Pol. J. Appl. Sci., **2018**, *4*, 36-39

RECENT CONTROVERSIES OVER THE DIAGNOSIS AND TREATMENT OF HYPERTENSION – NEPHROLOGICAL PERSPECTIVE

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Abstract: Recent controversies over the diagnosis and treatment of hypertension (HT) are reviewed from nephrological perspective. In 2017 American College of Cardiology (ACC) and American Heart Association (AHA), on behalf of 11 societies, presented Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, which lowered the threshold from >140/90 mm Hg to >120/80 mm Hg. The lowered threshold value caused an increase of HT in the U.S. by 31.1 million people (from 72.2 to 103.3 million). ACC/AHA guidelines advice self-measuring blood pressure (SMBP) after 5 min rest as superior to office-measured blood pressure. All organisations advice taking a mean of repeated measurements as a proper BP. The only exception is National Institute for Health and Clinical Excellence which reasonably recommends taking the lowest reading as the proper value of BP. Too intensive lowering of BP in cardiovascular high risk population may be beneficial for heart diseases and lower mortality, but may increase risk of AKI, which may contribute to progressive CKD and end stage kidney disease. The optimal BP target for dialysed patients is unknown but it is generally accepted that overhydration is the most important factor in the pathogenesis and treatment of hypertension in dialysed patients. It was proven that proper ultrafiltration and/or frequent hemodialysis allow for better control of blood pressure. Hypertension in renal transplant recipients increases cardiovascular morbidity and mortality and shortens allograft survival. In kidney diseases a personalized approach to the treatment of HT should be advised, starting from inhibitors of the renin–angiotensin system, unless there is indication for the other group of hypotensive drugs.

Key words: hypertension, intensive treatment, renal effect.

DOI: 10.19260/PJAS.2018.4.1.07

Introduction

Most patients with kidney diseases have arterial hypertension (HT) although it depends primarily on how it is measured as well as the definition being used. Until recently, most societies have recommended a threshold >140/90 mm Hg for diagnosing hypertension both in the general population and in patients with kidney diseases. In 2017 American College of Cardiology (ACC) and American Heart Association (AHA), on behalf of 11 societies, presented Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, which lowered the threshold from >140/90 mm Hg to >120/80 mm Hg [1]. According to the new definition, about 46% of U.S. adults would have hypertension, as compared with about 32% under the previous definition. The lowered threshold value caused an increase of hypertension in the U.S. by 31.1 million people (from 72.2 to 103.3 million) [2]

Measuring BP

ACC/AHA guidelines evaluated self-measuring blood pressure (SMBP) as superior to office-measured blood pressure. The previous recommendations included an appropriate sitting position and proper cuff size. In addition, blood pressure (BP) should be measured after at least 5 min rest and, when higher than normal, repeated at least once after 1-2 min. Lastly, verified devices should be used. The recommendation of taking the mean of all the repeated readings as a real BP is controversial. This is corroborated by the recent position statements of American Diabetes Association [3]. The only organisation with a different recommendation is the British National Institute for Health and Clinical Excellence [4] which recommends taking the lowest reading as the proper value of BP. According to this author, this is the most prudent advice although a unique one. In questionable cases, when SMBP is taken at least two times daily (morning and evening) for some days, and the results are not conclusive then Automatic BP Monitoring (ABPM) is advised. When postural symptoms are reported, sitting and standing BP should be checked. In postural hypotension (the difference in systolic BP >20 mm Hg and/or diastolic BP >10) hypotensive drugs should be stopped and reintroduced at lower doses or changed.

The ACC/AHA 2017 guidelines emphasize an aggressive management of blood pressure in patients with PB 140/90 mm Hg or higher and >10% cardiovascular 10-year risk. Patients with a blood pressure of 130 to 139/80 to 89 mm Hg should receive nonpharmacologic treatment, unless

they have a 10-year risk above 10%. In such cases, additionally taking a single antihypertensive drug is advised. The ACC/AHA guideline defines normal blood pressure as below 120/80 mm Hg and elevated blood pressure as 120 to 129 mm Hg systolic with a diastolic pressure below 80 mm Hg. Stage 1 HT is defined as 130 to139 mm Hg systolic or 80 to 89 mm Hg diastolic, and stage 2 hypertension as 140/90 mm Hg or higher (the old definition of hypertension). What is now called stage 1 HT was previously labelled "prehypertension".

Bakris et al [5] noticed that the new goal may be difficult to achieve particularly in those with poor vascular compliance (i.e., pulse pressures above 80 to 90 mm Hg), and who typically have dizziness as well as poor mentation as their systolic blood pressure approaches 140 mm HgIn. The new guideline focuses only on the systolic blood-pressure goal of less than 130 mm Hg, ignoring diastolic pressure and does not consider isolated systolic hypertension, which is a major problem among many people over 70 [5].

The ACC/AHA guidelines advise reducing sodium intake to less than 1500 mg in nonpharmacological treatment, which seems to be too stringent, as it is generally accepted that <2400 mg is enough and still difficult for patients to adhere to [5].

The BP goal of less than 130/80 mm Hg is even lower than suggested in the Systolic Blood Pressure Intervention Trial (SPRINT). It was a multicentre, randomized, controlled trial, comparing intensive with standard systolic BP control (120 versus, 140 mm Hg) in patients without diabetes and with high cardiovascular risk [6].

The trial was stopped early (after 3.26 years of follow-up) due to significantly lower rate of fatal and nonfatal major cardiovascular events in the intensive treatment group. The results of SPRINT were different from the ACCORD study, which did not show positive outcomes of intensive lowering BP (<120 mm Hg) in diabetics [7].

Due to a unique system of measuring BP (self-measurement with an automatic machine) in SPRINT trial, the systolic blood pressure should be 10 to 15 mm Hg lower than in general practice; therefore, it was prudent to select 130/80 mm Hg rather than 120/80 mm Hg as the target. On the other hand, it seemed doubtful to consider a similar target for all individuals over 65 years old, including 80+ although the intensive group had a lower rate of all-cause death (HR 0,72).

Renal function in SPRINT

It has been generally accepted that hypertension impairs renal function and accelerates the progression of chronic kidney disease (CKD). Therefore, proper treatment of hypertension has been considered the primary approach to protect kidney function. Unexpectedly, intensive treatment in SPRINT was associated with a faster decline of the kidneys' function (30% reduction in eGFR to <60 ml/min per 1.73 m^2) on two consecutive laboratory determinations collected at 3-month intervals with hazard ratio (HR) of 3.49. On the other hand, Cheung et al. performed a secondary analysis of SPRINT in patients with CKD and found that the effects of the treatment did not differ among participants with and without CKD [8]. The prespecified, main kidney outcome, defined as the composite of ⩾50% decrease in eGFR from the baseline or End Stage Renal Disease (ESRD), occurred in 15 cases from the intensive group and 16 standard group participants. Although the rate of decline in eGFR in the intensive treatment group and the standard treatment group was low, the eGFR decline curve in the intensive treatment group was actually steeper after the initial 6 months. It is possible that aggressive treatment of hypertension may decrease perfusion of the kidneys too much. After exceeding a certain value of around 30%, a reduction in intraglomerular pressure is not renoprotective but harmful. An observational study in patients with CKD showed an association between a 30% reduction in eGFR and a higher long-term risk of ESRD [9].

In a more detailed secondary analysis of the SPRINT database by Magrico et al, kidney function decline and less cardiovascular events were more frequent with greater Mean Arterial Pressure (MAP) reductions in both the intensive and standard treatment groups [10]. Patients who had a greater MAP reduction had significantly higher baseline: BP (MAP, systolic, and diastolic), total cholesterol, and ratio of urinary albumin to creatinine, therefore, presenting higher cardiovascular and kidney injury risks.

Magrico et. al. showed that within the intensive treatment group adjusted hazard ratios (HR) for kidney function decline were 2.10 for MAP reduction between 20 and 40 mm Hg and 6.22 for MAP reduction >40 mm Hg. In propensity score analysis, the mean arterial pressure reduction <20 mm Hg presented a number needed to treat of 44 and a number needed to harm (NNH) of 65, reduction between 20 and 40 mm Hg presented a number needed to treat (NNT) of 42 and an NNH of 35, and reduction >40 mm Hg presented an NNT of 95 and an NNH of 16. The explanation of these unexpected findings may lay in patients included in the SPRINT, who were older and had high cardiovascular risk, probably due to atherosclerosis. Therefore, they represent a population at higher risk for impaired renal autoregulation and increased susceptibility to kidney hypoperfusion with larger decreases in MAP.

In SPRINT the intensive BP lowering resulted in more frequent episodes of AKI (179 participants in the intensive arm and 109 in the standard arm; 3.8% vs 2.3%; HR, 1.64), mostly in elderly patients and with previous CKD, predo-

minantly due to volume depletion and/or hypotension [11]. Episodes of AKI were generally mild – first stage according to modified KDIGO criteria in about 60% and quite evenly distributed in the both arms. Dialysis was required in 8, and in 5 patients, respectively. About 90% of the patients recovered kidney function completely or partially. End-stage kidney disease developed in 2 intensive-arm and 3 standard-arm participants. Episodes of AKI have consistently been associated with an increased risk for in-hospital mortality. Although participants in the intensive arm had increased risk for AKI events, they still had reduced risk for the primary SPRINT outcome and all caused mortality compared with those in the standard arm [6]. This pattern was observed across the groups without basic kidney disease [12] and with CKD [8]. So, the physicians should be aware that intensive lowering of BP in high risk population may be beneficial for heart diseases and lower mortality, but may increase risk of AKI, which may contribute to progressive CKD and end stage kidney disease [13].

HT in dialysed patients

The optimal BP target for patients receiving dialysis is unknown. The Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommends a predialysis systolic BP (SBP) of <140 mm Hg in patients receiving hemodialysis (HD) and peritoneal dialysis but on the basis of an expert opinion [14]. Overhydration is the most important factor in the pathogenesis and treatment of hypertension in dialysed patients [15].

Observational studies in patients on HD have found increased mortality among those with SBP>140 mm Hg [16].

It was proven that frequent hemodialysis allows for better control of blood pressure [17].

Recently, Miskulin et. al. randomized 126 hypertensive patients on hemodialysis to a standardized predialysis systolic BP of 110–140 mm Hg (intensive arm) or 155–165 mm Hg (standard arm) [18]. During months 4-12 the average difference in systolic BP across arms was 12.9 mm Hg. In the intensive arm, systolic BP decreased from 160 mm Hg at baseline to 143 mm Hg at 4.5 months. In the intensive arm there were more frequent: major cardiovascular events, hospitalizations and vascular access thromboses (IRR were 1.18, 1.61, and 3.09, respectively). Intradialytic hypotension was also higher in the more intensive group. Four deaths occurred in the intensive arm and only one in the standard arm. The intensive and standard arms had similar median changes in left ventricular mass. The study must be repeated with more patients for a longer duration, but in the meantime it seems prudent to be very careful when lowering hypertension below 140/90. The blockade of the renin-angiotensin seems to be the preferred first-line antihypertensive drug therapy in HD patients, unless there is indication for the other group of hypotensive drugs, e.g. β-adrenergic blocker.

HT in kidney transplantation

Hypertension in renal transplant recipients was recently reviewed by Weir et. al [19]. It is common and ranges from 50% to 80% in adult recipients. Cardiovascular morbidity and mortality and shortened allograft survival are important consequences of inadequate control of hypertension. Donor and recipient factors, acute and chronic allograft injury, and immunosuppressive medications may each explain some of the pathophysiology of post-transplant hypertension.

BP treatment goals for renal transplant recipients remain an enigma because there are no adequate randomized controlled trials to support a benefit from targeting lower BP levels on graft and patient survival. Therefore, targets from general population are applied to kidney recipients. To date, no specific antihypertensive medications, including renin-angiotensin system inhibitors, have been shown to be more effective than others at improving either patient or graft survival. Hiremath et.al. performed a systematic review of 8 trials (1,502 participants) and found that RAS blockade did not alter all-cause mortality, transplant failure and creatinine level doubling, but it was associated with higher risk for hyperkalemia [20]. This analysis neither supports nor refutes the hypothesis that RAS blockade improves clinical outcomes in kidney transplant recipients. According to the authors, a trial with more than 10,000 patients would be needed to definitively answer whether RAS blockade reduces transplant loss in this population. The potential drug interactions with immunosuppresants and altered pharmacokinetics and pharmacodynamics of the different antihypertensive medications need to be carefully considered.

Conclusions

A proper measuring of BP is crucial in diagnosis and treatment of HT. Targets from the general population are applied to patients with kidney diseases. The aim of treatment of HT is lowering cardiovascular complications and preventing increased mortality. Personalized approach to the treatment of HT should be advised, starting from diuretics, calcium channel blockers and inhibitors of the renin –angiotensin system (ACE i/ARB). Blockers of $\alpha 1$ receptor and β-blockers should be reserved to specific additional indications. The initial step in treatment should be the gradual lowering MAP by not more than 40 mm Hg, aiming at $\leqslant$140/90 mm Hg. When well tolerated and without postural hypotension, after some months, it is reasonable to try to lower BP to $\leqslant$130/80 mm Hg particularly in patients

with a high risk of cardiovascular complications, which may be achievable in about 50%. The targets and the drugs are similar in patients with and without CKD, with exception of patients with high proteinuria, who should be treated with ACE inhibitors or ARB to rich PB $\leqslant$130/80 mm Hg, providing no major side effects have occurred. In patients with eGFR less than 30 ml/min/1,73 m^2, overhydration is the key for sustaining hypertension. In a non-dialysed loop diuretics should be chosen (furosemide or torasemide), whereas in a dialyzed one proper ultrafiltration is a mainstay in hypotensive measures. In patients with a transplanted kidney the targets and measures from the general population are applied but possible interaction of hypotensive drugs with immunosuppressive drugs should be considered.

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Received: 2018
Accepted: 2018