

Thiazides in advanced chronic kidney disease—time for a randomized controlled trial?

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ABSTRACT

Purpose of the review: Chronic kidney disease is common, associated with increased cardiovascular risk, and frequently complicated by hypertension requiring multiple agents for control. Thiazides are naturally attractive for use in this population, unfortunately they are classically thought to be ineffective in advanced chronic kidney disease based on both theoretical considerations and the earliest studies of these agents. This report reviews the studies of thiazide use in chronic kidney disease since the 1970s, including 5 randomized controlled trials, all of which report at least some degree of efficacy.

Recent findings: Two recent studies add further evidence for the utility and efficacy of thiazides in chronic kidney disease. Of these two, one uses gold standard ambulatory blood pressure monitoring in patients with poorly controlled hypertension and advanced chronic kidney disease and found chlorthalidone reduces blood pressure. The second is the largest study to date of thiazides in chronic kidney disease; adding a fixed low-dose chlorthalidone as the first diuretic to the antihypertensive regimen improved blood pressure.

Summary: These numerous small but positive studies reinforce the need for a randomized trial to demonstrate safety and efficacy of thiazides in advanced chronic kidney disease.

Keywords: chronic kidney disease, hypertension, thiazide diuretics, chlorthalidone

INTRODUCTION

Chronic kidney disease (CKD) is a common diagnosis of major public health importance. Defined as the presence of kidney damage or abnormal kidney function over a span of at least three months [1], CKD has a prevalence of 13.6% in the United States making it more common than diabetes mellitus [2]. Furthermore, CKD is strongly associated with cardiovascular events [3] with the presence of CKD increasingly recognized as a coronary heart disease equivalent, similar to diabetes [4]. This enhanced cardiovascular risk increases with worsening stage of CKD, and the prevalence of advanced CKD with glomerular filtration rate (GFR) below 30 mL/min/1.73 m² is estimated at 0.62% of the population².

In light of the high prevalence and associated cardiovascular complications of CKD, efforts to mitigate modifiable risk factors such as hypertension are needed. Indeed, hypertension is very common in CKD with a prevalence of 86% in a recent Chronic Renal Insufficiency Cohort (CRIC) report [5]. Notably, 58% of hypertensive CRIC patients were on treatment with at least 3 antihypertensive medications. Similarly, a recent prospective cohort study of 436 CKD patients employing ambulatory blood pressure monitoring (ABPM) found resistant hypertension to be prevalent in 23% [6], emphasizing the difficulty of controlling BP in this population.

Thus control of hypertension is a primary concern in a large proportion of the CKD population and multiple medications are frequently necessary for adequate treatment. With a limited number of drug classes in the antihypertensive armamentarium, the use of thiazide diuretics is an attractive option. Unfortunately, for decades the conventional wisdom has been that thiazides are ineffective in advanced CKD and thus these medications are often overlooked in the CKD population; this thought still prevails. This review will examine the history of thiazide diuretic use in CKD, current guidelines, and the evidence for efficacy of thiazide use in

advanced CKD. Notably, this review will update on recent reviews of this topic [7;8], with a particular focus on the latest evidence from the last year.

THIAZIDE BACKGROUND

By definition thiazides are all derivatives of benzothiadiazine, which include chlorothiazide, hydrochlorothiazide, and bendroflumethiazide. Other agents that are pharmacologically similar are properly termed thiazide-like diuretics, which include metolazone, chlorthalidone, and indapamide. In this review “thiazides” refers both to benzothiadiazine derivatives and to thiazide-like diuretics, which is consistent with common practice.

Thiazides were the first category of effective oral antihypertensive drugs with an acceptable safety profile, and they have remained in clinical use since their discovery in the 1950s [9]. Thiazides improve cardiovascular endpoints including stroke, heart failure, coronary events, and death across numerous trials [10;11]. Considering the classical importance of volume overload to the pathogenesis of hypertension in kidney disease [12], thiazides are ostensibly an attractive agent to use in CKD. However, for as long as thiazides have been in clinical use there has been concern that they may be ineffective in advanced CKD.

The reasons for this are both theoretical and empirical. Firstly, the primary site of action for thiazides is the Na⁺/Cl⁻ cotransporter (NCC) in the distal convoluted tubule of the nephron, which is responsible for only 5% of total filtered sodium reabsorption. Thus in advanced CKD where GFR falls leading to reduced filtration of sodium, the presumption has been that inhibiting such a small fraction of total sodium reabsorption would be clinically insignificant. Secondly, small early studies of chlorothiazide in CKD appeared to support the theoretical concerns [13;14]. One such trial from 1961 epitomizes the early evidence base [14]. In this study chlorothiazide 500 mg was administered intravenously once to subjects who were then closely monitored for the subsequent 3 hours while on a constant intravenous saline infusion [14]. Urine

flow and the sodium excretion rate increased in all 7 subjects with inulin clearance 60 mL/min or less. However, the 2 subjects with the lowest clearances at 6 and 11 mL/min did not have as great an improvement in urine flow or sodium excretion as the others. Based on these results, the authors concluded that thiazide efficacy is reduced in the setting of very low GFR. However, it should be noted that more recent investigators have suggested that the antihypertensive effect of thiazides may be due to a direct vasodilator effect [15;16], which may in part explain the positive findings below.

GUIDELINES ON THIAZIDE USE IN CKD

Based on such qualified conclusions from early studies, a consensus developed that thiazide diuretics were ineffective in advanced CKD, and while there have been acknowledgments that the evidence wasn't definitive [17], the dogma hardened and became reflected in influential guidelines. However, more recently guidelines on the use of thiazides in advanced CKD have been less prescriptive. For example, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) recommended changing from thiazide to loop diuretics [18] when estimated GFR falls below 30 mL/min/1.73 m², but the recently promulgated JNC8 recommendations take no position on the use of thiazides versus loop diuretics in CKD [19].

Similarly, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) recommends switching from thiazides to loop diuretics [20] when estimated GFR falls below 30 mL/min/1.73 m², while the more recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines are less dogmatic [21]. The KDIGO guidelines acknowledge that while many clinicians switch from thiazides to loop diuretics, the antihypertensive benefit of thiazides may still be preserved at low levels of GFR.

OLDER STUDIES OF THIAZIDES IN CKD

Starting in the 1970s numerous small trials began to show both diuretic and antihypertensive effects of varied thiazides in CKD. As detailed in Table 1, these early studies included 5 small heterogeneous trials of metolazone in CKD all with a before-and-after design [22-26], and in general GFR was low with 2 trials reporting creatinine clearances for individual subjects as low as 1 mL/min. These studies showed an improvement in reported diuretic or antihypertensive outcomes with metolazone administration, and these early positive results are likely the reason that there is a persistent belief that metolazone is the unique thiazide that is effective in advanced CKD [27].

Two small trials from the 1980s with alternative thiazides showed further evidence of efficacy in advanced CKD. The first included 8 hypertensive patients with mean serum creatinine 3.31 mg/dL and all subjects were treated with furosemide and hydrochlorothiazide leading to significantly reduced body weight, plasma volume, and BP [28]. The second trial enrolled 15 hypertensive subjects including 5 with CKD and mean creatinine clearance of 37 mL/min/1.73 m² who were all treated with escalating doses of indapamide, and those subjects with CKD had significantly greater reduction in body weight and similar reduction in BP as compared to those subjects with normal renal function [29].

Importantly, 5 randomized controlled trials (RCT) reported between 1979 and 2012 have investigated thiazide efficacy in CKD[30-34], also detailed in Table 1. The earliest was a double blind crossover study that enrolled 16 woman with mean creatinine clearance of 14 mL/min/1.73 m² who were treated with chlorothiazide 500 mg twice daily or placebo for 6 weeks before crossover [30]. Seven patients were withdrawn by protocol, but chlorothiazide significantly reduced BP in the 9 subjects that completed the study.

Two similar RCTs from the 1990s investigated natriuresis due to thiazides, loop diuretics, or the combination in a single blind, crossover fashion. The first enrolled 10 subjects with mean inulin clearance 13 mL/min/1.73 m² who were treated with single intravenous doses of either a loop diuretic alone or combined with intravenous isobutyl hydrochlorothiazide; the combination significantly increased sodium excretion [31]. The second RCT enrolled 19 subjects with average creatinine clearance 39 mL/min and treated them with single oral doses of either a loop diuretic, or oral hydrochlorothiazide, or the combination of the two. This trial found that while the loop diuretic and hydrochlorothiazide individually increased sodium excretion, the combination was subsequently significantly more potent [32].

In the last 10 years Dussol and colleagues performed two similar double blind RCTs of thiazides in CKD, both also with a crossover design [33;34]. The first RCT enrolled 7 subjects with average measured GFR of 25 mL/min who were randomized to either oral furosemide 60 mg daily or oral hydrochlorothiazide 25 mg daily for 30 days. After washout they then crossed over to the other drug. Finally, they received 30 day period of combination therapy [33]. The second RCT was reported in 2012 and enrolled 23 subjects with measured GFR of 25 mL/min [34]. This second RCT used the same doses of both medications, but the intervention periods were each 90 days long. Both RCTs found furosemide and hydrochlorothiazide individually significantly and similarly reduced mean arterial BP with the combination of diuretics more potent in the larger study for a reduction of 15 mmHg.

RECENT STUDIES OF CHLORTHALIDONE IN CKD

The positive studies of thiazides in CKD above have included most clinically available examples of the drug class including chlorothiazide, metolazone, hydrochlorothiazide, and indapamide. However, the absence of chlorthalidone is conspicuous as there is ample direct RCT evidence for the benefit of chlorthalidone in the general hypertensive population including

from the Systolic Hypertension in the Elderly Program (SHEP) trial [35] and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [36]. More recently, post hoc analyses of the Multiple Risk Factor Intervention Trial (MR FIT) suggest that chlorthalidone may be superior to hydrochlorothiazide for regression of left ventricular hypertrophy [37] and reduction of cardiovascular events [38]. It is in this context that two trials of chlorthalidone in CKD published in the last year merit close attention.

Both studies were uncontrolled trials using a before and after design. The first was a pilot study of subjects recruited for estimated GFR between 20 and 45 mL/min/1.73 m² and poorly controlled hypertension defined as average BP \geq 135/85 mmHg on ABPM despite treatment [**39]. The antihypertensive regimen for all subjects was standardized to lisinopril 20-40 mg/day, atenolol 50-100 mg daily, amlodipine 10 mg daily, and torsemide 10-20 mg daily based on the original clinical regimen while doses of other antihypertensive drug classes were left unchanged. After confirmation of uncontrolled hypertension by ABPM on the standardized regimen, the open label forced titration intervention was started with chlorthalidone 25 mg daily and the dose was increased on subsequent visits up to a maximum of 100 mg daily over the 12 week trial unless the subject had symptomatic hypotension, a drug related adverse event, or average home systolic BP < 125 mmHg.

12 of 14 subjects completed the study; one subject withdrew consent after 2 days of treatment and another was excluded per protocol 2 weeks into treatment due to home BP persistently elevated > 160/100 mmHg [**39]. All subjects were male, average age was 67.5 years, 8 of 14 were African American race, average estimated GFR was 27 mL/min/1.73 m², and average 24 hour ambulatory BP was 143/75 mmHg despite a mean of 3.8 antihypertensive drugs at the end of the run-in phase.

Modeled mean chlorthalidone dose was 51 mg daily at the last visit, and there was a significant reduction of 10.5 mmHg in average 24 hour ambulatory systolic BP from baseline [**39]. Both total body volume measured by air displacement plethysmography and body weight

were significantly reduced by 1.5 L and 1.2 kg from baseline respectively. This study is important for employing the gold standard of ABPM to show that the addition of chlorthalidone to a clinically significant hypertensive regimen in patients with advanced CKD may be effective at reducing BP as mediated by volume reduction.

The second chlorthalidone trial recruited subjects with estimated GFR < 60 mL/min/1.73 m² and poorly controlled hypertension defined as office BP ≥ 140/90 mmHg despite treatment with nondiuretic medications [**40]. After enrollment, subjects were started on a fixed dose of chlorthalidone 25 mg daily while other antihypertensive drugs were unchanged, and they were followed for 8 weeks of study.

Fully 58 of 60 subjects completed the study, the 2 drop outs having stopped chlorthalidone outside the protocol [**40]. Average age was 57 years, 60% of subjects were male, average estimated GFR was 39 mL/min/1.73 m², and average office was BP 151/90 despite a mean of 1.8 non-diuretic antihypertensive drugs at baseline.

At the final visit, office systolic BP and body weight were both significantly reduced from baseline by 19 mmHg and 0.88 kg respectively [**40]. Importantly, both the subgroups of 28 subjects with estimated GFR 30 to 44 mL/min/1.73 m² and 9 subjects with estimated GFR 15 to 29 mL/min/1.73 m² had similar reductions in systolic BP at 19 and 20 mmHg respectively. This study is important for being the largest by the factor of 3 to investigate thiazide use in CKD, and for showing that even fixed lower dose chlorthalidone may be effective at reducing office BP as a first diuretic for hypertension in CKD.

It is important to note that laboratory abnormalities and adverse events were common in both studies with 50% of subjects in the forced titration study of 14 subjects with advanced CKD [**39] and in 15% of patients in the fixed dose study with less severe CKD [**40]. Not surprisingly, the most frequent complications in both studies were hypokalemia, hyponatremia, and hyperuricemia.

CONCLUSION

The early observation that thiazide potency is reduced in advanced CKD is uncontroversial, especially as it has since been widely recognized that loop diuretic potency too is reduced in advanced CKD [41]. However, that early observation developed into dogma reinforced by influential guidelines that thiazides are ineffective in advanced CKD. Over the span of decades varied small studies using multiple different thiazides and including 5 RCTs have challenged that dogma by showing thiazides to be effective alone or in combination with a loop diuretic even in advanced CKD with GFR < 30 mL/min/m². Most recently, two studies further add to the evidence for clinical utility and efficacy based on their use of chlorthalidone in advanced CKD for the first time, for the use of gold standard ABPM to assess hypertension, and for a large study size relative to prior trials.

The time has come to perform a randomized trial of safety and efficacy of thiazides on top of existing antihypertensive among hypertensive people with advanced CKD.

- Thiazides have been shown to be effective for reducing blood pressure in advanced chronic kidney disease in small studies, including randomized trials.
- Thiazides have been shown to be effective for natriuresis in advanced chronic kidney disease in small studies, including randomized trials.
- Most clinically available thiazides have direct evidence for efficacy in advanced chronic kidney disease, not just metolazone.

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Table 1: Chronological list of studies of thiazides in CKD

Author	Year	Number of CKD subjects	Baseline kidney function	Design	Protocol	Diuretic effect	BP Effect
Dargie	1972	14	Mean Cr clearance 4.2 mL/min	Before-After	Single oral dose of metolazone given ranging from 20-150 mg.	Significant increase in urine flow and sodium excretion.	Not reported.
Bennett	1973	17	Mean Cr clearance 33 mL/min	Before-After	Oral metolazone 5 mg daily titrated up to maximum 25 mg over 3 months.	Weight reduced 1.3 kg and edema improved.	Diastolic BP reduced by 12.5 mmHg among 12 subjects who were hypertensive.
Craswell	1973	12	Mean Cr clearance 38 mL/min among 8 subjects, remaining 4 subjects had mean serum Cr 8.4 mg/dL	Before-After	Oral metolazone given in doses ranging from 2.5 to 25 mg daily over 2-20 weeks.	Weight reduced 1.4 kg and edema improved.	BP reduced by 14.2/3.2 mmHg.
Dargie	1974	6	"GFR" in 6 CKD patients ranged from 1-7 mL/min	Before-After	Oral metolazone given in doses of 5 mg to 200 mg daily for 7-180 days.	Weight reduced 3.8 kg.	Not reported.

Paton	1977	10	Mean Serum Cr 4.9 mg/dL	Before-After	Oral metolazone given between 2.5 mg and 30 mg daily over mean 13 weeks.	Weight reduced 2.0 lbs.	BP reduced by 15/8 mmHg.
Jones	1979	16	Mean Cr clearance 14 mL/min	Double blind placebo controlled crossover RCT	Oral chlorothiazide 500 mg twice daily versus placebo for 6 week periods.	No difference in weight reduction.	BP reduced significantly by 13/6 mmHg.
Wollam	1982	8	Mean serum Cr 3.3 mg/dL	Before-After	Hydrochlorothiazide 25 to 50 mg twice daily added to furosemide up to 480 mg daily.	Weight and plasma volume both significantly reduced by 2.6 kg and volume by 370 mL respectively.	Addition of hydrochlorothiazide significantly reduced BP by 22/11 mmHg.
Leenen	1988	5	Mean Cr clearance 37 mL/min	Single blind forced titration study	Placebo or indapamide 1.5 mg, 2.5 mg, or 5 mg given daily for 4 week periods.	Weight significantly reduced by 1.9 kg.	BP reduced.
Fliser	1994	10	Mean inulin clearance 13 mL/min /1.73 m ²	Single blind placebo controlled crossover RCT	Single intravenous doses of torsemide 50 mg + placebo versus torsemide 50 mg + buthiazide 20 mg.	Combination significantly increased sodium excretion by 134 mEq/day.	Not reported.

Knauf	1995	19	Mean Cr clearance 39 mL/min	Single blind placebo controlled crossover RCT	Single oral doses of hydrochlorothiazide 25 mg or 50 mg versus single oral doses of furosemide 40 mg or 80 mg versus combination of hydrochlorothiazide 25 mg + furosemide 40 mg.	Combination significantly increased sodium excretion by 141.5 mEq/day.	Not reported
Dussol	2005	7	Mean DTPA clearance 25 mL/min/1.73m ²	Double blind crossover RCT, open label combination	Oral hydrochlorothiazide 25 mg daily versus furosemide 60 mg daily versus combination for 30 day periods.	No differences in weight reduction or 24 hour sodium excretion.	All 3 regimens significantly reduced mean arterial BP by 12-15 mmHg from baseline.
Dussol	2012	23	Mean DTPA clearance 25 mL/min/1.73m ²	Double blind crossover RCT, open label combination	Oral hydrochlorothiazide 25 mg daily versus furosemide 60 mg daily versus combination for 90 day periods.	No differences in 24 hour sodium excretion. Furosemide significantly reduced weight by 4 kg, hydrochlorothiazide reduced weight nonsignificantly by 2 kg, and the combination had a significant reduction of 3 kg.	Hydrochlorothiazide and furosemide both significantly reduced mean arterial BP by 7 and 8 mmHg respectively. The combination had a significant reduction of 15 mmHg.

Agarwal	2014	14	Mean estimated GFR 27 mL/min/1.73m ²	Before-After forced titration study on top of standardize d antihyperten sive regimen	Forced titration study of oral chlorthalidone 25 mg to 100 mg daily for 12 weeks.	Body weight and total body volume reduced significantly by 1.2 kg and 1.5 L, respectively.	Ambulatory systolic BP significantly reduced by 10.5 mmHg.
Cirillo	2014	60	Mean estimated GFR 39 mL/min/1.73m ²	Before-After fixed dose study on top of existing anthyperten sive therapy	Fixed dose study of oral chlorthalidone 25 mg daily for 8 weeks.	Body weight reduced significantly by 0.88 kg.	Office systolic BP significantly reduced by 19 mmHg.

Table legend: CKD, chronic kidney disease; BP, blood pressure; Cr, creatinine; GFR, glomerular filtration rate; RCT, randomized clinical trial.