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MINIREVIEWS

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

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[1]. Blood pressure (BP) lowering is associated with reduction in cardiovascular morbidity and mortality[2,3]. 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, ⩽ 140-160/90-100 mmHg, does not reduce mortality or morbidity[4]. Over-treatment of diastolic blood pressure (DBP) has been associated with adverse cardiovascular (CV) events in patients with coronary artery disease (CAD)[5,6]. In patients at risk of or with established CAD, adverse events appear when DBP is lowered beyond values of 60 to 80 mmHg[7-11]. This J-curve phenomenon, first described by Stewart over 30 years ago[12], 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[13]. 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[14].

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[13,14]. These represent diverse ages and populations, different cutoff values of BP targets, varying outcome measures, and inconsistent findings[15-18]. Some studies were not appropriately designed to address pre-specified questions, others were underpowered[19-21], 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[22-26]. 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[8].

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[27]. 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[28,29]. A recent cohort of Kaiser 398419 patients showed differences in the j-curve nadir based on age and presence of diabetes[30].

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[31]. In a large cohort of 126092 newly diagnosed diabetics with CAD, risk of all-cause mortality increased when DBP was lowered below 75 mmHg[32]. Other studies of standard *vs* lower BP targets in diabetics have produced mixed results[33-36].

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[4,37-39]. In patients with chronic kidney disease, two meta-analyses showed conflicting results[40,41]. 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[42]. 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[1]	CAD[2]	DM[2]	CKD[2]	CVA[2]	Baseline DBP[3]	DBP J-curve by outcome	DBP J-curve Nadir[3]
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 morality	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

[1]Mean and [2]Units are %; [3]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 *vs* 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 *vs* 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 *vs* 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 *vs* less tight BP control (target < 150/85 *vs* 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 *vs* placebo; achieved DBP of 75 *vs* 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 eat SBP < 115 for all cause mortality
2010 *N Engl J Med* (ACCORD)	SBP < 120 *vs* < 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)[43]. 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[1]	Findings	Limitations
2009 *Cochrane Database Syst Rev*	22089	7	Not observed at 85	In hypertensive patients, lower *vs* standard BP targets (DBP 85 *vs* < 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 *Ann Intern Med*	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 *Cochrane Database Syst Rev*	2580	4	Not observed at 76	In diabetics, comparing lower *vs* 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 *CMAJ*	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 *Lancet*	44989	19	Not observed at 76	In high risk patients, intensive *vs* 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 *JAMA*	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 *BMJ*	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

[1]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[44].

In 2016, the sixth joint task force of the ESC, along with 10 other European societies including the ESH, updated their 2012 guidelines[45]. 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[46] 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[47].

JNC updated their guidelines in 2014 with the eighth panel[48]. 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) trail, 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[49].

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[50]. 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[51,52].

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[1]	DBP lower threshold[1]	Individualized to comorbidities				Discuss
				Age	CAD	DM	CKD	J-curve
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	-

[1]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[53]. 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[54]. The French Society of Hypertension made the same recommendation in 2013[55].

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[56,57]. Many questions still exists as to what targets achieve maximal benefit for patients[58].

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[57]".

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[59]. Patients with CAD, especially following acute coronary syndromes, are more affected by the J-curve than patients with stroke[5,60]. Many societies are now publishing guidelines with goals based on age and co-morbid 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[61]. Observational studies of patients free from CV disease have confirmed this linear relationship in DBP levels as low as 75 mmHg[2]. 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[62]. Systolic function is lower in the aorta than the peripheral system and can be less responsive to various

antihypertensive agents[63].

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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MINIREVIEWS

Hypertension, type Ⅳ cardiorenal syndrome and chronic kidney disease: Pathophysiological and therapeutical approach

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Abstract

Hypertension represent one of the most important co-morbid factors in chronic kidney disease (CKD) patients and its prevalence increases from 65% to 95% according to glomerular filtration rate decline. CKD patients need to maintain their blood pressure levels into 130/80 mmHg according to most recent guidelines. Despite of many therapeutic agents, achievement of ideal blood pressure levels remains so far from the ideal ones. Hypertensive disease represent most important risk factor to develop a type Ⅳ cardiorenal syndrome, while prevalence of end stage renal disease is still raising and it represents world-wide epidemiological challenge. Correct management of hypertensive disease can obtain better control on CKD progression.

Key words: Hypertension; Type Ⅳ cardiorenal syndrome; Renin-angiotensin system inhibitors; Calcium channel blockers; Chronic kidney disease

Core tip: Treat hypertensive disease can delay chronic kidney disease progression and type Ⅳ cardiorenal syndrome onset.

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INTRODUCTION

Hypertensive disease represents major risk factor in

CKD-related cardiovascular disease. Table 1 shows risk factors involved in the pathogenesis of CKD-related hypertension. The prevalence of hypertension increases from 65% to 95% according to glomerular filtration rate (GFR) decline from 85 to 15 mL/min per 1.73 m^2[1]. Hypertension itself is actually recognized as a risk factor for renal disease progression till to end-stage renal disease (ESRD)[2,3]. Hypertension can be also accounted for higher risk of all-cause and cardiovascular mortality in CKD patients, as referred in several randomized controlled clinical trials[4-9]. Current guidelines actually suggest to reach less than 130/80 mmHg BP values in CKD patients' population. Despite of many therapeutic agents, achievement of ideal blood pressure levels remains so far from the ideal ones[10,11].

Table 1 Selected factors implicated with hypertension in chronic kidney disease

Factor	Dominant mechanism
Impaired Na excretion	Expansion of ECF volume
Activation of RAS	Direct vasoconstriction
	Sympathetic activation
Sympathetic activation	Direct vasoconstriction
	Stimulation of renin release
Imbalance in PG or kinins	Vasoconstriction
Endothelin	Direct vasoconstriction
	Renal injury
Reduced nitric oxide	Loss of vasodilatator effect

RAS: Renin-angiotensin system; ECF: Extracellular fluid; PG: Prostaglandins.

TREATMENT

RAS inhibitors

RAS is an important therapeutic target and drugs that block this system have been extensively developed, such as ACE inhibitors (ACE-I) and Angiotension Ⅱ receptor blockers (ARB). This blocking has been postulated as the first choice for treatment of hypertension in CKD patients[12,13]. Several ARB inhibitor trials for CKD patients were conducted and showed a slower decline in renal function with the use of this class of antihypertensive medication related mainly to proteinuria reduction than to intensive blood pressure control[9,14-17]. Antiproteinuric effect was postulated as the corner stone of renoprotection and it is more effective if it's associated to low sodium diet or to combination therapy with diuretics leading to extracellular volume (ECV) depletion. ECV depletion and RAS inhibition is particularly suitable in proteinuric CKD patients allowing to reach because the best renal outcomes[18].

RAS inhibitors are highly effective in diabetic patients with renal involvement, reducing protein excretion and preventing to shift from microalbuminuria to proteinuria and renal failure, as it occurs in proteinuric normotensive patients[19,20]. Renoprotective properties of ARBs has been pointed up in type 2 diabetic nephropathy, but combination therapy with ACEi is still a critical issue[21,22]. Additive antiproteinuric effect has been reported in proteinuric nondiabetic CKD patients affected by glomerular nephropathies (*i.e.,* IgA nephropathy). At the same time an increased efficacy in terms of slowing CKD progression has been proven in the same patients' population[13]. Combination therapy approach could be indicated in the in the majority of CKD patients because ACEi stand alone therapy doesn not allow to obtain less than 500 mg/d proteinuria[23]. Preliminary exclusion of patients suffering adverse effects of strong RAS inhibition (hyperkalemia, marked increase in serum creatinine concentration) has to be realized as far as extensive abuse of diuretics. Plasma creatinine and potassium concentrations should be measured in the first weeks of therapy.

Salt restriction

Sodium and fluid retention paly fundament role in the pathogenesis of CKD-related hypertension, even if extracellular volume (ECV) expansion is not able to induce edema, as it occurs in heart failure patients. Urinary fractional excretion of sodium increases as GFR declines contributing to hypertension, especially in those patients undergoing on RAS inhibitors therapy[24]. CKD patients take benefits by small reduction of salt intake in respect of essential hypertensive patients undergoing major restriction of salt intake, probably due to basal ECV amount[25-27].

CKD patients compliance with the dietary prescription is generally poor in the setting of clinical practice. The determination of urinary excretion of sodium (target: $\leqslant$ 100 mEq/d, equal to $\leqslant$ 6 g NaCl/d), is very important to monitor the patient's adherence to dietary prescriptions, specifically reducing added salt in the diet, cooking with spices rather than salt, choosing fresh food, eating low-salt bread.

Diuretic treatment

Natriuretic agents become the cornerstone of treatment of CKD-related hypertension, especially in patients with poor compliance to salt restriction (urinary sodium excretion > 100 mEq/d)[28]. In patients with stage Ⅰ to Ⅲa CKD, thiazide diuretics are indicated, since they can restore the antiproteinuric effect of ACE-I in patients not compliant to a low-salt diet. Thiazides could also prevent development of cardiovascular events in older people with isoled systolic hypertension and mild renal function impairment[29]. Loop diuretics are indicated when GFR falls under 40 mL/min and titrated until BP reaches guidelines recommended values (< 130/80 mmHg). Diuretics have to be carefully employed when so called patient's "dry weight" is reached. Dry weight that is defined as the weight at which further fluid losses will lead to symptoms (orthostatic hypotension, cramps) or decreased tissue perfusion (an unexplained elevation of azotemia and plasma creatinine concentration can be observed). In Stage Ⅲa CKD patients torasemide (40 mg/d) or furosemide (80 mg/d) induce an antihypertensive effect closely linked to natriuretic response and ECV contraction[30]. Once sodium retention

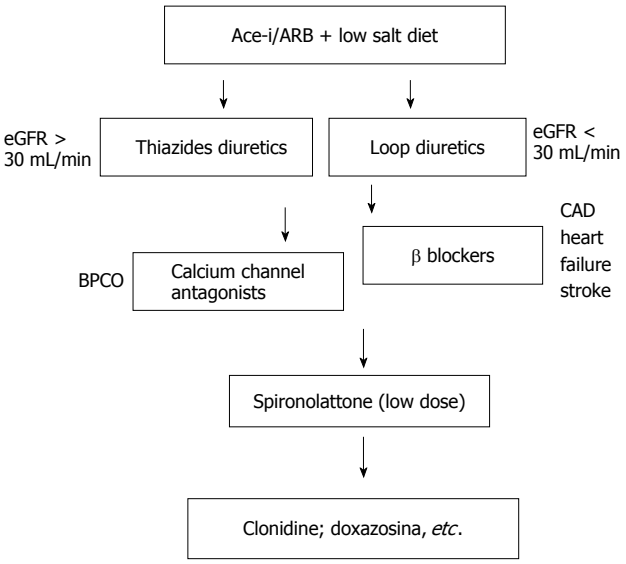

Figure 1 Algorithm of hypertension treatment in chronic kidney disease proteinuric patients. ARB: Angiotension Ⅱ receptor blockers; GFR: Glomerular filtration rate; CAD: Coronary artery disease.

is corrected (induction phase), and the achievement of normal BP values is reached, down-titration of loop diuretic dosage can be started and maintained (maintenance phase). Maintenance dose of loop diuretic is lower than that of the induction one and it should be clear that therapeutic dose of furosemide is characterized by a large inter-individual variability due to different bioavailability. It's good clinical practice to start with a low diuretic dose gradually increasing to achieve progressive body weight reduction. On the other side, maintenance phase is fundamental to downtitrate the dose and detect the lowest target dose.

In the real world nephrologists are not confident with loop diuretics in their hypertensive CKD patients, because of their side effects, that can be avoided if renal function and serum electrolyte levels are periodically checked in the first weeks of treatment.

Aldosterone antagonists

Aldosterone antagonists can provide reduction in urine albumin levels excretion, especially in combination therapy for resistant hypertension in CKD patients. Aldosterone antagonists also provide clinical benefits in non-CKD patients with heart failure, including heart failure following myocardial infarction. Because of the risk of hyperkalemia and reduction in GFR, they should be used at lower doses (*i.e.*, 25-50 mg/d) and with caution in CKD patients.

Other antihypertensive drugs

RAS inhibitors and diuretics are the cornerstones of therapy in hypertensive CKD patients, but they are not the only therapeutic strategies in CKD-related hypertensive disease. If specific cardiovascular disease and therapeutic targets are needed, additional agents shold be choosen in order to avoid side-effects and interactions, as it is showed in Figure 1[31].

Beta blockers

Beta-blockers are especially indicated in patients with cardiac chronic ischemic disease, congestive heart failure (and consequent diastolic dysfunction), tachycardia, headaches, and glaucoma. These agents should in general avoided in patients with bradycardia, second- or third-degree heart block, asthma, chronic obstructive pulmonary disease, severe peripheral vascular disease, depression. In CKD patients beta-blockers can induce hyperkalemia due to impaired transcellular distribution of potassium, especially for whom concerning non-selective beta-blockers. All beta-blockers can induce hyperglycemia, due to insulin resistance, and dyslipidemia with a decrease in HDL cholesterol plasmatic levels.

Calcium channel blockers

Among calcium channel blockers (CCB), the nondihydropyridine ones show positive effects on CKD progression and cardiovascular outcomes. Reduction in proteinuria levels is observed in diabetic patients with renal disease treated with diltiazem and verapamil[31]. Nondihydropyridine calcium-channel blockers can provide poor cardiovascular outcomes due to negative effects on cardiac contractility and conduction. Therefore, they should not be used in patients with severe left ventricular dysfunction, sick sinus syndrome, or second- or third-degree heart block. Constipation represent very common side effects occurring in up to 25% of patients on verapamil treatment. Among long-acting dihydropyridine agents, some of them do not hold cardiac depressant activity, as amlodipine and lacidipine and they have to be preferred rather than short-acting CCB. Therefore dihydropyridines are associated with vasodilation-related side-effects as peripheral edema, dizziness, headache, and flushing[31].

Alpha-adrenergic agents (methyldopa, doxazosine, clonidine)

Alpha-adrenergic agents should not be considered as first-line therapy in CKD patients because of higher side effects incidence, such as dry mouth, sedation, and sexual dysfunction[31]. Headache, weakness, dizziness, and syncope are frequent in patients on selective α-1 blockers. Dizziness and syncope can be minimized by starting with a low dose of a long-acting agent such as doxazosin and administering the initial dose at bedtime[31].

Peripheral vasodilators

Direct powerful vasodilators, as minoxidil, are often administered together with beta-blocker and loop diuretic to minimize reflex tachycardia, hirsutism, pleural or pericardial effusion and lower extremity edema. It should be reserved for those patients on three drugs combination therapy who cannot achieve adequate BP levels according to international hypertension guidelines[31].

TYPE Ⅳ CARDIORENAL SYNDROME

Type Ⅳ cardiorenal syndrome (CRS), also defined as

chronic renocardiac, is characterized by cardiovascular involvement in patients affected by chronic kidney disease at any stage according to National Kidney Foundation (NKF) classification.

Hypertensive disease represent most important risk factor to develop a type Ⅳ CRS. Prevalence of end stage renal disease (ESRD) is still raising and it represents worldwide epidemiological challenge[32]. Last US data estimate up to 13% population present CKD at any stage of disease.

It's well established how renal dysfunction is an independent risk factor for cardiovascular disease; CKD patients show higher mortality risk for myocardial infection and sudden death[32].

At present time pathophysiological mechanisms leading to increased cardiovascular risk in CKD patients are not completely known but we are confident in strict connections between heart and kidney.

Decline of glomerular filtration rate (GFR) leads to activation of RAAS and sympathetic nervous system and, on the other hand, it stimulates calcium-parathyroid axis; this can be due to primary diseases such as diabetes or hypertension, main causes of CKD development in western countries.

Loss of kidney function usually leads to accumulation of sodium and water with consequent stimulus to angiotensin Ⅱ and aldosterone production and development of arterial hypertension. Hypertension, together with angiotensin and aldosterone, accelerates left ventricular hypertrophy and cardiac fibrosis.

Pathophysiology

To better understand pathophysiological pathways underlying type-4 CRS (Figure 2), we have to consider various aspects of this cardio-renal syndrome from atherosclerotic damage to vascular calcifications development up to left ventricular hypertrophy development and cardiomyocites remodelling. Finally galectin-3 and FGF-23 roles will be cleared based on last experimental evidences.

Coronary atherosclerotic heart disease

Epidemiological and clinical evidences have been proved association between renal dysfunction and cardiovascular disease; it's well established that late stages of CKD are closely associated to higher cardiovascular morbidity. On the other hand it's still unclear increased incidence of cardiovascular disease at early stages of chronic kidney disease.

CKD patients present increased rates of atherosclerotic coronary disease, acute coronary syndrome, left ventricular hypertrophy and sudden death.

Cardiovascular risk for patients with eGFR less 30 mL/min per 1.73/m^2 is ten fold higher in respect of patients with eGFRs above 60 mL/min per 1.73/m^2.

These higher rates are in contrast with risk expected from typical risk factor present in CKD patients (hypertension, diabetes, dyslipidemia and so on); CKD is probably able to directly contribute to cardiovascular complications[33,34].

CKD patients present, at early and late stages of disease, higher prevalence of coronary artery disease at angiographic evaluation; these patients also show multivessel disease and ECG evidence of previous silent ischemia[35].

Recent data showed that dobutamine stress echocardiography presents best accuracy for non-invasive coronary artery disease (CAD) screening in renal transplant candidates[36].

To assess CAD prevalence in early stages of CKD, an accurate review has evaluated coronary catheterization in 261 patients with eGFR between 30 and 90 mL/min; despite preserved renal function, more than half patients with eGFR > 90 mL/min had a 70% stenosis in at least one coronary artery. On the other hand, more than 84% patients with late stages of CKD (eGFR < 30 mL/min) showed significant CAD with higher involvement of left coronary artery and multivessel disease[37].

Coronary calcification, myocardial calcification and aortic compliance

Accelerated coronary atherosclerosis is not sufficient to completely explain higher rates of cardiovascular involvement in CKD patients.

We are now confident that osteoblastic transformation of smooth muscle cells is a key point in pathogenesis of vascular and valvular calcification during CKD.

Impaired vitamin D synthesis, secondary hyperparathyroidism and altered calcium-phosphate metabolism contribute to vascular calcification because of their direct effects on osteoblastic cells[38].

Coronary calcifications can predict major cardiac events contributing to reduced coronary reserve in CKD patients and higher risk of coronary acute syndromes[39,40] raising with progression of renal disease.

Clinical studies conducted with high resolution multislice computed tomography (CT) demonstrated early detection of coronary calcifications since CKD stage 3 according to NKF classification; patients data showed how 83% of them presented coronary calcification did not related to CKD stage[41]. Calcifications were also extended to low limbs arteries explaining high rates of lower extremity amputation among ESRD patients presenting also greater quantity and density of calcium deposits not limited to intima, but extended to vessels' media[42]. In other studies immunostaining assay of calcified areas demonstrated presence of bone matrix proteins such as osteopontin, type Ⅰ collagen and bone sialoprotein[43].

An autoptic evaluation showed how medial calcification was present in 16% of uremic patients but only in 3% of patients with normal renal function; medial calcification was also associated to presence of osteocalcin, inflammatory markers (TGF-α) and activated complement elements (C3 and C4)[44].

Increased calcium content can be accountable both reduced left ventricular compliance and prevalence of

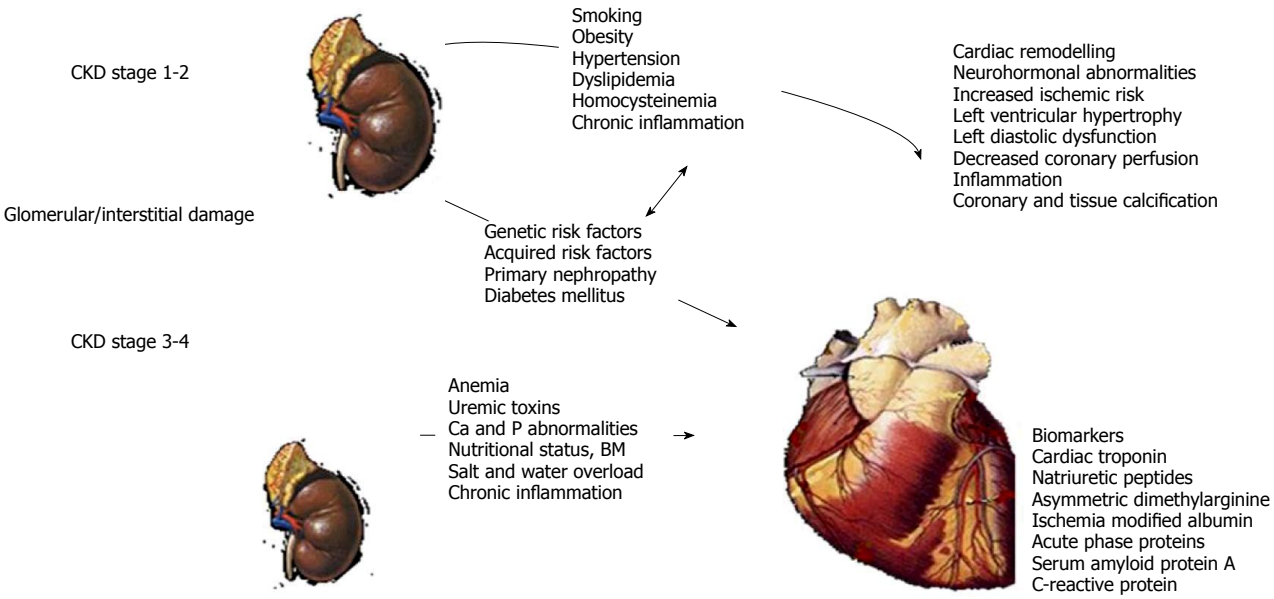

Figure 2 Pathophysiology of type IV **cardiorenal syndrome.** CKD: Chronic kidney disease.

arrhythmias.

Aortic calcification is strongly associated to reduced aortic compliance and coronary artery perfusion leading to increased central pressure inducing sub-endocardial ischemia because of reduced diastolic filling[45].

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) has been always recognized, together left ventricular systolic and diastolic dysfunction, main cardiovascular damage marker in CKD patients. LVH prevalence surely increases with declining renal function because of traditional risk factors as hypertension, diabetes and volume overload. More recent data have focused their attention of secondary hyperparathyroidism, malnutrition and even dialysis as further risk factors for development of LVH in CKD. LVH prevalence varies from 16%-31% in patients with GFR > 30 mL/min up to 60%-75% in ESRD and 90% prevalence in people starting renal replacement therapy[46].

Foley et al found that 74% of ESRD patients had echocardiographic evidence of LVH and 30% presented left ventricular failure[47].

In another survey including 596 incident hemodialysis patients with no history of cardiac disease, Foley demonstrated that, after 18 mo of dialysis, left ventricular mass index (LVMI) increased in 62% patients with left ventricular failure in 49% of them[48].

At present time mechanisms contributing to left ventricular dysfunction in CKD patients are unknown but many evidences suggest uremia products can directly affect cardiac structure; many of these toxins are highly protein bound and they present limited clearance by conventional dialyzers; these limitations could be accountable of dialysis effects on LVH and left heart failure[49].

Clinical conditions leading to LVH in CKD patients are similar to those observed in other clinical patterns including hypertension, atherosclerosis, pressure overload and RAAS activation. Atherosclerosis and hypertension directly promote myocites hypertrophy with consequent increased left ventricular mass, increased ventricular wall thickness, secondary myocardial fibrosis and compensatory hypertrophy[50].

In CKD patients aortic compliance is affected by accelerated atherosclerotic damage but other typical CKD variables, such as hyperphosphatemia, can affect aortic compliance[51].

In middle and end stage of CKD progression, progressive loss of nephron leads to salt and water accumulation with hypertension and volume/pressure overload; these changes up-regulate RAAS with release of profibrotic factors such as galectin-3, TGF-β and endogenous cardiac steroids[52].

As a LVH consequence, myocytes enlarge capillaries density because of increased oxygen demand; myocite diameter and interstitial volume space are increased in CKD patients compared to other patients groups: Long lasting periods of hemodynamic load promote cardiac remodeling and increase cardiac expression of interstitial myofibroblasts not ever present in normal myocardium[53].

Reduction in myocardial capillary density may explain marked CKD patients susceptibility to myocardial ischemia, LVH and myocardial fibrosis[53].

Uremia and cardiac fibrosis

Lot of evidence now suggest that CKD patients, especially late stages, develop particular pattern of cardiac fibrosis. CKD and ESRD patients present inter-myocardial fibrosis features quite different from those of hypertensive and chronic ischemic heart disease patients in which endocardial and epicardial fibrosis predominate[54].

Mechanisms leading to CKD cardiac fibrosis are still understood but recent evidences suggest that uremic toxins such as indoxyl sulfate and p-cresol can contribute to cardiac fibrosis in renal patients. In CKD patients indoxyl

sulfate concentrations are 300 fold higher than control population and it directly contributes to cardiac fibrosis by synthesis of TGF-β, tissue inhibitor of metalloproteinase-1 (TIMP-1) and alpha-1 collagen[54].

Fibroblast growth factor 23

Once verified close linkage between eGFR decline and cardiovascular structure changes, other further biomarkers have to be investigated.

One of them is represented by fibroblast growth factor-23 (FGF-23), member of fibroblast growth factor family (implicated in regulation, growth and differentiation of cardiac myocytes) holding paracrine functions in kidneys because of its phosphaturic properties; it blocks vitamin D3 synthesis and inhibits proximal nephron reabsorption[55].

During CKD progression, accumulation of phosphate leads to increase in FGF-23 incretion, which prolonged high levels can contribute to LVH and cardiac remodeling.

New data have shown that modest reduction in GFR can stimulate FGF-23 production; echocardiographic assays demonstrated a 5% LVMI rise for every log increase in plasma FGF-23 levels. Patients included in highest tertile of FGF-23 also have a 2.4 fold higher risk for coronary artery calcifications[56].

Diagnosis

Type-4 CRS diagnosis is based on serological and instrumental diagnosis of both chronic heart and kidney disease.

On one hand, cardiac function is more widely assessed by NT-proBNP serum levels, while, on the other hand, eGFR represent most employed biochemical test to evaluate kidney function.

Based on recent evidence, evaluation of FGF-23 levels can be helpful in monitoring secondary hyperparathyroidism status but it is also involved in cardiac fibrotic remodeling. Ultrasound diagnosis of type-4 CRS is classically based upon kidney and heart evaluation. Kidneys ultrasound evaluation usually shows classic features of chronic nephropathy such as thin and hyperechogenic cortex with reduced cortico-medullary ratio. It's quite frequent to observe small dilation of urinary tract and parapyelic cysts.

Echocardiographic assay allows to point out signs of volume overload, left ventricular dysfunction and right ventricular dysfunction especially in ESRD and hemodialysis patients.

At echocardiographic evaluation we can find increased atrial volumes or areas, pleural or pericardial effusion and lung comets (all signs of volume overload)[57].

Cardiac ultrasound also allow to discover presence of valvular calcifications (related to secondary hyperparathyroidism)[57] and possible right heart dysfunction features (high pulmonary artery pressure, low tricuspid annulus plane systolic excursion or right chamber dilation)[58].

Outcomes and treatment

Since type-4 CRS is characterized by chronic cardiovascular involvement in CKD patients, correction of traditional and non traditional cardiovascular risk factors is crucial.

Therapeutic interventions for traditional risk factors are less effective in patients with chronic kidney disease[59]. also for certain kind of "therapeutic nihilism" for which treatments with antiplatelets, statins, β-blockers and ACEi in CKD patients with coronary artery disease are often denied[59].

Strategies to reduce cardiovascular risk in CKD patients have to target both traditional (hypertension, dyslipidemia, diabetes, obesity) and non traditional (anemia, chronic inflammation, secondary hyperparthyroidism, LVH, oxydative stress, RAAS and SNS hyperactivity, renal replacement therapy complications).

Specific treatment targets are quite complicated especially in hemodialysis patients in which a lot of evidences support existence of a U-shaped curve associating mortality with blood pressure levels, BMI, dyslipidemia and hyperphosphatemia[60,61].

While it's clearly established role of secondary anemia correction[62] controversies are aroused about other risk factors corrections such as secondary hyperparathyroidism, hypertension and dyslipidemia.

For whom to concern secondary hyperparathyroidism, EVOLVE study conduced in hemodialysis patients found that cinacalcet therapy did not significantly reduce the risk of death or major cardiovascular events in patients with moderate-to-severe secondary hyperparathyroidism who were undergoing dialysis[63].

SHARP study investigated dyslipidemia treatment in CKD patients and it has been able to demonstrate a significant reduction in cardiovascular events, such as myocardial infarction, stroke, or need for coronary artery revascularization, with the use of a combination of ezetimibe plus simvastatin[64].

Pre-dialysis patients are closely recommended to maintain blood pressure levels below 130/80 mmHg, HbA1c levels below 7%, hemoglobin levels between 11 and 12 g/dL, C-LDL below 90 mg/dL. Patients should avoid nephrotoxic drugs and follow low protein diet (0.6 g/kg per day)[10].

Patients on dialysis should keep their blood pressure below 140/90 before starting dialytic session and below 130/80 after dialysis session.

Special consideration have to be focused on mineral bone disorders preventing hyperphosphatemia and vascular calcifications, also in early stages of CKD[65].

Treatment of arrhythmias and sudden death is still a challenge for nephrologists and cardiologists; together with prior attention to electrolytes disorders prevention (low potassium dialysate), use of β-blockers appears beneficial. ACE inhibitors and ARBs efficacy have to be proven in more prospective trials[66].

Implantation of cardiac defibrillators in dialysis patients is associated with increased risk for bleeding and infection and does not significantly affect morbidity and mortality[66].

CONCLUSION

Hypertension management is crucial in CKD patients to achieve correct both renal and cardiovascular protection. Despite the availability of several drug classes, optimal BP control still remains an open question. Management of CKD-related hypertensive patients appears more complex when real world data of clinical practice are compared to those deriving from randomized controlled clinical trials. What clinicians should perform is to encourage the use of antihypertensive agents other than RAS inhibitors also acting on ECV expansion by salt restriction and appropriate diuretics prescription.

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MINIREVIEWS

Hypertension in low and middle-income countries: Challenges, gaps and limited resources specific strategies

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Abstract

In this article we aim to discuss the burden of hypertension in middle-income countries, the challenges and opportunities, identify some implementation gaps in some of the published initiatives and propose a few pillars that could benefit an upstream population health and health promotion. One billion people suffer from hypertension worldwide; however, the prevalence of hypertension in low and middle-income countries is higher than that in the industrialized countries. Hypertension affects 45% of African adults aged 25 and above, compared to the 36% North American prevalence rate; moreover, the death rate from hypertension in LMICs is higher the than that of the European countries (141 *vs* 93 per 10000, respectively). The association between increased systolic blood pressure and income reversed between the early 80s and the first decade of the 20th century; the higher the per capita income the lower the risk of hypertension. Hence, unless an effective interventions, such as improving diagnosis and treatment, lowering salt intake, enhancing access and availability of fresh fruit and vegetable, and increasing leisure time physical activities are implemented, then low income countries epidemic is inevitable. In this article we aim to discuss the global burden of hypertension in low and middle-income countries, the gaps and challenges, identify the high-risk groups and propose a prevention and cost effective treatment strategic framework.

Key words: Hypertension; Screening; Low and middle-income countries; Socioeconomic characteristics; Strategic framework

Core tip: The burden of hypertension in middle-income countries is high. There are many challenges and opportunities, including lack of reliable accurate data and facing the existing correlation between socioeconomic characteristics and hypertension. A few successful models are presented and we suggest a strategic framework that would promote Population health approach.

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INTRODUCTION

In this article we aim to discuss the burden of hypertension in middle-income countries, the challenges and opportunities, identify some implementation gaps in some of the published initiatives and propose a few pillars that could benefit an *upstream* population health and health promotion.

THE BURDEN

From 1990 to 2010, hypertension had jumped from 4th to 1st place as a leading risk factor of the years of life lost and years lived with disability; making hypertension the leading global burden of disease risk factor[1]. Moreover, more than 25% of the adult population suffers from hypertension globally, and more than three quarters of them reside in low and middle-income countries (LMIC); defined by the world Bank identifies the LMICs as those having per capita gross annual income of less than $12275 USD[2-4]. Furthermore, hypertension affects 45% of African adults aged ⩾ 25 years, compared to the 36% North American prevalence rate, and hypertension mortality rates in LMICs are higher than those of European countries (141 *vs* 93 per 10000, respectively)[5].

A recent meta-analysis of 242 published studies, and 1.5 million adults having blood pressure ⩾ 140/90 mmHg or self reported use of BP medications estimates the 2015's hypertension prevalence of 37.8% in middle income countries, with a projected 30% increase by the year 2025[6]. Consequently > 75% of the global hypertensive population will be living in LMICs; in addition, the prevalence was 53%-78% in the elderly population ⩾ 65 years old, 46.4% in the overweight or obese sector with BMI ⩾ 25, 50.2% in non-formally educated individuals, 32.7% in urban and 25.2% in rural communities and 39.1% in South America compared to 26.5% in the Middle East. No gender difference was observed[6,7].

Furthermore, the systolic blood pressure severity is constantly increasing in LMICs compared to high class. Between 1990 and 2008, Kenya had 5-mmHg increases in SBP, and this coincided with 3-mmHg drop in the United States[8,9].

CHALLENGES

Strained healthcare systems

Effective hypertension management is multifactorial and complex. LMICs lack effective screening and diagnosis, suboptimal life style modification strategies, lack of non-pharmacological upstream approach, and limited funding for in depth hypertension research and strained resources. In addition, healthcare systems are not well equipped, are consumed and directed towards communicable disease management rather than non-communicable disease prevention. Consequently, these factors were the reason more than 2/3 of the eligible population in India and Chennai did not receive guideline driven hypertension management. Similarly 43% lack awareness and 31% are-sub-optimally treated in China, while only 2% have a good control rate in Africa[4,10].

Lack of access and disparity

WHO survey in 2007-2010 among five LMICs on 1867 subjects illustrated both lack of access, and access disparity based on the patients' socioeconomic status, and showed that proper access was available in 16% in Uganda and 49% in Jordan, while those with insurance coverage were three times more likely to have access compared to those without[11].

Lack of reliable accurate data

The lack of geographically representative, accurate, and reliable national or multinational databases and/or registries in LMIC, impedes further development of evidence based policies and guidelines[12]. Consequently, LMICs are forced to rely on the data and models that are developed in high income groups that have higher public awareness and more established healthcare policies. Such reliance might affect accuracy and size of the magnitude of the problem and adversely affect outcome by taking expensive measures that are directed to the part and not all segments of the problem.

Research misconduct

Research misconduct has been a global and is not exclusively a LMICs phenomenon; for instance, authorship misuse is prevalent with an average rate of 55%, South Africa (64%), India (38%), Bangladesh (60%) and China (34%)[13-15].

SOCIOECONOMIC CHARACTERISTICS (SES)

Correlation between SES and hypertension

The common wisdom theory of the linear negative correlation between SES and hypertension has been challenged in the literature. The correlation between the SES and population health outcome is internationally recognized[16,17].

There is a prevalence of 23.1% hypertension in LICs; in comparison to 37% and 31% of that in middle and high-income countries respectively[6]. Moreover, education level was observed to have positive association with hypertension risk in South Asia; in contrast to an inverse relation in East Asia[18].

Education gradient paradox

A recent systematic review of 36 articles from 15 countries, challenged the negative correlation between

education and hypertension, and concluded the absence of any significant correlation[18]. In another study, education had no significant correlation to the prevalence of hypertension, and contrary to expectations, there was an inverse gradient between the SES and hypertension[19].

Self-reporting vs standardized methods of screening

Although self-reporting, the commonly used public screening method of hypertension in LMICs is simple, easy, and cost effective, it may underestimate the prevalence of the disease; compared to the more resource intensive standardized symptom/criterion-based measures[20].

LESSONS LEARNED FROM RECENT INTERVENTIONS

Healthcare access based intervention in Uganda

A nurse-led program in Uganda focusing on knowledge, skills and attitudes (KSA) of hypertensive patients in the outpatient setting showed marked improvement. Seven nurses had 50 patients attending daily with either hypertension or diabetes, who received 22 h of face-to-face training sessions, and home study CD-ROMs[21].

Mobile digital intervention in Mexico and Honduras

This study illustrated an example of efficient use of mobile technology, automated phone call messaging, email communication and home blood pressure monitoring initiative in 181 patients with low SES in Mexico and Honduras. The patients received automated phone calls focusing on self-management skills, health education, medicine intake reminders baseline and 6-wk office visits with either a physician or a nurse practitioner, and pre and post questionnaires that measured perceived mental and physical health, end user experiences, and overall satisfaction. Post intervention, there was a modest, yet statistically significant SBP decrease, depressive symptom improvement (-2.5 points), medication adherence improvement, sense of well being perception, and favorable patient experiences[2].

Health education and awareness initiative in Pakistan

A two-year research guided health promotion initiative family based home health education by trained healthcare workers, in Pakistan, received three-monthly education sessions at home by 6 healthcare workers. The initial session was 90 and the rest were 30 min each. The primary outcome measure was 3-consecutive BP readings and BMI value at the end of the 2 years. This resulted in statistically significant decrease in both systolic and diastolic BP but non-statistically significant change in smoking cessation rate or in BMI value[22,23].

The 12th five-year plan in China

In 2009, China elected to administer top-down implementation of healthcare system reform (also known as the 12th five year plan). The Chinese government performed mass media campaigns, regulated nutritional labeling, enforced time allocation for daily exercise at schools, and tried to enforce some antismoking efforts, the detailed results of individual NCDs such as hypertension and diabetes are not yet published.

STRATEGIC FRAMEWORK

Politico-socioeconomic pillar

We hypothesize that managing hypertension in LMICs requires a politico-socioeconomic intervention. Patchy pharmaceutical services, patient education, adherence to medication advice and/or life style change messages at the healthcare access point strategies, oversimplify the issue. Decreasing the burden of hypertension is a national priority that requires multifaceted inter-sectoral national and internationally collaborated top down implementation of well-planned public health and health promotion strategies that efficiently engage targeted and disadvantaged population at risk. In addition, it requires expanding primary care services, executing a model of national insurance coverage, adopting quality based funding that encourages good performance, exploring the national pharmaceutical program for rational use of both formulary-listed and generic medications, eliminating or decreasing user fees, optimal use of tele-health and mobile technology, and innovating remuneration initiatives that ensures health for all and engages all for health.

Measuring the current status

Conducting situational assessment through accurate precise research is a corner stone for any health promotion planning. Since precise large representative databases are not well established yet in LMICs', policies will have to depend on customized data originating from the HICs' databases. However, this process needs a robust knowledge translation and a defined list of appropriate performance measures.

Public engagement and reporting strategy

Public involvement in healthcare decision-making is a continuum that ranges from communication and listening to actively engaging and developing partnerships. It enriches public policies, strengthens community actions, results in less resistance and more engagement that result in improving the health program. Town hall meeting methodology may not be a feasible option for public engagement, but the spiritual leaders and organizations may have a large role to play through their weekly services or at their spiritual gatherings and celebrations.

Transparent public reporting of the performance measures, and initiatives' results, enhances accountability and improves the service efficiency and quality and avoid public loss of interest in participation, feeling a loss of independence[24].

The opportunities for utilizing technological data base on/off line databases are provocative if resources allow.

Opportunistic screening

In our opinion, opportunistic hypertension screening may be the optimal cost effective methods that would utilize the available resources already existing in LMICs. Opportunistic screening would affect policy implementation on choosing physician remuneration methods, optimizing the scope of nurse specialists in community care centers, and pharmacists prior to medication refill to bill for BP check, and finally, on linking the BP measurement results to the national or multinational hypertension database. One large study of elderly population of 50 years or older in 6 LMICs countries, estimate that opportunistic screening with wrist BP machine during routine doctor visits, increases the awareness of hypertension from 25% to 81%[25].

Population health approach

Hypertension management strategic planning in LMICs, could utilize and customize frameworks of certain internationally recognized health promotion milestones that go beyond healthcare, such as the Ottawa Charter of Health[25]; Such goals can be achieved *via* building evidence based public policies of salt reduction, effective food label monitoring, subsidized health services, guaranteed minimum income. It might also be achieved by creating a supportive environment of encouraging physical activities in the work place such as gym time permission during working hours, enforcing a daily period of moderate physical education incorporated into all school levels' curricula, and regulating new town walking trails building codes.

A third approach is through strengthening community actions *via* supporting and funding civil and spiritual organization health initiatives, and sponsoring mass media campaign coverage of successful stories and promising community initiatives.

A fourth approach is by developing personal skills through facilitating life-long education of health care workers, providing hypertension training courses and diplomas for nurses and physicians, collaborating with self-regulatory authorities to broaden the scope of services of specialized nurses.

A fifth tactic is by empowering patients by knowledge acquisition of self-management tools, symptom awareness and recognition, and chronic disease and stress coping skills, efficient utilization of hypertension specialized clinics to improve access, and optimizing the use of mobile technologies and home BP monitoring to enhance patient compliance.

Finally, the reorientation of health services requires strategic shift to allocate resources for well-planned primary care service availability, especially for population at risk and vulnerable groups. Emphasizing healthcare cultural shift towards prevention, public health promotion and improving health literacy level, especially for the marginalized groups with low SEP.

CONCLUSION

Hypertension management in LMICs is a problem of great magnitude–requiring collaborative leadership effort going beyond availability of effective medications, and requiring effective patient engagement, visionary proactive leadership, tailored knowledge translation of the HICs initiatives and programs, and most importantly top down implementation of health promotion national socioeconomically-driven programs.

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