placebo in elderly isolated systolic hypertension; reduced CV events and mortality but not all-cause mortality with Rx
2008 N Engl J Med (HYVET)	Indapamide ± Perindopril <i>vs</i> placebo; reduction of CVA, all-cause mortality and CHF
2016 JAMA (SPRINT)	Significant reduction in primary and secondary outcomes
Studies in CAD	
2005 J Hypertens (ACTION)	Non-significant trends towards higher CV events in normotensives on Nifedipine
2006 Ann Intern Med (INVEST)	J-curve more prominent in DBP; DBP categories of < 60 through > 110 with 10 increments
2009 J Hypertension (ONTARGET)	High risk patients with known CAD or DM with target organ damage; Rx increased CV mortality if baseline SBP < 130; But CVA risk increased with high baseline SBP, but reduced with further BP lowering
2010 Am J Med (INVEST)	Prespecified secondary analysis; Verapamil SR or Atenolol based Rx, add-on ACE-I, HCTZ allowed; J-curve DBP nadir similar in all age groups, while SBP nadir increasing with age
2010 Eur Heart J (TNT)	Exponential increase in primary outcome for SBP < 110-120 or DBP < 60-70 except CVA which was further reduced with lower SBP
2010 Circulation (PROVE IT-TIMI)	All ACS patients; DBP categories of < 60 through >100 with 10 increments exponential increase in outcomes for SBP < 110 or DBP < 70
2011 Circulation (ONTARGET)	High risk patients with known CAD or DM with target organ damage, stratified by % of on-treatment visits in which BP was < 140/90 or < 130/80; no MI benefit for lowering < 130/80; but better CVA outcome with lower BP
2012 Hypertension (SMART)	DBP nadir 82 for all CV events, including CVA; DBP nadir 84 for mortality
2016 Eur Rev Med Pharmacol Sci	Small sample size when randomized to 5 groups; J-Curve for all outcomes except CVA
2016 Eur Heart J (VALUE)	High CV risk patients stratified by % of on-treatment visits in which BP was < 140/90 or < 130/80; data adjusted for baseline covariates by propensity score; worse outcomes with BP lowering < 130/80 except CVA
Studies in DM	
1998 BMJ (UKPDS)	All newly diagnosed DM patients; tight <i>vs</i> less tight BP control (target < 150/85 <i>vs</i> 180/105) with Captopril or Atenolol as main agent and follow-up > 8 yr; tight BP control improved mortality and DM complications.
2002 Kidney Int (ABCD)	All diabetic normotensive patients; Rx with ACE-I or CCB <i>vs</i> placebo; achieved DBP of 75 <i>vs</i> 81 after 5 yr
2005 J Am Soc Nephrol (IDNT)	Achieving DBP < 85 associated with a trend towards increased all-cause mortality, a significant increase in risk of MI, but a decrease in risk of CVA
2010 JAMA (INVEST)	J Curve nadir at SBP < 115 for all cause mortality
2010 N Engl J Med (ACCORD)	SBP < 120 <i>vs</i> < 140 did not further reduce the rate of composite CV outcomes, except CVA
2012 BMJ	All newly diagnosed DM; DBP < 75 and SBP < 110 in CAD patients associated with worse outcome
Epidemiology studies	
1991 BMJ (Framingham)	J curve between DBP and CV death only in those with MI, independent of age, sex, BP Rx; J curve not significant for SBP after adjusting for confounders
2003 Ann Intern Med (NHANES II)	J curve between DBP and all mortality in age ≥ 65
2011 J Gen Intern Med (NHANES I)	J-curve for DBP even after adjusting for SBP
2014 J Am Coll Cardiol	DBP categories of < 50 through > 100 with 10 increments; data adjusted for confounders by CCI; DBP nadir lower for DM and age > 70 yr

ABCD: Appropriate Blood Pressure Control in Diabetes; ACCORD: Action to Control Cardiovascular Risk in Diabetes; CV: Cardiovascular; HOT: Hypertension Optimal Treatment; HYVET: Hypertension in the Very Elderly Trial; IDNT: Irbesartan Diabetic Nephropathy Trial; INVEST: International Verapamil SR Trandolapril Study; MI: Myocardial Infarction; NHANES: National Health and Nutrition Examination Survey; ONTARGET: Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial; PROVE IT-TIMI: Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction; RCT: Randomized Controlled Trial; SHEP: Systolic Hypertension in the Elderly Program; SMART: Secondary Manifestations of Arterial Disease; SPRINT: Systolic Blood Pressure Intervention Trial; Syst-Eur: Systolic Hypertension in Europe; TNT: Treating to New Targets; UKPDS: United Kingdom Prospective Diabetes Study; VALUE: Valsartan Antihypertensive Long-term use Evaluation.

the same criteria.

## REVIEW OF CURRENT GUIDELINES

Nearly all of the major society guidelines for hypertension have been updated in the last 5 years (Table 4). Some have included discussions regarding the J-curve and whether or not the evidence is strong enough to support minimum thresholds in both DBP and SBP. Yet in the final

analysis, none have concluded that there is sufficient evidence to make a recommendation for a minimum diastolic threshold.

The most robust discussion between the J-curve and the “lower the better” concept was found in the 2013 guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC)<sup>[43]</sup>. Following an explanation of the reasons why the J-curve is popular and rational, they cite observational data that



**Table 3** Meta-analyses and systematic reviews of blood pressure lowering trials

Study	No.	Trials	DBP J-curve Nadir <sup>1</sup>	Findings	Limitations
2009 <i>Cochrane Database Syst Rev</i>	22089	7	Not observed at 85	In hypertensive patients, lower <i>vs</i> standard BP targets (DBP 85 <i>vs</i> < 90) did not improve mortality or CV events	Difference in mean DBP was 3.4 mmHg between groups. In 2 trials, most did not achieve lower DBP targets. Failure to demonstrate harms with “lower targets” may be due to reporting bias
2011 <i>Ann Intern Med</i>	2272	3	Not observed at 75-80	In patient with CKD, lower BP targets (DBP < 75-80) did not improve renal outcomes	Data on deaths and CV disease outcomes were not informative given the lack of ascertainment or low event rate. Included very few patients with CKD; trial duration may have been too short to detect events
2013 <i>Cochrane Database Syst Rev</i>	2580	4	Not observed at 76	In diabetics, comparing lower <i>vs</i> standard DBP targets, no difference observed in CV mortality or CV events. Lower groups showed trend towards reduced non-cardiac mortality	High risk of selection bias for every outcome analyzed in favor of the “lower” DBP target
2013 <i>CMAJ</i>	9287	11	Not observed at 75-92	In patients with CKD, intensive BP lowering, compared to standard therapy, reduced risk of kidney failure, but not the risk of CV events (CV outcome data available only in 5 of 11 trials)	Did not include patient with diabetes. Heterogeneity of individual study limits the strength of conclusions
2015 <i>Lancet</i>	44989	19	Not observed at 76	In high risk patients, intensive <i>vs</i> standard BP therapy reduced major CV events, including CVA; but more intensive BP lowering no further benefits on mortality	Many trials did not achieve target BP levels in most patients. Mean BP in intensive groups was 133/76
2015 <i>JAMA</i>	100354	40	Not observed at 64-83	In diabetics, BP lowering improved mortality and CV events if baseline SBP > 140, but no outcome benefit if baseline SBP < 140 except CVA and albuminuria	Scarcity of large trials with achieved BP levels of < 70-80 (baseline DBP 70-106)
2016 <i>BMJ</i>	73738	49	78	In diabetics, if SBP < 140, risk of CV mortality increased by 28 percentage points for each 10 mmHg decrease in baseline DBP ( $P = 0.013$ )	Most included trials were not designed to evaluate different BP targets, but randomized patients to drugs or placebo

<sup>1</sup>mmHg. BP: Blood pressure; CKD: Chronic kidney disease; CV: Cardiovascular; DBP: Diastolic blood pressure.

both validate and refute the relationship. Regarding patients with overt CAD, they report that there is inconsistent evidence to treat hypertension to a systolic target of < 130 mmHg. These patients may be most affected by a J-curve phenomenon. Prior to the publication of the 2013 ESH/ESC guidelines, the ESH issued a task force document that expanded upon the 2007 guidelines and expanded the discussion of the J-curve<sup>[44]</sup>.

In 2016, the sixth joint task force of the ESC, along with 10 other European societies including the ESH, updated their 2012 guidelines<sup>[45]</sup>. These are the first to include a lower threshold for both diastolic and systolic BP targets. After reviewing post-hoc analyses that investigate the J-curve, they conclude that this phenomenon cannot be excluded in lower SBP < 130 mmHg, especially in patients with atherosclerosis. They recommend blood pressure goals of 130-139/80-85 mmHg in all hypertensive patients.

The Canadian Hypertension Education Program (CHEP) also debated this topic in their 2013 guidelines<sup>[46]</sup> but decided to wait for more evidence. A lower threshold was revisited in 2016 and a new recommendation was made for patients with CAD. The authors caution against lowering DBP below 60 mmHg for concern that myocardial ischemia may be exacerbated. This was graded as weak evidence<sup>[47]</sup>.

JNC updated their guidelines in 2014 with the eighth panel<sup>[48]</sup>. Based largely on the HOT trial, the authors

concluded that the evidence shows no benefit in treating patients to DBP goals of < 80 or 85 mmHg, even among diabetics. Their recommendations differed from 2003 when the panel recommended a target of < 80 mmHg in diabetics.

While the United Kingdom's Renal Associate did not issue any recommendations on a lower threshold for DBP targets, they did make such a recommendation for SBP. They referenced the Irbesartan Diabetic Nephropathy Trial and the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint (ONTARGET) trial, both of which found increased mortality in patients who achieved a SBP of < 120 mmHg. They conclude that (1) antihypertensive therapy should be individualized and (2) in chronic kidney disease patients, there is no evidence to support lower SBP below 120 mmHg<sup>[49]</sup>.

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines advised caution in patients with comorbidities, but did not feel the evidence would allow for a specified lower limit for BP lowering<sup>[50]</sup>. In patients with microalbuminuria, they recommend more aggressive control down to a DBP of 80 mmHg. The American Diabetes Association (ADA) guidelines increased their upper threshold from a maximum DBP of 80 mmHg in 2013 to 90 mmHg in the 2016 guidelines<sup>[51,52]</sup>.

In the elderly, recommended BP goal by guidelines for uncomplicated hypertension remains at < 140/90 mmHg. In an expert consensus, the American College of Cardiology Foundation (ACCF), and the American Heart

**Table 4** Hypertension guidelines

Society	Year updated	DBP upper threshold <sup>1</sup>	DBP lower threshold <sup>1</sup>	Individualized to comorbidities				Discuss J-curve
				Age	CAD	DM	CKD	
ACCF/AHA (elderly)	2011	< 90	-	Yes	-	-	-	Yes
ADA	2016	< 90	-	Yes	-	-	-	-
CHEP	2016	< 90 (< 80 in diabetes)	60 in CAD	Yes	Yes	Yes	Yes	Yes
ESH/ESC	2013	< 90 (< 85 in diabetes)	-	Yes	Yes	Yes	Yes	Yes
ESC	2016	< 85	80	Yes	-	Yes	-	Yes
French	2013	< 90	-	Yes	-	-	-	-
JNC8	2014	< 90 (including DM and CKD)	-	-	-	-	-	Yes
KDIGO	2012	≤ 90 (≤ 80 if microalbuminuria)	-	Yes	-	Yes	Yes	Yes
NICE	2011	< 85	-	-	-	-	-	-
Renal Association (United Kingdom)	2011	< 90 (< 80 if proteinuria)	-	-	-	-	Yes	-

<sup>1</sup>mmHg. ACCF/AHA: American College of Cardiology Foundation and the American Heart Association; ADA: American Diabetes Association; ASH: American Society of Hypertension; CAD: Coronary artery disease; CHEP: Canadian Hypertension Education Program; CKD: Chronic kidney disease; DM: Diabetes mellitus; ESC: European Society of Cardiology; ESH: European Society of Hypertension; JNC8: Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; KDIGO: Kidney Disease: Improving Global; NICE: National Institute for Health and Clinical Excellence.

Association (AHA) recognize that this goal is based more on expert opinion rather than randomized controlled trials<sup>[53]</sup>. Questions that remain to be answered include target BP across a range of ages and the application of the J-curve in the elderly. The ACCF/AHA discuss a target SBP of 150 mmHg as “the diagnostic criterion for hypertension and the treatment target in octogenarians and beyond”. However, the formal recommendation leaves this as an area of uncertainty. The National Clinical Guideline Centre (United Kingdom) updated their recommendations in 2011 and provide a separate target for people aged 80 years and over of 150/90 mmHg<sup>[54]</sup>. The French Society of Hypertension made the same recommendation in 2013<sup>[55]</sup>.

## DISCUSSION

Currently, the ESC and CHEP have issued the only guidelines that include goals with a lower threshold for DBP target. While the ESC recommends a DBP 80–85 mmHg, CHEP issues a caution below a lower threshold for DBP target. This threshold is specific to patients with CAD. These are important steps in addressing lower thresholds in general and for specific populations. Other societies, including the International Society of Hypertension and the Latin American Society of Hypertension, are cautious in recommending reduction in SBP to levels below 130 mm Hg, as was accomplished in the SPRINT trial<sup>[56,57]</sup>. Many questions still exists as to what targets achieve maximal benefit for patients<sup>[58]</sup>.

A J-curve in CV events is most consistently seen in patients with existing CAD. The current evidence for adverse CV events at lower diastolic pressures is based largely on observational and post-hoc analyses. Indeed, the Latin American Society of Hypertension recently reported that only 14 antihypertensive treatment trials have compared the effects of more vs less BP lowering. The ongoing debate between the lower the better concept and the J-curve hypothesis is “a good demonstration that evidence on the issue is lacking<sup>[57]</sup>”.

Individual comorbid conditions play a significant role

in overall CV risk as well as tolerance to lower blood pressures. Sophisticated statistics used in data analyses to adjust for confounders still cannot match the impartiality of well-designed and well-conducted RCTs. Diabetic patients receive an added benefit of reduction in nephropathy as well as CV events when BP is lowered to < 140/80 mmHg<sup>[59]</sup>. Patients with CAD, especially following acute coronary syndromes, are more affected by the J-curve than patients with stroke<sup>[5,60]</sup>. Many societies are now publishing guidelines with goals based on age and comorbid conditions.

In 2003, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) stated that the relationship between BP and CV events is continuous, consistent, and independent of other risk factors<sup>[61]</sup>. Observational studies of patients free from CV disease have confirmed this linear relationship in DBP levels as low as 75 mmHg<sup>[2]</sup>. Yet these finding do not consistently apply to patients with significant comorbid conditions.

While we advocate that major societal guidelines discuss the effect of aggressive BP lowering among different populations, we recognize that there are practical concerns with recommending a lower limit. First, since the cutoffs derived from post-hoc and observational analyses vary widely, as well as the outcomes, it is difficult to define what that lower limit should be. Second, in patients where a J-shaped relationship occurs between DBP and outcomes, specifying a lower limit could encourage targeting (as close to but not below) that limit, leading to unintended overtreatment. Third, the increased pulse pressure with age poses a challenge for clinical decision on achieving balanced therapeutic targets (lowering SBP without over treating DBP). Attempting to further decrease SBP for stroke and chronic kidney disease risk reduction may compromise outcomes for coronary artery disease risk *via* reduction in DBP. Additionally, while challenging to measure, central BP may correlate more closely with cardiovascular events than brachial BP<sup>[62]</sup>. Systolic function is lower in the aorta than the peripheral system and can be less responsive to various

antihypertensive agents<sup>[63]</sup>.

## CONCLUSION

Reduction of DBP to less than 60-80 mmHg appears to lead to adverse CV events in high risk patient populations. Currently, only two major society guidelines on hypertension include a minimum threshold for diastolic blood pressure. Available studies demonstrating adverse events at lower DBP vary in their cutoff values and patient populations. Randomized controlled trials comparing outcomes across different DBP targets are limited. We anticipate that more guidelines will include recommendations individualized to comorbid conditions as future studies focus on risk factors within specific disease populations, especially CAD, stroke, chronic kidney disease, and diabetes.

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