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Review Article

Intensive blood pressure control on dementia in patients with chronic kidney disease: Potential reduction in disease burden

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ABSTRACT

Chronic kidney disease (CKD) and dementia are both common comorbidities creating considerable morbidity and mortality, especially in the elderly population with potential interactions. Even though various hypothetical mechanisms underlying the pathophysiology of increased risk of dementia and cognitive impairment in CKD patients have been implicated, no consensus has been reached so far. Recent clinical trials have investigated the therapeutic role of intensive blood pressure control on the risk of dementia in CKD patients with potentially improved outcomes. However, such trials have significant limitations that may influence the outcome and lack specific management guidelines. We reviewed the role of blood pressure and other factors on the risk of dementia in CKD patients which is an issue with high potential for clinical implications that may improve morbidity, mortality, and health expenditures along with its' potential pathophysiological mechanisms and future guidance.

1. Introduction

Chronic kidney disease (CKD) is defined by either presence of a decline in renal function, mostly assessed via creatinine or cystatin C-based estimated glomerular filtration rate (eGFR) measurements, or clinical or laboratory signs of kidney damage, mostly assessed via albuminuria or urine sediments over 3 months[1]. CKD is the 9th leading cause of mortality in the United States in 2019 with more than 50.000 deaths while the burden of CKD includes considerable debilitating morbidities including chronic heart failure, arrhythmia, hypertension, uremic complications, infections, cerebrovascular diseases, atherosclerosis, thromboembolism, cognitive impairment and dementia [2,3]. Even though hypertension, CKD, and dementia are common comorbidities frequently seen in elderly individuals, shared underlying pathophysiological mechanisms among those comorbidities which may create a potential therapeutic target for reduction in the global burden of CKD are yet to be proven. Prevalence of cognitive impairment reaches up to 60% in individuals with advanced CKD depending on the stage of CKD and degree of kidney damage while both low eGFR and albuminuria are independent risk factors for cognitive impairment[4,5]. Effects of reduced eGFR and albuminuria, specifically the effect of albuminuria on executive functioning including information processing speed, have been hypothesized [6,7]. However, it is important to acknowledge the differences in the evaluation of cognitive impairment with various assessment tools while most studies lack detailed neurocognitive tests and brain imaging modalities and differences in the definition of cognitive impairment among individual studies. Additionally, most studies conducted so far include elderly participants in whom confounding factors are numerous and difficult to minimize. We hereby aim to review the current knowledge regarding the pathophysiology of cognitive impairment in patients with CKD and assess the effect of intensive blood pressure control on cognitive function.

2. Pathophysiological mechanisms of cognitive impairment in CKD

Due to the diversity of comorbid conditions observed in patients with CKD and various confounding factors seen in elderly individuals, it is not surprising to demonstrate the role of multiple pathophysiological mechanisms underlying cognitive impairment in such patients. Alzheimer's disease is the predominant cause of dementia in the general population since patients with CKD are mostly elderly individuals, nevertheless, the prevalence of Alzheimer's disease does not demonstrate any statistically significant difference between elderly individuals

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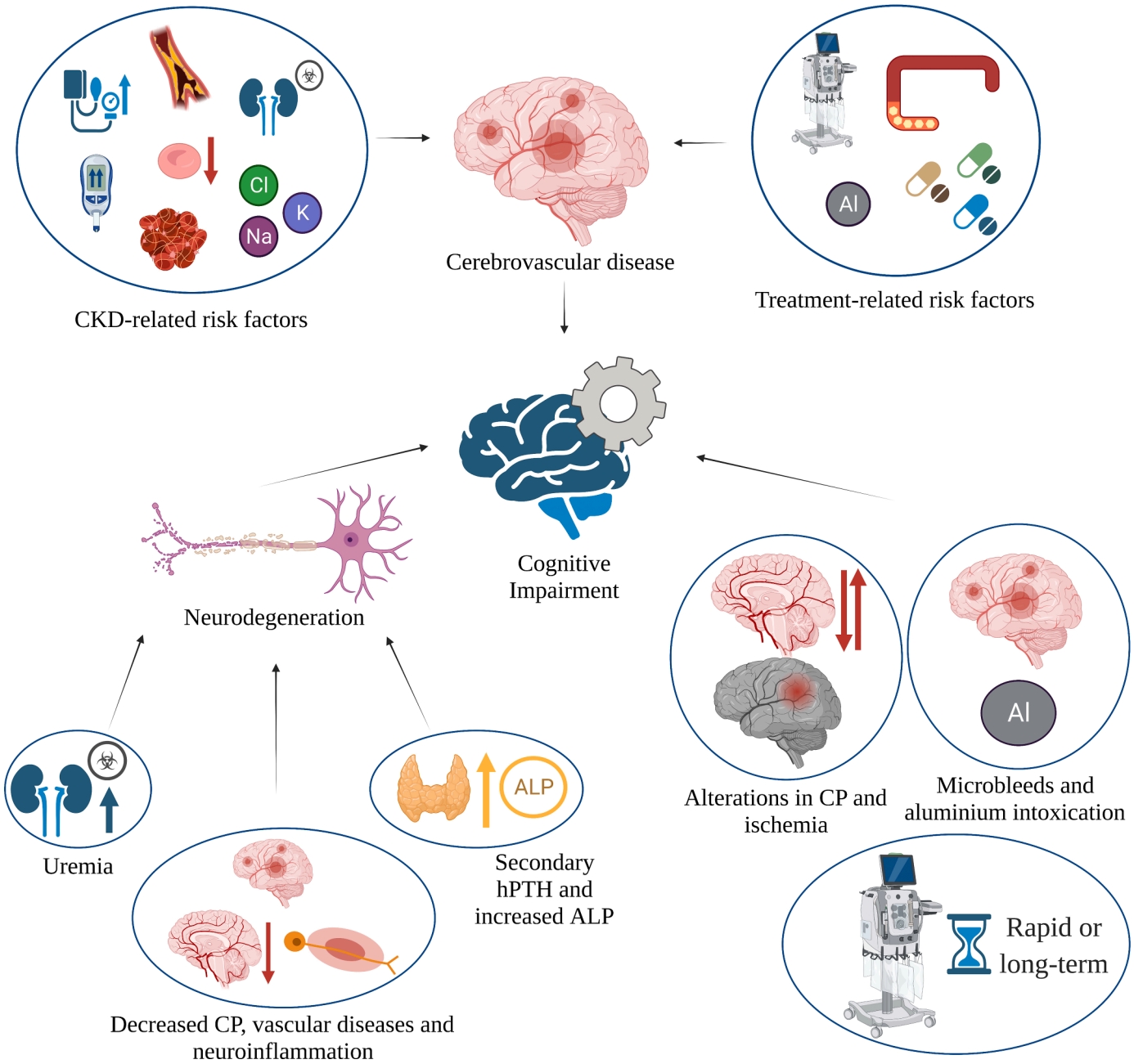

Fig. 1. Different pathophysiological mechanisms underlying cognitive impairment in CKD patients. Cerebrovascular disease related to CKD-related and treatment-related factors, factors leading to neurodegeneration and rapid dialysis resulting in alterations in cerebral perfusion and long-term dialysis are different underlying mechanisms of cognitive impairment in CKD patients, *CKD, chronic kidney disease; CP, cerebral perfusion; hPTH, hyperparathyroidism; ALP, alkaline phosphatase.*

with or without CKD [8]. Thus, the additional risk of cognitive impairment in CKD patients may not be attributable to the most common etiology of dementia. A therapeutically significant aspect of CKD-associated cognitive impairment is the potential reversibility with kidney transplantation which may be due to restoration of renal functions and elimination of hemodialysis or polypharmacy-related risk factors (Fig. 1) [9,10].

***Cerebrovascular Disease*:** CKD patients are prone to develop the cerebrovascular disease (CVD), especially small vessel cerebrovascular disease, due to certain modifiable and non-modifiable risk factors. CKD-related risk factors for CVD include hypertension, dyslipidemia, hyperglycemia, pro-thrombotic state, uremic toxins, anemia, and electrolyte abnormalities while treatment-related risk factors include dialysis-related hypotension or heparin-induced complications, aluminum intoxication and polypharmacy [8]. The prevalence of stroke is approximately 17% in patients on long-term hemodialysis therapy and 10% in mild-to-moderate stage CKD according to the study conducted by the US Renal Data System in 2010 while silent brain infarcts, micro-bleeding sites and white matter lesions are more commonly detected in CKD patients [11,12]. eGFR is inversely proportional to the rates of white matter lesions, cerebrovascular calcifications, micro-bleeding sites and silent brain ischemia in both individuals with CKD and the general population[13,14]. In addition to the pro-thrombotic state caused by CKD mainly due to loss of anti-thrombotic proteins, accumulated uremic and non-uremic toxins and hyperhomocysteinemia results in oxidative stress and pro-inflammatory status in cerebral vasculature leading to endothelial dysfunction and small-vessel disease, all of such alterations result in

Table 1
The general characteristics of the studies investigating the potential therapeutic role of intensive BP therapy on cognitive impairment and dementia.

Study	Participant Characteristics (Study Group)	Participant Characteristics (Control Group)	Intervention	Follow-up duration (Years)	Measurement Method
The SPRINT study	*N* = 4678, Prevalence of CKD = 1330/4678, Mean age = 67.9	*N* = 4683, Prevalence of CKD = 1316/4683, Mean age = 67.9	Intensive SBP treatment (SBP<120 mm Hg) without any specific anti-HT therapy choice	5.1	Clinic BP measurements Blood and urine tests In-person cognitive screening assessments The MOCA Self-reported CVO UACR and eGFR
The SPRINT-MIND study	*N* = 1448 Mean age= 68.6 Gender= 63% Male Mean baseline BP= 138.6/77.3 mm Hg Mean baseline eGFR= 70.5 Mean baseline BMI= 29.9	*N* = 1473 Mean age= 68.3 Gender= 63% Male Mean baseline BP= 138.8/77.4 mm Hg Mean baseline eGFR= 71.3 Mean baseline BMI= 29.8	Intensive SBP treatment (SBP<120 mm Hg) without any specific anti-HT therapy choice	4	Clinic BP measurements Blood and urine tests In-person cognitive screening assessments The MOCA Logical Memory I-II Digit Symbol Coding The Hopkins Verbal Learning Test-Revised Modified Rey-Osterreith Complex Figure The 15-item Boston Naming Test Category Fluency–Animals Trail Making Test Digit Span
The SPRINT-MIND-MRI study	*N* = 355 Mean age= 67.7 Gender= 56.3% Male Baseline eGFR= 72 Baseline MOCA: 24 Baseline ICV= 1372 cm3 WML volume= 3.0 cm3 Mean baseline BP= 138.2/77.3 mm Hg	*N* = 315 Mean age= 66.9 Gender= 63.2% Male Baseline eGFR= 72.6 Baseline MOCA= 24 Baseline ICV= 1391.7 cm3 WML volume= 0.3.3 cm3 Mean baseline BP= 137.8/78.5 mm Hg	Intensive SBP treatment (SBP<120 mm Hg) without any specific anti-HT therapy choice	3.4	Clinic BP measurements Blood and urine tests In-person cognitive screening assessments The MOCA MRI assessment
The CRIC study	*N* = 1502 Mean age= 63 Gender= 56% Male Mean baseline BP= 126/69 mm Hg Mean baseline BMI= 32 Mean baseline UPCR= 0.1 Mean total anti-HT drugs= 2.6 Mean baseline serum creatinine= 1.9	Multiple subgroups exist	N/A	4	Clinic BP measurements Blood and urine tests The Modified Mini Mental State Examination The Physical Performance Ancillary Study Short Physical Performance Battery score

(Abbreviations: N—Number, CKD-Chronic kidney disease, ESRD-End stage renal disease, UACR-Urine albumin to creatinine ratio, UPCR-Urine protein to creatinine ratio, HT-Hypertension, SBP-Systolic blood pressure, BP- Blood pressure, CVO—Cardiovascular outcome, BMI-Body mass index, eGFR-Estimated glomerular filtration rate, WML-White matter lesion, ICV-Intracranial volume, MOCA- The Montreal Cognitive Assessment and the Functional Assessment Questionnaire, SPRINT-The Systolic Blood Pressure Intervention Trial, MRI-Magnetic resonance imaging, CRIC-The Chronic Renal Insufficiency Cohort).

atherosclerosis and decline in cerebral perfusion[15,16]. Higher rates of hypertension observed in CKD patients are another contributor to CVD due to a potential link between hypertension and lacunar infarcts due to imbalances in the renin-angiotensin-aldosterone system, endothelin and nitric oxide levels[17,18]. However, contradictory findings demonstrating higher cerebral blood flow and perfusion have been established in a few studies conducted via arterial spin-labeling magnetic resonance imaging (MRI) [19].

Neurodegeneration: First, uremic toxins may contribute to the development of cognitive impairment in CKD patients by leading to a degeneration of neurons and glial cells, especially astrocytes [20]. Although overt uremia has mostly been documented in advanced stages of CKD when eGFR declines below 15 10 to 15 mL/min/1.73 m2, it is well established that the accumulation of toxins occurs at earlier stages [21]. Despite clearance of most uremic toxins with hemodialysis, currently utilized hemodialysis membranes are shown to be ineffective in the clearance of highly protein-bound medium-sized toxins such as 4-hydroxyphenylacetate which is involved in cognitive impairment [22,23]. Second, the paravascular system involved in the clearance of waste products and toxins in the central nervous system is impaired due to neuroinflammation, reduced cerebral perfusion, and vascular diseases [24,25]. Elevated levels of fibroblast growth factor-23 (FGF-23) and reduced levels of Klotho observed in CKD patients appear to have a detrimental effect on memory and behavior due to the presence of alpha-Klotho on serotonergic and hippocampal neurons [26–28]. Additionally, alpha-Klotho is important in the preservation of the integrity of the blood-brain barrier [29]. Furthermore, secondary hyperparathyroidism and elevated levels of alkaline phosphatase lead to tau protein dephosphorylation which is associated with neuronal cell death [30,31].

Hemodialysis: Rapid fluid shift occurring during hemodialysis leads to considerable short-term shifts in blood pressure which may lead to alterations in cerebral perfusion and ischemia. Latest studies conducted via real-time near-infrared spectroscopy on 635 subjects demonstrate evidence of cerebral hypoperfusion in 25% of the subjects among which one-third develop symptomatic ischemia [32,33]. Another study conducted on elderly patients demonstrates similar outcomes while reduction of perfusion is greater in the thalamus, cerebellum, occipital and

frontal lobes [34]. Additionally, higher rates of aluminum intoxication and cerebral micro-bleeds are recorded in patients undergoing long-term hemodialysis treatment [35,36].

However, it is important to emphasize that most of the studies investigating the pathophysiological mechanisms are based on the results obtained from either end-stage kidney disease patients or patients on renal replacement therapy, thus, such results may lack generalizability to the general population or even to patients with mild kidney dysfunction.

3. Intensive blood pressure control on dementia

Multiple clinical studies have investigated the effect of intensive SBP control on the risk of cognitive impairment and dementia in patients with CKD. The general characteristics of individual studies have been summarized in Table 1.

Effects of daily SBP variability on cognitive function have been evaluated in a study conducted with 1502 participants for whom 24-hour ambulatory BP have been obtained from the Chronic Renal Insufficiency Cohort (CRIC) which is a prospective observational cohort investigating the factors involved in the progression of CKD [37,38]. No statistically significant association has been established between cognitive impairment and day or nighttime systolic or diastolic BP and BP dipping patterns. Only a marginally higher incidence of cognitive impairment has been demonstrated in patients with extreme BP dipping patterns compared with normal dippers (HR, 1.83; 95% CI, 0.99 to 3.34). Major limitations of this study include the possibility of selection bias (1502/3939 subjects have ambulatory BP reading) and the presence of only one ambulatory BP reading per subject. Another study conducted on CRIC participants demonstrate statistically significant association between high baseline SBP (HR [95%CI] = 1.09 [1.03, 1.16]) with attenuated effect on time-updated SBP P (HR [95%CI] = 1.04 [0.99, 1.10]) after 6-years of follow-up on average [39]. On the other hand, a Korean nationwide retrospective cohort study conducted with 7.884.814 subjects without baseline dementia with a median follow-up period of 6.2 years has demonstrated a statistically significant association between BP variability and risk for dementia while potential measurement and diagnostic bias due to lack of study characteristic and lack of baseline cognitive assessment constitute the major limitations [40]. A meta-analysis study including twenty studies has concluded that both higher systolic or diastolic BP and higher systolic or diastolic BP variability are individually associated with cognitive impairment and dementia while the effect of BP variability is higher compared to mean BP values in a statistically significant manner (OR, 0.92 [95% CI, 0.87–0.97], $P<0.01$) [41]. Furthermore, there are contradictory studies regarding the effects of BP variability during hemodialysis on cognitive function while it is crucial to emphasize that studies conducted in this field on hemodialysis patients include a low number of participants and has higher rates of loss of follow-up due to either mortality and kidney transplantation [42,43].

The Systolic Blood Pressure Intervention Trial (The SPRINT) is a randomized clinical trial that investigated the effect of intensive (<120 mm Hg) versus standard (<140 mm Hg) systolic blood pressure (SBP) lowering therapy on eGFR, urinary albumin-to-creatinine ratio (ACR), mild cognitive impairment (MCI) and dementia on 9361 hypertensive CKD patients with a median follow-up period of 5.1 years [44,45]. They demonstrated a statistically significant association between eGFR decline at or over 30% and risk for MCI or dementia in time-varying analysis during the follow-up period (HR, 1.76; 95% CI, 1.03 to 2.77), whereas, the risk of MCI or dementia is not associated with the baseline eGFR or ACR. Additionally, intensive SBP control has no beneficial effect on the risk of dementia or MCI, nevertheless, intensive treatment in patients with baseline eGFR over 60 ml/min/1.73 m2 results in lower rates of MCI (HR, 0.71; 95% CI, 0.58 to 0.87) which may indicate potential prevention of dementia or MCI in earlier stages of CKD and emphasize the importance of early intensive SBP control. Similar trends of association between eGFR decline and incidence of dementia have been demonstrated in multiple other studies conducted without SBP treatments [46,47]. Major limitations of the SPRINT trial include lack of baseline cognitive status assessment, exclusion of patients with certain comorbidities (Diabetes mellitus, proteinuria >1 g/day, polycystic kidney disease, history of prior stroke, symptomatic heart failure, and left ventricular ejection fraction <35%) which constitute great proportion of CKD comorbidities, relatively short period of follow-up for the development of cognitive outcomes (Detection of MCI in 7.6% and dementia in 3.8% of the participants), significant loss of follow-up and variations in pharmacotherapeutic choice for SBP control among individuals.

A subgroup study of the SPRINT, referred to as SPRINT-MIND, includes 2921 participants with a mean age of 68.4 and a mean follow-up period of 4.1 years [48]. No statistically significant benefit of intensive SBP lowering therapy has been documented compared to standard therapy in any cognitive domain or mean score, nevertheless, they record statistically non-significant beneficial effects of intensive therapy on certain cognitive domains which may indicate that beneficial effects of intensive therapy are distributed to domains and may not reach statistically significant level due to short follow-up period mainly caused by the early termination of trial due to benefit observed in composite cardiovascular event. Another subgroup study of the SPRINT referred to as SPRINT-MIND-MRI, includes 670 subjects, 355 participants with intensive SBP reduction below 120 mm Hg and 315 participants with standard therapy below 140 mm Hg, with MRI taken after a median period of 3.4 years following the intervention [49]. Participants in the intensive SBP therapy group demonstrated an increase in total white matter lesion volume from 4.57 to 5.49 cm3 and a decrease in mean total brain volume from 1134.5 to 1104 cm3. On the other hand, participants in the standard SBP therapy group demonstrated an increase in total white matter lesion volume from 4.40 to 5.85 cm3 and a decrease in mean total brain volume from 1134 to 1107.1 cm3. Intensive SBP reduction therapy is associated with a smaller increase in the total volume of white matter lesions (Between-group difference in change, −0.54 cm3 [95% CI, −0.87 to −0.20]) and a higher decline in total brain volume (Between-group difference in change, −3.7 cm3 [95% CI, −6.3 to −1.1]) in a statistically significant pattern. However, changes in total brain volume differ with age since female subjects demonstrate no statistically significant difference between-group differences. Additionally, only 67% of the participants enrolled at baseline completed the MRI follow-up later on, thus, implicating a significant loss of follow-up.

An important therapeutic concern in intensive SBP lowering therapy is the possibility of inducing a higher risk for cerebral hypoperfusion due to a considerable decline in diastolic BP. A study conducted on the participants of the SPRINT determined that lowering diastolic BP does not impose an additional risk of cognitive impairment or dementia while lower baseline diastolic BP values are linked to a higher risk for cognitive impairment and dementia [50].

Another important aspect of SBP reduction therapy is the potential differences between various therapeutic alternatives in terms of their effects on cognitive impairment or dementia. Nevertheless, studies investigating the differences between anti-hypertensive medication types and their effects on blood pressure control and cognitive functions are lacking as this issue is a novel area of research there. There is a clear need for future studies comparing those therapeutic alternatives.

4. Future perspectives

CKD and dementia are both common causes of morbidity and mortality, especially in elderly individuals with various confounding factors and potentially shared underlying pathophysiological mechanisms. One such modifiable risk factor involved in the progression of both conditions is high BP. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend targeting SBP lower than or equal to 120 mm Hg in CKD patients, if tolerated, excluding dialysis patients and patients with a kidney transplant [51]. Nevertheless, the target BP

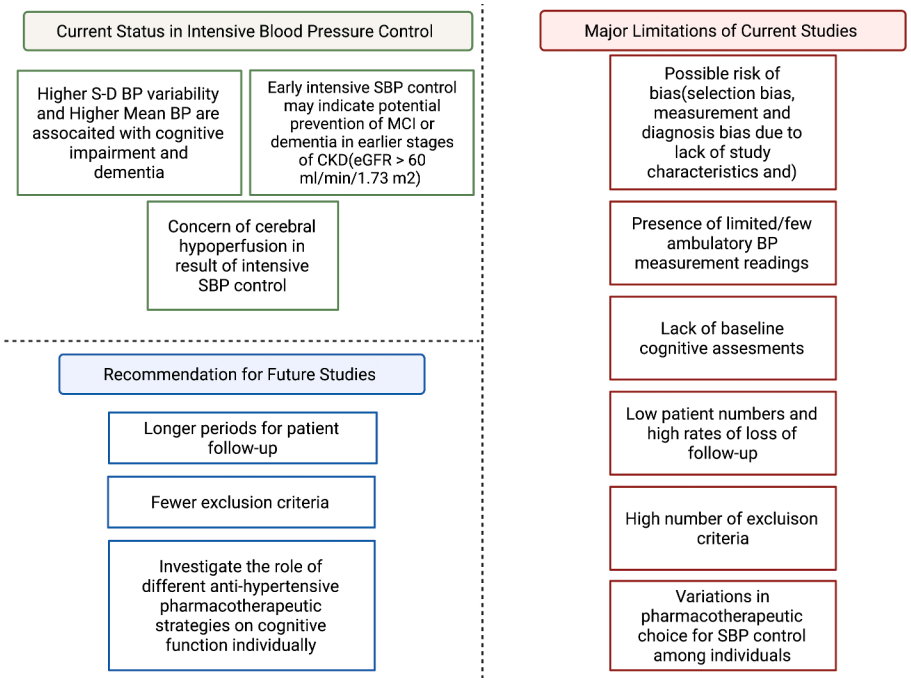

Fig. 2. Findings and major limitations of current studies and recommendations for future studies, *S-D, systolic-diastolic; BP, blood pressure; SBP, systolic blood pressure; MCI, mild cognitive impairment; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.*

recommendation of the KDIGO guidelines is not based on its' effect on cognitive functions while potential beneficial effect at similar SBP values creates a feasible method for intervention. Higher systolic or diastolic BP or daily BP variations have been linked to cognitive impairment in CKD patients despite the presence of a few contradictory findings in the literature. However, interventional studies investigating the effect of intensive SBP (SBP≤120 mm Hg) control on cognitive function are limited to the SPRINT and its' subgroup studies all of which have considerable limitations (Fig. 2). There are also ongoing clinical trials in this field among which the SPRINT-MIND 2.0 Study is the most promising one which is the 2-year extension of the SPRINT-MIND study. Nevertheless, the need for future studies with longer follow-up periods and with fewer exclusion criteria is clear. Additionally, one major limitation of the SPRINT study should not be overlooked in future studies by investigating the role of different anti-hypertensive pharmacotherapeutic strategies on cognitive function individually.

5. Compliance with ethical standards

Funding: This study was not funded by any grant.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

6. Contribution of authors

Contributed substantially to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: Sidar Copur, Metehan Berkkan, Mehmet Kanbay, Drafted the work or revised it critically for important intellectual content:

Mehmet Kanbay, Pantelis Sarafidis

Declaration of Competing Interest

Authors declare that they have no conflict of interest.

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