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Short Communication

Blood pressure goals in CKD-SPRINTing away from JNC-8?

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The awareness and control of hypertension (HTN) in the US continues to improve with increasing application of evidence database derived from landmark clinical trials originating since the late 1960s [1,2]. Not with standing disease awareness and success achieved in the general population, control of HTN in Chronic Kidney Disease (CKD) patients still lags behind that of the general population [3]. This is unfortunate giventhat the high prevalence of HTN in CKD and the already elevated risk of cardiovascular disease (CVD) in this population magnifies morbidity and mortality from hypertension [3,4]. Not only this, the kidney itself is a victim of target organ damage with observational studies show a direct and graded relationship between baseline blood pressure with risk of End Stage Renal Disease (ESRD) when followed over extended periods of time [5]. In view of this it comes as no surprise that HTN follows Diabetes Mellitus as the second most common cause of ESRD in the US population bringing with it the challenge of translating ground breaking research in cardiovascular medicine into meaningful renal outcomes [3].

Ever since the seminal research by the eminent physiologist-Arthur Guyton nearly five decades back, the kidney has been implicated as the prime driver of sustained hypertension [6]. Guyton demonstrated that the fundamental defect in HTN is a rightward shift in the pressure natriuresis curve which, coupled with an infinite feedback gain property of the kidney, leads to modulation of blood pressureto a set point where urinary salt excretion balances sodium input in order to preserve volume homeostasis [6]. However, subsequent renal damage from HTN is a complex process involving multiple downstream events which includeautoregulatory failure causing direct systemic BP transmission to the glomerulus that incite hyperfiltration, podocyte damage, proteinuria and eventual glomerular sclerosis [7]. Other obscure pathways include (in the very least) oxidative stress, endothelial dysfunction and renin-angiotensin system reactivationleading to chronic hypoxia and tubulointerstitialfibrosis[7]. Thus a vicious cycle is set in motion wherein hypertension begets renal injury and vice-versa making it exceeding complex to tease out the primary event in clinical settings. Given the myriad pathways of injury, it is reasonable to assume, that single agents will eventually fail to control blood pressure in CKD unless backed up with specific agents to block renin-angiotensin pathway and promote natriuresis. Another fallout from this complex pathway is that renal damage may occur from both HTN related endothelial damage andtissue hypoxia from low systemic perfusion pressures accounting for suboptimal renal outcomes in interventional trials on HTN, unlike stroke or heart failure [8].

In this backdrop it is ironic that lower BP targets continue to be the sole driver of decision making process based on demonstration of better cardiovascular outcomes in major interventional trials even as renal outcomes are unknown since these trials systematically excluded CKD patients [2]. In order to address large knowledge gaps on this issue, an international committee of hypertension experts under the Kidney Disease: Improving Global Outcomes (KDIGO) met in 2012 and published HTN management guidelines in non-dialysis CKDpopulation by synthesizing expert opinion with limited primary data [9]. The KDIGO recommended treating at and to a goal less than 140/90 in both diabetic and non-diabetic CKD with a urinary albumin excretion (UAE) of less than 30 mg/day even though the evidence base was limited [9]. However, recommendations for diabetic and non-diabetic CKD with UAE of > 30 mg/day was lowered to <130/80 based on the committee opinion and expertise even though there was poorevidence [9].

The recently published 8th Joint National Committee report in 2013 fundamentally differed from the KDIGO in suggesting a common therapeutic threshold and goal of 140/90 regardless of the etiology of CKD or the extent of proteinuria [10]. The Committee found little evidence to support different BP goals through scrutiny of high quality primary data [10]. As per the committee report only 3 randomized trials met its quality standards of large sample size and sufficient follow up duration to give greater precision in recommendations [10]. Even amongst the 3 included trials (MDRD: Modification of Diet in Renal Disease, AASK: Afroamerican Study of Kidney Disease and Hypertension, Ramipril in Nephropathy: REIN-2) there was no uniformity in study population, etiology of CKD and primary end points including the use of systolic, mean arterial or diastolic BP goals as therapeutic targets [11-13]. Additionally, with regard to a lower BP goal for patients with substantial proteinuria only the MDRD showed benefit of intensive MAP goal <92 based on post-hoc analysis while baseline proteinuria did not fundamentally alter results in the REIN-2 or the AASK trials even when it was pre-specified [11-13]. A discussion of specific antihypertensive agents for BP is beyond the scope the present article, although suffice to say that both KDIGO and JNC-8 concur that Angiotensin- Converting enzyme(ACE) inhibitorsor Angiotensin Receptor blockers(ARBs) should be the first lineanti-hypertensive agents in all forms of CKD [9,10].

In this context, the SPRINT trial results, which came close at heels of the JNC-8 report, is a breakthrough in HTN research since it corroborates observational data linking reduced cardiovascular

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mortality to intensive BP control [14,15]. The major conclusions from the SPRINT trialwas that aSBP goal of less than 120 mmHg (intensive arm) was significantly better than a goal of less than 140 mmHg (standard arm) in terms of nearly 25% risk reduction of primary outcome(a composite CVD endpoint of first occurrence of Myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure or CV death) and a 27% reduction in all-cause mortality (secondary outcome) within a short follow up period of 3.26 years [14]. Importantly, the benefits of such intensive treatment extended uniformly across patients of different ages(less than 75 yrs or above), sex, race (Afro-American vs others) and baseline CVD or CKD. While SPRINT was primarily a CVD outcome trial, the study design included patients with CKD with estimated GFR ranging between 20-60 ml/min [14]. Additionally, the study did include composite renal outcomes aspart of its pre-specified secondary analysis [14]. Even though intensive SBP goal in patients with preexisting CKD did not alter composite renal outcomes (a combination of >50% GFR reduction, ESRD or renal transplantation) the absolute event rates were too small to give meaningful insights. However, the sub-group population without pre-existing CKD experienced significantly greater number of renal events(defined as drop in >30% GFR from baseline) when randomized to intensive SBP goal (hazard ratio of 3.48, 95% CI 2.44-5.10) even as adverse events such as orthostatic hypotension, hyponatremia, hypokalemia and Acute Kidney Injury (AKI) were significantly higher in the intensive SBP arm.The authors disclosed that differences in incidence of electrolyte disturbances could be due to a preferential use of thiazide- like diuretic in the intensive arm although it is important to emphasize that the SPRINT study was not designed to test the efficacy of specific medications to achieve different BP goals [14].

Meanwhile, the SPRINT trial has added a new dimension to our efforts at CVD prevention by demonstrating the feasibility and efficacy of intensive hypertensive therapies directed towards a high CVD risk cohort. This is even more meaningful in the context of CKD given that it is a high-risk population and the fact that nearly 28% ofthe study population had CKD of varying severity [14]. At this point the results are a mixed bag for the nephrologist. The euphoria of substantial CVD risk reduction with intensive SBP control is somehow neutralized by faint indications of treatment harms which go beyond simply orthostatic hypotension and include serious events such as AKI. This is all the more significant since clinical practice is expected to be much different than a controlled research setting in the context of resources available for monitoring patient safety. Coupled with this, the short follow up period and large attrition rate in the SPRINT trial will continue to intrigue us as to what are the actual risk-benefits of such intensive therapies in real life situations [14].

Does this newfound confidence with attempting lower SBP goals foreshadow the conclusions of the 8th JNC on BP goals in the perspective of CKD? On a closer look, BP pressure measurements in SPRINT differed from conventional office manual BP measurements in that it used automated oscillatory BP (AOBP) technique [14]. The AOBP instrument records readings without any human intervention at regular intervals after at least 5 minutes of rest, simulating a period of rest and thus reducing "white coat effect" typically associated with office BP readings [16]. The reported reading is a mean of 3 readings recorded at regular intervals with SBP values 7-10 mmHg lower than manual measurements taken for the same patients on the same day and time [16]. The consistency of such readings is believed to be higher due to elimination of observer bias andcorrelates well with awake ambulatory BP [16]. It is , therefore, not surprising that in a sub-study of the SPRINT trial using the 24 hour ambulatory BP monitoring (SPRINT-ABPM) performed at 3 weeks into the study period, the intensive SBP arm had significantly lower 24 hr, daytime, and night time ambulatory BP and BP variability than standard SBP arm [17]. This may explain the impressive CVD reduction noted in the SPRINT trial since there is growing evidence that short term (ambulatory) or long term (clinic-to-clinic) BP variability, over and above mean BP is associated with cardiovascular events and mortality [18].

Notwithstanding all this good news, the issue of reno-protection with intensive BP targets will continue to perplex us in the post-SPRINT era, intimidated by fears of therapeutic-nihilism if we continue to ignore the strong epidemiological association of poor baseline BP control with both cardiovascular disease and ESRD even as patient safety is not compromised [5]. Unfortunately, the SPRINT trial excluded diabetics, uncontrolled hypertensives or patients with substantial proteinuria (>1 g/day), who are traditionally at high risk for progression of CKD, to be widely applicable to a gamut of patients commonly seen in nephrology practice [14]. As of now it seems the inter-twining of the renal origins of essential HTN with hypertensive renal damage is the proverbial Gordian knot in our understanding of appropriate therapeutic BP targets for nephroprotection. It is possible that potentially unknown factors driving hypertensive renal damage have not yet been discovered. While it is too premature to speculate, recent demonstration of the high incidence of masked hypertensionin CKD and its link with low Glomerular Filtration Rate, proteinuria and cardiovascular target organ damage could pave the way for newer approaches to optimize both cardiovascular and renal outcomes [19].

Amidst all this uncertainty, the need to individualize BP goals in CKD, while weighing risks to benefits for each patient will continue to be the guiding mantra until more trials clear the mist. Regardless of the issue of generalizability, the SPRINT trial results have given an impetus to general practitioners and nephrologists alike to advocate intensive SBP goals to a cohort of well compliant non-diabetic hypertensives in their office practice so as to maximize benefits in terms of CVD events and survival. The issue of sustaining impressive cardiovascular benefits of intensive BP control with close monitoring of adverse events, including among others, hypo-perfusion related AKI or electrolyte imbalances, should become a key priority for hypertension research in the near future.

Disclaimer

The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

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