The Management of Hypertension in Elderly Patients with Chronic Kidney Disease

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ABSTRACT

Objective: To review the available literature regarding hypertension and chronic kidney disease (CKD) in the elderly and provide a framework for clinical management of hypertension in this subset of the elderly population.

Methods: Review of the available literature.

Results: Though several large, well-designed randomized trials exist examining the treatment of isolated hypertension in the elderly, these trials have uniformly excluded patients with CKD, thus reducing the generalizability of these results to this subgroup. CKD in the elderly is poorly studied overall, and whether CKD in the elderly is an expected product of senescence or a pathology from modifiable risk factors is debatable. Concern exists regarding the increased potential of acute kidney injury events and a more rapid progression of CKD with more aggressive hypertension lowering in elderly patients.

Conclusion: Though data is limited regarding hypertension treatment in the subset of elderly patients with CKD, given the consistent benefits in cardiovascular reduction with hypertension treatment in the general elderly population, it is likewise recommended that elderly patients with hypertension and CKD receive antihypertensive therapy, though with more careful monitoring for adverse renal effects. We provide a practical approach to management for this clinical scenario.

Chronic kidney disease (CKD) is an increasingly recognized finding in elderly patients, with approximately half of all patients over the age of 70 meeting the most common currently accepted definition of CKD stage III, an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 [1]. Whether this finding is a result of normal physiologic aging or whether it represents a true disease process in elderly patients has been a matter of considerable debate [2–4]. Nonetheless, the decline in eGFR in elderly patients has important implications regarding drug dosing and the potential risk of acute kidney injury (AKI) in this population [5–9]. Additionally, elderly patients with reduced GFR may have an increased risk of cardiovascular events and progression to end-stage kidney disease (ESKD), though extensive studies are lacking in this population [10–13].

In contrast, isolated hypertension and its treatment in the elderly population has now been extensively evaluated in several well-designed, prospective randomized studies, with generally favorable results arguing for the treatment of hypertension in elderly individuals [14–17]. Unfortunately, however, these studies have uniformly excluded patients with CKD in their study designs. Thus, the impact of aggressive hypertension management in elderly patients with CKD is unknown. As a considerable proportion of CKD in this population has been felt secondary to vascular disease and poor overall vascular health, many have questioned whether aggressive blood pressure reduction, particularly in patients with wide pulse pressure as an indicator of vascular disease, may result in decreased overall renal perfusion and greater risk for AKI, and thus potentially accelerate renal decline in this population [18–22].

In this paper, we review the epidemiology and physiology of renal disease in the elderly, provide an analysis of the available data regarding management of hypertension in the elderly, and suggest an approach to management of hypertension in this specific patient population. Though a multitude of age cutoffs defining elderly have been proposed, for the purposes of this paper we define

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elderly as age greater than 65 years unless otherwise specified.

Definition of CKD

The currently accepted definition of CKD represents any composite of pathology resulting in impaired kidney function, defined as a drop of GFR < 60 mL/min/1.73 m^2 for 3 months or longer, or a higher GFR but with evidence of structural or functional abnormalities, such as proteinuria [23]. However, there are key aspects and important limitations to the above diagnostic criteria to be considered in the elderly patient population. Importantly, the most commonly used GFR estimation equations use serum creatinine as the marker for impaired renal function. As serum creatinine levels are also determined by overall muscle mass, significant error in estimating GFR can occur using these equations in elderly patients, who may have widely varying degrees of musculature and thus creatinine production. Additionally, these equations were often derived using all CKD or mostly CKD patients, which may result in healthy individuals having a higher GFR at the same serum creatinine levels than CKD patients, thus incorrectly classifying many patients with normal kidney function as having CKD [24].

Serum cystatin C has been proposed as an alternative surrogate marker for impaired kidney function, particularly in the elderly, as it is not affected by muscle mass. However, cystatin C levels are affected by obesity, inflammation, and atherosclerosis, and thus equations using this marker to determine GFR also face some limitations in the elderly population [25]. Evidence comparing various GFR estimating equations in the elderly suggest that formulas that use a combination of serum creatinine and cystatin C do best at predicting GFR when compared to gold standard techniques, such as iohexol clearance, though it is important to note that yet the ideal GFR estimating equation for elderly patients has not been determined [26–28].

It has been suggested that given these limitations and potential to underestimate GFR in the elderly population, a lower GFR reference range of 45 mL/min/1.73 m^2 be used in the absence of other signs of kidney damage given the multiple unique characteristics of the aging kidneys, as we will explore in this review [29]. In general, we are in agreement with this suggestion that all elderly patients with a creatinine based estimated GFR of < 45 mL/min/1.73 m^2 can safely be assumed to have CKD, and it is our opinion that elderly patients with a GFR > 45 mL/min/1.73 m^2 but less < 60 mL/min/1.73 m^2, without other signs of structural of functional renal disease such as proteinuria, have additional evaluation for the presence of impaired renal function, including but not limited to the addition of cystatin C to estimate GFR.

Epidemiology of CKD in the Elderly

According to the Centers for Disease Control and Prevention (CDC), the number of elderly patients in the United States is expected to double in the next 25 years to 72 million patients, representing approximately 20% of the adult population by 2030 [30]. Analysis of the National Health and Nutrition Examination Surveys (NHANES) from 1999–2004 revealed an overall prevalence of CKD in the US population of 13.1%. However, when sub-grouped into patients greater than or equal to 70 years of age, the prevalence of CKD in this population increased to a staggering 47.5% [31]. Likewise, analysis of other elderly populations from Canada, China, Italy, and Spain indicated a roughly 3- to 7-fold increase in CKD prevalence in those elderly populations compared to younger patients [3]. Additionally, according to the United States Renal Data System there is evidence of a progressive rise in the number of end-stage renal disease (ESRD) patients enrolled in Medicare-funded programs over the past decades [32]. In extrapolating these estimates, it is conceivable to predict that approximately 30 million elderly patients may have CKD in the United States by year 2030, with enormous implications to treatment recommendations and healthcare associated costs.

The Aging Kidney and Expected Rate of Nephron Loss

A progressive, age-related decline in GFR has been demonstrated in many studies. In an earlier analysis of the Baltimore Longitudinal Study of Aging by Lindeman et al, a decline in measured creatinine clearance of 0.75 mL/min/year was demonstrated. It is important to note that in this analysis, patients with suspected pre-existing renal or urologic disease and those on diuretics or other an-

tihypertensives were excluded from analysis, and a normal Gaussian distribution of creatinine clearance slopes versus time was demonstrated, suggesting the GFR loss was a process of normal aging [4].

In support of the theory of a physiologic age-related decline in renal function, a study by Rule et al analyzed potential kidney transplant donors for age-related decline in renal function and determined an approximately 6.3 mL/min/1.73 m^2 decline in GFR for each decade. In this investigation, core needle biopsies were obtained at the time of donation and transplantation. The investigators found a progressive increase in the histologic prevalence of nephrosclerosis with each age group analyzed, increasing from 2.7% at ages 18 to 29 to 16% for ages 30 to 39, 28% for ages 40 to 49, 44% for ages 50 to 59, 58% for ages 60 to 69, and finally 73% in donors older than age 70. It is important to note that this study only examined live kidney donors, a group heavily screened and selected on the basis of optimal health, thus strongly arguing for progressive renal decline as a consequence of "normal" aging. Furthermore, though controlled hypertensive patients (treated with 2 or less medications) were allowed to be donors in this study, exclusion of this group had only a minimal impact on the findings of the study [33].

However, whether this age-related decline is purely a result of normal senescence or is a consequence of modifiable risk factors that could alter this outcome remains debatable. Additionally, vascular disease is clearly implicated in more accelerated renal decline. This concept was well demonstrated in an analysis of the longitudinal Age, Gene/Environment Susceptibility – Reykjavik Study, which showed that although age was associated with both reduced GFR and albuminuria, reduced GFR and albuminuria in elderly patients (mean age 80.8 yr) was strongly associated with midlife systolic and diastolic blood pressure, thus suggesting that potentially modifiable vascular pathology may play a much stronger role in CKD in the elderly than aging alone [34].

Finally, it has been hypothesized that reduced nephron mass at birth may contribute to CKD in the elderly [29]. Reduced nephron mass appears to be associated with low birth weight and prematurity, and this has been associated with an increased risk for ESRD later in life [35,36].

Hypertension in the Elderly

Pathophysiology

Age-associated hypertension is felt to arise from several mechanisms and hemodynamic changes. Systolic blood pressure has been noted to progressively rise with age, whereas diastolic blood pressure rises to the 5th or 6th decade, after which it appears to slowly decline. This pattern is felt likely secondary to increasing large vessel stiffness from collagen deposition and calcification with aging, and fracturing and degradation of elastin fibers. As large vessels become less distensible, pulse pressure and pulse wave velocity increases with this drop in diastolic BP, with less forward flow seen in diastole, leading to decreased organ perfusion. Additionally and alternatively, concentric left ventricular hypertrophy develops with aging, leading to reduced cardiac output from decreased stroke volume, which may also contribute to reduced organ perfusion [37,38]. These findings have led many to speculate that hypertension in the elderly may actually serve as a protective mechanism to maintain organ perfusion, and have led to great concern regarding excessive lowering of diastolic blood pressure and increasing of pulse pressure in this population with antihypertensive therapy. This theory was initially corroborated with a sub-analysis of the Systolic Hypertension in the Elderly Program (SHEP) where an increase in pulse pressure by 10 mm Hg was accompanied by increased risk of stroke and congestive heart failure in the treatment arm [39]. Nonetheless, the bulk of evidence continues to support a lower overall risk of cardiovascular events with treatment of hypertension in elderly patients, and general expert consensus recommends treatment with gradual reduction to normal levels of systolic blood pressure accompanied by careful monitoring for adverse effects [40,41].

In addition to these above changes, reduced GFR in elderly likewise results in impaired natriuresis, thereby fostering hypertension via volume expansion. Age-related arteriolosclerosis may result in renal artery stenosis, resulting in decreased renal perfusion and upregulation of the renin-angiotensin-aldosterone cascade. Further challenging treatment decisions is the frequent development of autonomic dysregulation in the elderly, a major risk factor for falls and cardiovascular events [40].

The result of these abnormalities is that roughly 65%

of patients greater than the age of 60 have at least isolated systolic hypertension [42]. Similarly corresponding to the underlying physiology highlighted above, rising pulse pressure, rather than systolic or diastolic blood pressure, appears to be the greatest risk factor for cardiovascular events in the elderly population [43,44]. In an interesting analysis of the Framingham Heart Study by Franklin et al, the authors noted that in patients < 50 years of age, diastolic blood pressure was the strongest risk factor for events. However, at age 50 to 59, a change occurred where all 3 blood pressure indexes were comparable risk predictors, and then from age 60 years and on pulse pressure became the superior predictor, with diastolic blood pressure being negatively correlated to cardiovascular risk, highlighting the potential importance for organ perfusion during diastole in this group [45].

Likewise, in the elderly population pulse pressure also appears to be inversely related to GFR, suggesting that vascular stiffness and the reduced forward flow in diastole may contribute to microvascular damage and CKD [46]. In elderly patients with untreated isolated systolic hypertension, increasing systolic blood pressure (a reflection of rising pulse pressure) was associated with the greatest risk of renal decline when compared to diastolic blood pressure, pulse, and mean arterial pressure [47]. In the normal state, high renal blood flow and low renal arterial resistance can contribute to regular large intrarenal pressure variations. Because of vascular stiffness, these pressure variations increase with time, increasing up to 4-fold in the elderly compared with young peers, and likely contribute to renal damage seen in older patients [48].

Treatment

In comparison to the paucity of randomized trials examining CKD progression in the elderly, 4 very large, well designed randomized trials (SHEP, MRC trial, Syst-Eur trial, and HYVET) specifically examining the treatment of hypertension in the elderly have now been conducted [14–17] and confirmed earlier and smaller trials demonstrating the benefits of treatment of hypertension in the elderly [49,50]. In addition to this, several of the other large landmark hypertension trials such as ALLHAT, ACCOMPLISH, and the SPRINT trial included a considerable number of elderly patients [51–53]. Though the primary aim of those trials was not to determine the effects of hypertension treatment in the elderly per se, sub-analysis of this population in these trials has further added to our knowledge of this condition.

In the largest initial trial of hypertension in the elderly (SHEP), the researchers randomized 4376 patients over the age of 60 with an average blood pressure of 170/77 mm Hg into a treatment versus placebo arm. Such a study would be inconceivable today due to the consistent benefit derived from antihypertensive therapy now demonstrated in multiple trials. An achieved systolic blood pressure of 143 mm Hg in the treatment arm versus 155 mm Hg in the placebo arm was obtained. Stroke and nonfatal cardiac events were significantly reduced with treatment. The development of renal dysfunction occurred in 7 patients in the treatment arm and 11 patients in the placebo arm, a nonsignificant difference. As we have noted previously, however, patients with pre-existing kidney disease were excluded from the study [14]. A subsequent analysis of the SHEP trial results by Vaccarino et al, however, showed that in patients on treatment who developed an increase in pulse pressure of 10 mm Hg or more carried a 23% higher risk for developing heart failure and a 24% higher risk for stroke. This effect was not seen in the placebo arm [39].

Shortly following the publication of the SHEP results, the Medical Research Council trial of treatment of hypertension in older adults (MRC) further confirmed the initial findings by demonstrating a 25% reduction in stroke and a 17% reduction in all cardiac events in 4396 patients aged 65 to 74 with a systolic blood pressure greater than 160 mm Hg randomized to treatment of hypertension with either atenolol or a diuretic combination of amiloride and hydrochlorothiazide versus placebo. Like SHEP, however, patients with pre-existing renal disease were excluded, and no report of renal outcomes was published in the initial results [15]. Similarly, the Systolic Hypertension in Europe Trial (Syst-Eur) revealed a 42% reduction in stroke and a 26% reduction in all cardiac endpoints in 4695 patients with a systolic blood pressure of greater than 160 mm Hg randomized to receive nitrendipine with addition of enalapril and hydrochlorothiazide as required. However, CKD patients were likewise excluded in this trial [16].

Finally, the Hypertension in the Very Elderly Trial (HYVET) was unique in that it sought to enroll only patients greater than 80 years of age, a significant departure from the earlier hypertension in elderly trials. This trial randomized 3845 patients, again with a systolic blood pressure of 160 mm Hg or greater, to a placebo arm versus a treatment arm of the thiazide type diuretic indapamide, with addition of the ACE inhibitor perindopril if blood pressure was still greater than 150 mm Hg on monotherapy. Despite the older age of the participants in this trial, patients still benefited from blood pressure reduction with a 30% reduction in rate of stroke, a 21% reduction in the rate of death from any cause, and an impressive 64% reduction in the rate of heart failure [17]. These findings from HYVET, combined with the earlier SHEP, MRC and Syst-Eur trials, confirmed that treatment of hypertension in the elderly of any age should be attempted.

Recomendations for Managing Hypertension in the Elderly with CKD

Though a lack of data exists regarding the treatment of hypertension in elderly patients with the comorbidity of CKD, given the consistent and robust data that exists demonstrating a reduction in cardiovascular risk and mortality in the general elderly population without renal impairment, it is our opinion that elderly patients with CKD and hypertension should receive antihypertensive treatment. This opinion is supported by the fact that in the recently published SPRINT trial, 28.1% of patients in the standard treatment arm (targeting a blood pressure of less than 140 mm Hg), and 28.4% of patients in the intensive treatment arm (blood pressure target less than 120 mm Hg) had CKD, and similarly 28.2% of the trial participants in each group were greater than the age of 75. The percentage of patients with both CKD and age greater than 75 years was not reported in the initial trial results, though it is assumed a significant portion of these patients had both CKD and age greater than 75 years. It is nonetheless reassuring that patients with CKD in the SPRINT trial, as well as those with age > 75 years, both seemed to derive the same benefit in cardiovascular and mortality benefit in the intensive treatment arm compared to the standard treatment arm [53].

It should be noted, however, that though cardiovascular events and mortality were lower in the more intensive treatment arm of the SPRINT trial, CKD progression did not differ between the two treatment groups. Additionally, the risk of acute kidney injury was significantly greater in the intensive treatment arm when compared to the standard treatment arm, with 3.8% of patients in the intensive treatment arm suffering AKI compared to 2.3% in the standard arm [22]. Thus, it should be understood by both the clinician and the elderly patient with hypertension and CKD that the goal of more aggressively lowering blood pressure is to prevent cardiovascular events and not slow renal disease progression.

The recently published 2017 hypertension guidelines by the American College of Cardiology/American Heart Association is the most comprehensive set of hypertension treatment recommendations published to date and includes a section regarding patients with CKD as well as a section on the elderly [54]. Regarding CKD, the guidelines recommend a goal blood pressure of less than 130/80 mm Hg in patients with CKD, and that patients with macroalbuminuria (defined as a daily urine protein excretion of greater than 300 mg/dL or a urine albumin to creatinine ratio of 300 mg/g) be treated with and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). We feel these are reasonable recommendations for CKD targets and agree with the guideline, with the understanding that the target of 130/80 mm Hg is based largely on the SPRINT data. It is important to recognize that in the Action to Control Cardiovascular Risk in Diabetes trial (ACCORD), a more intensive blood pressure target of 120 mm Hg did not result in further improvement in cardiovascular events compared to a traditional target of 140/90 mm Hg [55]. However, given the larger and more robust sample size from SPRINT, we feel the target of 130/80 mm Hg is warranted and therefore should be the first target for elderly patients with CKD. With this goal in mind, it has been our clinical experience that some elderly patients with CKD have difficulty tolerating this goal, either from the development of worsening of GFR, acute kidney injury events, or due to orthostatic hypotension. Additionally, it should be noted that patients with orthostatic hypotension were excluded from SPRINT, though an increase in falls was not seen in the primary study. Therefore, for

patients who are unable to tolerate the SPRINT goal of 130/80 mm Hg, an individualized goal of at least less than 160 mm Hg systolic and ideally less than 140 mm Hg, reflecting achieved blood pressure endpoints from earlier trials, may be a reasonable alternative [55]. The recent hypertension guidelines also recommend that for elderly adults with a high burden of comorbidities or limited life expectancy, "clinical judgement, patient preference, and at team-based approach to risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs." We agree that all treatment decisions must be individualized based upon each patient's clinical scenario, and that a guideline is only a general aid for treatment decisions, not a mandate for care.

Therefore, with the acknowledgement that there is a lack of literature specifically examining blood pressure goals in elderly patients with CKD, it is our opinion based on available evidence that the following suggestions constitute a reasonable approach to this scenario: (1) a blood pressure target of less than 130/80 mm Hg should be sought as the primary blood pressure target; (2) if the patient cannot tolerate this due to rapidly declining GFR, acute kidney injury, orthostatic hypotension and or falls; or in other situations where this is not a practical a goal, individualized goal of at ideally less than 140 mm Hg, though at least less than 160 mm Hg systolic, could be considered; (3) the clinician should attempt careful and gradual reduction of blood pressure, with no more than one agent added or one escalation of medication dose attempted per visit; (4) the patient should have close follow up-after medication changes with an adjustment period of at least 4 weeks before additional medication or dose escalations are made; (5) if CKD is accompanied by albuminuria (daily urine protein excretion of greater than 300 mg/dL or a urine albumin to creatinine ratio of 300 mg/g) an ACEI or ARB should be used in management; (6) a rise in serum creatinine of up to 30% of baseline after addition of an ACEI may be acceptable; however, a rise greater than this amount should prompt discontinuation of the drug and evaluation for renal artery stenosis; (7) frequent monitoring of creatinine is required, with repeat chemistry performed after medication adjustments; (8) patients with a high pulse pressure should be monitored especially closely for symptoms or changes in renal function; and finally (9) individualized treatment and clinical judgement, with the patient being an informed participant, should take priority over all other recommendations and guidelines. We feel that further research in this growing subgroup of elderly patients is needed and will be sought, and we expect recommendations will continue to evolve as future literature becomes available.

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