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STATE-OF-THE-ART PAPERS

Combination of Loop Diuretics With Thiazide-Type Diuretics in Heart Failure

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Volume overload is an important clinical target in heart failure management, typically addressed using loop diuretics. An important and challenging subset of heart failure patients exhibit fluid overload despite significant doses of loop diuretics. One approach to overcome loop diuretic resistance is the addition of a thiazide-type diuretic to produce diuretic synergy via "sequential nephron blockade," first described more than 40 years ago. Although potentially able to induce diuresis in patients otherwise resistant to high doses of loop diuretics, this strategy has not been subjected to large-scale clinical trials to establish safety and clinical efficacy. We summarize the existing literature evaluating the combination of loop and thiazide diuretics in patients with heart failure in order to describe the possible benefits and hazards associated with this therapy. Combination diuretic therapy using any of several thiazide-type diuretics can more than double daily urine sodium excretion to induce weight loss and edema resolution, at the risk of inducing severe hypokalemia in addition to hyponatremia, hypotension, and worsening renal function. We provide considerations about prudent use of this therapy and review potential misconceptions about this long-used diuretic approach. Finally, we seek to highlight the need for pragmatic clinical trials for this commonly used therapy. (J Am Coll Cardiol 2010;56:1527–34) © 2010 by the American College of Cardiology Foundation

Heart failure is the leading hospital discharge diagnosis among elderly Americans, accounting for more than 1 million hospital admissions each year in the U.S. (1). Prognosis after heart failure hospitalization is poor, with 50% of patients rehospitalized within 6 months and 25% to 35% mortality at 1 year (2). Despite several clinical trials, no single pharmacologic therapy has been clearly shown to reduce mortality or rehospitalization rates in acute heart failure (3). Congestion in acute heart failure syndromes appears to be more complicated than fluid accumulation alone (4,5). The vast majority of patients admitted for decompensated heart failure are treated primarily with intravenous loop diuretics (LD), and until the recently completed DOSE (Diuretic Optimization Strategies Evaluation) trial, there were limited prospective trial data evaluating the efficacy or safety of diuretics (6). Before the DOSE trial, many thought patients with acute heart failure receiving high doses of LD were at increased risk of serious adverse events (7) and renal failure (8). Patients with heart failure who are resistant to LD have poor outcomes, which may be a function of their more severe underlying disease process (9).

Overcoming Diuretic Resistance in Edematous States

Fluid overload refractory to conventional treatment with LD can complicate acute or chronic heart failure management. Diuretic resistance in heart failure results from an interaction between the pathophysiology of sodium retention in heart failure and the renal response to diuretic therapy (Fig. 1) (10). By eliciting significant counter-regulatory responses during acute and chronic use, several effects such as the "braking phenomenon," post-diuretic effect, rebound sodium retention, and renal adaptation lead to diuretic resistance. The braking phenomenon describes an acute reduction in diuretic efficacy with repeated LD dosing, while the post-diuretic effect refers to increased sodium retention after the LD has worn off. Rebound sodium retention occurs when chronic LD use leads to increased distal nephron sodium reabsorption. Renal adaptation occurs with prolonged exposure to LD and is described as hypertrophy and hyperfunction of distal tubule cells causing increased local sodium

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Abbreviations and Acronyms

CDT = combination diuretic therapy

LD = loop diuretic(s)

TD = thiazide-type diuretic(s)

uptake and aldosterone secretion, which markedly limits the response to LD (11,12). Distal tubule hypertrophy also appears to be an important contributor to rebound sodium retention and reduced response to chronic LD therapy over time (13). The activities of different diuretics should be considered to overcome the potential problems with diuretic resistance (Fig. 1).

Consideration of pharmacokinetic parameters of LD therapies may help to optimize strategies for overcoming diuretic resistance. Increasing LD doses is often considered initially to increase plasma drug concentrations and hopefully enhance LD effectiveness. Additional consideration may be given to drug half-life. For example, significant differences in the half-life of intravenous torsemide and furosemide in patients with heart failure have been documented (14). To overcome diuretic resistance, a more frequent administration schedule might be preferred for intravenous furosemide with a mean half-life of 1.5 h compared with intravenous torsemide with a mean half-life of 6.3 h. Ideally, critical evaluations of the effectiveness of a drug regimen occur at steady state when the rate of drug administration is equal to the rate of drug elimination. In most clinical situations, steady state can be assumed after 4 half-lives. Similarly, in most clinical situations, it can be assumed that all drug has been eliminated after 4 half-lives have passed without further drug administration. If the dosing interval for intravenous LD therapies extends beyond 4 half-lives, it is expected that there will be periods of time when no drug is available for pharmacologic activity and suboptimal effect may be observed. Thus, optimization

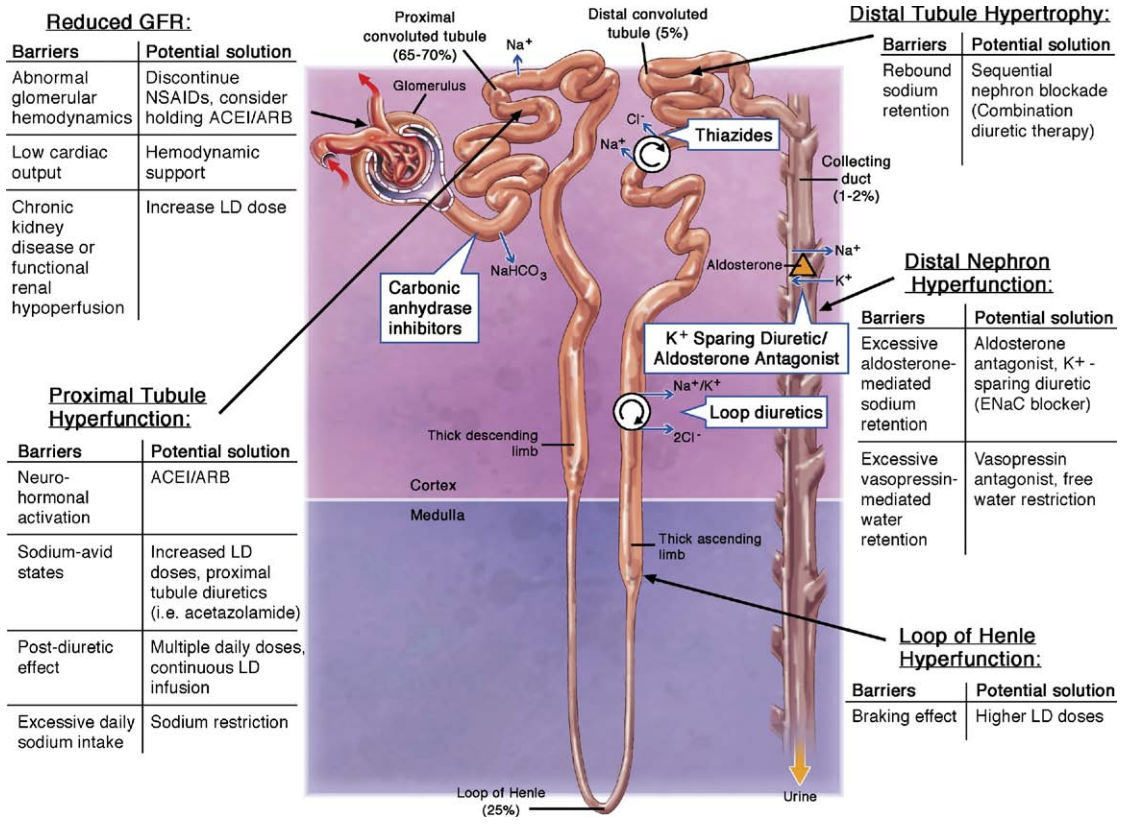

Figure 1 Diuretic Resistance and the Nephron

Sites of diuretic action and sodium retention with suggested strategies to overcome diuretic resistance. Sodium delivery into tubular fluid is determined by glomerular filtration rate (GFR). Percentage of filtered sodium reabsorbed in each nephron segment is denoted in parentheses. Proximal convoluted tubule reabsorbs the majority of filtered sodium and proximal reabsorption is increased in sodium-retaining states under the control of neurohormones (alpha-1 adrenergic, angiotensin-II), producing the post-diuretic effect. Loop of Henle is the site of action of loop diuretics (LD) and absorbs most of the sodium that escapes the proximal tubule; braking effect appears to occur here due to up-regulation of the Na/K/Cl cotransporter after exposure to LD. Distal convoluted tubule reabsorbs a lesser amount of filtered sodium via NaCl cotransporter (inhibited by thiazide-type diuretics [TD]) but size and function may increase dramatically after chronic LD exposure, accounting for rebound sodium retention. Distal nephron collecting duct is the site of regulated sodium and water reabsorption under control of aldosterone and vasopressin via epithelial sodium channels (ENaC) and aquaporins, respectively. Multiple mechanisms of diuretic resistance may occur in a single patient, requiring a systematic approach to diuretic therapy. Figure illustration by Craig Skaggs based on the author's description and an example nephron from Ernst ME, Moser M. Use of diuretics in patients with hypertension. N Engl J Med 2009;36:2153–64. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker.

Table 1 Mechanism of Action of Diuretic Classes

Drug Class	Examples	Mechanism of Action
Carbonic anhydrase inhibitors	Acetazolamide	Inhibition of proximal convoluted tubule sodium bicarbonate reabsorption
Loop diuretics	Furosemide Bumetanide Torsemide	Inhibition of Na/K/2Cl cotransporter in thick ascending loop of Henle
Thiazide-type diuretics	Hydrochlorothiazide Metolazone	Inhibition of Na/Cl cotransporter in distal convoluted tubule
Potassium-sparing diuretics	Amiloride Triamterene	Inhibition of aldosterone-responsive epithelial Na channel (ENaC) in distal nephron + collecting tubule
Aldosterone antagonists	Spironolactone Eplerenone	Inhibition of aldosterone receptors in distal nephron + collecting tubule, reducing Na channel and Na/K ATPase
Vasopressin antagonists	Conivaptan* Tolvaptan	Inhibition of V_2 receptors in distal nephron + collecting tubule, reducing aquaporin (water) channel density

*Conivaptan has nonselective V_{1A}/V_2 antagonism.

of LD regimens may be considered as a possibility to overcome apparent diuretic resistance.

After optimization of LD, other causes of diuretic resistance should be considered, particularly braking and postdiuretic effects. Physiologically, sequential nephron blockade by addition of a second diuretic class to ineffective optimized LD therapy can address other forms of diuretic resistance. By blocking distal tubule sodium reabsorption, thiazide-type diuretics (TD) can antagonize the renal adaptation to chronic LD therapy and potentially improve diuretic resistance due to rebound sodium retention (12,15). Several of the other mechanisms of action of different diuretic classes are summarized in Table 1 (16).

Combination Diuretic Therapy to Overcome Resistance to LD

The earliest studies examining the addition of TD to LD in patients with resistant edema due to heart failure or other edematous states date back more than 40 years to the early days of diuretic therapy (17). Despite more than 50 published reports, the experience is limited to 300 heart failure patients (Table 2) (17–45), raising many questions about this potent diuretic combination. The aggregate body of literature is limited by the small size of studies, study design with lack of control groups, heterogeneous patient populations, wide variation in diuretic regimens, and focus on physiologic rather than clinical outcomes. In fact, most studies have evaluated weight loss or clearance of persistent edema as the end point. The main findings date back to a series of randomized, cross-over laboratory studies performed in the early 1970s that showed that TD increased urine sodium excretion and urine volume compared with increasing the LD dose (21,25).

Among the largest randomized clinical trials was a 40-patient study comparing 2 different TD added to existing LD therapy (41). In a 2 × 2 factorial design, in patients with New York Heart Association functional class III/IV heart failure symptoms despite intravenous furosemide 80 mg twice daily were randomized to the addition of bendroflumethiazide 10 mg daily versus metolazone 10 mg daily as well as limited duration (3 days) versus indefinite duration (physician's discretion) of combination diuretic therapy (CDT). Both drugs significantly augmented diuresis and produced a similar (>5 kg) mean weight loss over 5 to 6 days; diuresis continued for the same amount of time regardless of CDT treatment duration. Clinical response occurred in 92.5%, with symptomatic improvement allowing hospital discharge in 90% of patients. Metolazone had greater adverse effects on potassium levels and renal function than bendroflumethiazide, but no clinical adverse effects were reported; nearly two-thirds of patients developed significant hypokalemia (serum potassium <3.5 mEq/l).

Other observational studies have shown the addition of moderate-dose TD often induced diuresis in patients resistant to very large doses of LD, with or without potassium-sparing diuretics (43). Outpatients previously dependent on intermittent intravenous LD could be maintained on oral diuretics after addition of metolazone (35). The majority of inpatients with acute heart failure refractory to maximal therapy, including intravenous LD, responded to the addition of low-dose metolazone within 48 to 72 h, allowing hospital discharge; metolazone nonresponders had a particularly poor prognosis (37). In a small study, the addition of chlorothiazide to LD during an episode of decompensated heart failure allowed clinical stabilization and remained effective for prevention of edema reaccumulation after hospital discharge for >2 years in some patients (42).

TD in Combination Therapy: Common Misconceptions and Evidence of a Class Effect

Although there are some commonly held beliefs about TD in CDT, the literature varies regarding many of these concepts. Metolazone is touted as being superior to other TD for CDT, possibly due to inhibition of proximal tubule function (46). Direct comparison of metolazone with bendroflumethiazide in a randomized, double-blind trial found no superiority of metolazone (41); comparison of quinethazone (metolazone's parent compound) with bendroflumethiazide revealed similar effects of both drugs (21). However, a response to metolazone plus furosemide was

Table 2 Summary of Reviewed Studies in Heart Failure Patients

First Author (Ref. #), Year	Patients	Design	TD Dose	LD Dose	Benefits	Adverse Events
Robson et al. (18), 1964	1 CHF	Observational	HCTZ 100 mg IV	FSM 50–100 mg IV + 1–5 mg/min	None	Not reported
Dettli and Spring (17), 1966	18 mixed edematous	Observational	HCTZ 200 mg	FSM 30–240 mg/day	Improved diuresis, similar to 4× higher FSM dose	Hypochloremic alkalosis + hypokalemia
Olesen et al. (19), 1970	24 CHF	Randomized active-control	QEZ 50–100 mg/day	FSM 40–80 mg/day	Superior diuresis to doubled FSM dose in mild CHF only	Hypokalemia (−0.5 mEq/l) bigeminy
Olesen et al. (20), 1971a	12 CHF	Randomized active-control	QEZ 50 mg/day	FSM 40 mg/day	Doubled UNa, mean weight loss 0.5 kg/day	Not reported
Olesen et al. (21), 1971b	24 CHF	Randomized active-control	QEZ 50 mg/day BDFZ 5 mg/day	FSM 80 mg BID	Doubled UNa, weight loss ~0.7–0.8 kg/day	Hypokalemia (−0.3 mEq/l)
Beck and Asscher (22), 1971	1 CHF	Observational	MTZ 5 mg/day	FSM 80 mg/day	Clearance of edema	Hypokalemia
Gunstone et al. (23), 1971	13 CHF	Observational	MTZ 2.5–10 mg/day	FSM 120–400 mg/day	≥2 kg weight loss over 4 days in >2/3 overall	Azotemia in most patients, hypokalemia
Asscher (24), 1974	4 CHF	Observational	MTZ 5 mg/day	FSM ≥500 mg/day	Mean weight loss 8.1 kg	Hypokalemia
Sigurd et al. (25), 1975	18 CHF	Randomized active-control	BDFZ 5 mg/day	BMT 2 mg BID	Doubled UNa, mean weight loss 0.8 kg/day	Hypokalemia (−0.45 mEq/l)
Epstein et al. (26), 1977	1 CHF	Observational	MTZ ≥5 mg/day	FSM 160 mg PO BID	Increased UNa even with severely reduced GFR	Hypokalemia
Ram and Reichgott (27), 1977	5 CHF + CKD	Observational	MTZ 5 mg/day	FSM 160–320 mg/day	Mean weight loss 4.4 kg	Hypokalemia (−0.3 mEq/l), creatinine ↑ 28%
Sigurd and Olesen (28), 1978	18 CHF	Randomized active-control	BDFZ 5 mg/day	BMT 2 mg BID	Tripled UNa, similar effect to aminophylline 200 mg BID	None
Furrer et al. (29), 1980	11 ADHF	Observational	MTZ ≥2.5 mg/day	FSM 40–370 mg/day	Mean 6.7 kg weight loss	Excessive/uncontrolled diuresis
Ghose and Gupta (30), 1981	3 CHF	Observational	MTZ 2.5–5 mg/day	Various	~0.3–0.6 kg/day weight loss	Not reported
Allen et al. (31), 1981	4 CHF	Observational	MTZ 5 mg/day	FSM 1–2 g/day	8–13L diuresis over 4–5 days	Hypokalemia
Bamford (32), 1981	1 CHF	Observational	MTZ 5 mg QOD	FSM 500 mg/day	13 kg weight loss	Not reported
Grosskopf et al. (33), 1986	10 ADHF	Randomized active-control	MTZ 5 mg/day	FSM 120 mg/day IV	Improved diuresis, weight loss ~2.2 kg over 3 days	Hypokalemia (−0.4 mEq/l)
Gage et al. (34), 1986	14 CHF	Observational	MTZ 2.5 mg QOD up to 15 mg/week	FSM 160 mg/day	Mean 4.4 kg weight loss + edema clearance	Hypokalemia (−0.6 mEq/l), BUN ↑ ~33%
Aravot et al. (35), 1989	12 CHF	Observational	MTZ 2.5–5 mg 2×/week	FSM 160 mg/day	Eliminated need for IV diuresis	Not reported
Friendland and Ledingham (36), 1989	1 ADHF	Observational	MTZ 5–10 mg/day	FSM 240 mg/day IV	16 kg weight loss	Not reported
Kiyingi et al. (37), 1990	10 CHF	Observational	BDFZ 10 mg/day	FSM 200–400 mg/day IV	Mean weight loss 7.7 kg	Hypokalemia (<2.9 mEq/l) in 20%
Channer et al. (38), 1990	17 ADHF	Observational	MTZ 1.25–10 mg/day	FSM 250–500 mg/day PO	Responders (71%) had mean 8.3 kg weight loss + d/c home	Hypokalemia, creatinine ↑ 25%
Kröger et al. (39), 1991	10 ADHF	Observational	MTZ 2.5–5 mg/day	FSM 80–500 mg/day	Mean 8.9 kg weight loss	Hyponatremia, hypokalemia
Dormans and Gerlag (40), 1993	8 CHF	Observational	HCTZ 25–100 mg/day	FSM 500– 4000 mg/day	Doubled UNa, mean 1.3 kg/day weight loss	Creatinine ↑ 50%, ClCr ↓ 33%, hypokalemia
Channer et al. (41), 1994	40 ADHF	Randomized active-control	MTZ 10 mg/day BDFZ 10 mg/day	FSM 80 mg IV BID	5–5.6 kg mean weight loss, hospital d/c in 90%	Hypokalemia (<3.5 mEq/l) in 65%
Mouallem et al. (42), 1995	32 ADHF	Observational	CTZ 500 mg/day	FSM 160–320 mg/day	Mean 4.8 kg weight loss, clearance of edema	Hypokalemia (−0.4 mEq/l)
Dormans and Gerlag (43), 1996	20 ADHF	Observational	HCTZ 25–100 mg/day	FSM 250–4000 mg/day	Doubled UNa, mean weight loss 6.7 kg, d/c home in 70%	Hypokalemia (−0.8 mEq/l), persistent dehydration
Vanky et al. (44), 1997	20 post-CABG	Observational	HCTZ 50 mg/day + amiloride 5 mg/day	FSM 80 mg/day	Mean 2.3 kg weight loss after one dose	None
Rosenberg et al. (45), 2005	21 CHF	Observational	MTZ 2.5–5 mg/day	FSM mean 260 mg/day	Mean 2 kg weight loss + 10/8 mm Hg BP reduction	BUN ↑ 58%, hypokalemia (−0.8 mEq/l), creatinine ↑ 27%

Some studies included patients with diagnosis other than heart failure.

ADHF = acute decompensated heart failure (inpatients); BDFZ = bendroflumethiazide; BID = twice daily; BMT = bumetanide; BP = blood pressure; BUN = blood urea nitrogen; CABG = coronary artery bypass grafting; CHF = chronic heart failure (outpatients); CKD; = chronic kidney disease; ClCr = creatinine clearance; CTZ = chlorothiazide; d/c = discharge; FSM = furosemide; GFR = glomerular filtration rate; HCTZ = hydrochlorothiazide; IV = intravenous; MTZ = metolazone; PO = oral; QEZ = quinethazone; QOD = every other day; UNa = urine sodium.

documented in a single patient resistant to chlorothiazide plus furosemide (24). Numerous TD have been evaluated in combination with various LD with similar results overall, and no clear evidence that any single TD is superior, suggesting a class effect. The most commonly used TD were metolazone, bendroflumethiazide, quinethazone, and hydrochlorothiazide. In addition to metolazone (45), LD augmentation was demonstrated using chlorothiazide (13,42), hydrochlorothiazide (43,47), quinethazone (20,21), indapamide (48), bendroflumethiazide (21,25), and butizide (49). Metolazone has been suggested to be superior to other TD in patients with advanced kidney disease (24,50), but other TD augment the response to LD, even in patients with advanced renal failure (26,47,49,51). Finally, the assertion that a TD should be given at least 30 min before the LD was not studied in any article we reviewed (52). Most studies reporting benefits of CDT administered the 2 drugs at the same time. Metolazone has slow and variable absorption in edematous patients, such that the peak effect occurs only after several hours (15,45). The benefit of TD (with their long duration of action) added to LD appears to be primarily in maintaining diuresis after the shorter-acting LD has worn off (49,53).

Anticipated Benefits of CDT

Given the baseline differences between the patient populations and the variations in diuretic regimens evaluated, it is difficult to quantify the effects of adding a TD to LD therapy. Across studies, mean daily weight loss was variable, with 1 kg per day more typical but as much as 3 to 5 kg over the first 24 h reported (24). Total weight reductions of 5 to 6 kg over several days in edematous patients were usual, but weight loss >10 kg was described by several reports (37,42,43) and weight loss >20 kg was rarely reported (24). The response rate to CDT varied based on the patient population, ranging from ~70% to 75% in more severely ill patients (37,43,45) to >90% in many studies. In 1 observational study, lower baseline serum potassium identified patients less likely to respond to the addition of metolazone to existing LD therapy (45).

Potential benefits of CDT include fluid removal with resolution of volume overload and congestion, even in patients with impaired renal function refractory to LD alone. Improved diuresis and relief of fluid overload could facilitate earlier hospital discharge and/or prevent rehospitalization to reduce the total number of hospital days, although it has been difficult to correlate weight loss during heart failure hospitalization with subsequent outcomes (54). CDT has been associated with improved quality of life in some patients with heart failure (41,45). Heart failure therapies should ideally improve mortality, but CDT may not provide such a benefit, considering the powerful neurohormonal activation produced beyond the effect of a LD alone (13) and lack of proven mortality benefit with LD (6). Metolazone use has been associated with poor outcomes in chronic heart failure, but may be a marker of increased disease severity (9). The anticipated benefits of CDT at a low cost make this a potentially attractive therapeutic option; increased urine sodium concentration with CDT overcomes 1 of the limitations of LD monotherapy for fluid removal. CDT has not been directly compared with ultrafiltration for fluid removal in heart failure, and ultrafiltration remains an important modality for refractory fluid overload (55).

Adverse Effects of CDT

Clinically important adverse effects with CDT are common, requiring careful monitoring of serum electrolytes and renal function (56). Hypokalemia is particularly frequent and reductions in serum potassium from 0.4 to 0.8 mEq/l are common despite aggressive potassium supplementation. Potassium-sparing diuretics such as spironolactone can reduce but do not entirely prevent potassium loss (21,25). Urine potassium loss and resultant hypokalemia tend to correlate with total urine sodium excretion and sodium concentration in the final urine. TD produce greater urine potassium loss per unit of urine sodium excretion than LD, and CDT is particularly prone to massive urine potassium excretion, especially with higher baseline LD doses (47). In select hospitalized patients prone to hypokalemia, twice-daily monitoring of potassium levels may be needed, with aggressive supplementation of potassium deficits. Hypokalemia is often associated with hypochloremic (chloride-responsive) metabolic alkalosis because urine chloride losses typically exceed urine sodium losses; hypomagnesemia often occurs and can worsen hypokalemia. Hypokalemia, with or without hypomagnesemia, may increase the risk of cardiac arrhythmias, particularly in patients taking digoxin or antiarrhythmic agents. Diuretic-induced electrolyte disturbances may contribute to arrhythmic death in heart failure patients (57). Hyponatremia can occur because the increase in urine sodium excretion is greater than the increase in urine water excretion with more hypertonic urine after CDT than after LD alone. Hyponatremia appears less common than hypokalemia and was rarely symptomatic but can be a marker of adverse heart failure outcomes (58). Massive diuresis with several liters of urinary fluid loss per day has been reported (24), potentially leading to progressive volume depletion requiring fluid resuscitation (40). Hypotension can occur, with a mean reduction of 10/8 mm Hg in blood pressure recorded in 1 study (45).

Renal Function and CDT

Changes in serum creatinine and creatinine clearance with CDT may be highly variable. Early short-term controlled studies did not reveal a significant acute reduction in creatinine clearance when a TD was added to existing LD therapy (21,25); later controlled studies support this conclusion (33,49). Several studies reported severe, albeit generally reversible, azotemia developing in patients treated

with CDT, particularly in the setting of more advanced baseline renal dysfunction with higher baseline serum creatinine (59). The rise in blood urea nitrogen was usually greater than the rise in serum creatinine (26,34,41,45) and typically stabilized after 3 to 5 days (51). Increases in serum creatinine on the order of 20% to 30% were frequently reported. TD alone initially produce a reversible reduction in glomerular filtration rate during peak natriuresis (47), which may be attenuated by the addition of LD (53). Chronic TD use is 1 predictor of worsening renal function in chronic heart failure patients (60), and the potential for worsening renal function is an important concern with CDT, given the adverse prognosis associated with worsening renal function in patients with heart failure (61). A decrease in serum creatinine can be seen after diuresis with CDT, depending on the hemodynamic state of the patient and the pathophysiology of their underlying renal dysfunction, potentially by relief of renal venous congestion (62). An initial rise in serum creatinine may be followed by a sustained fall as diuresis occurs (41). Impaired renal function with diuretic therapy can result from direct alterations in glomerular hemodynamics due to neurohormonal and intrarenal feedback mechanisms or from overt volume depletion (63). When excessive diuresis occurs, withdrawal of both diuretics is necessary due to the prolonged half-life of TD, which prolongs further in the presence of significant renal insufficiency (46).

Use of CDT in Clinical Practice

Leading professional society guidelines all recommend use of combined LD and TD therapy as 1 of several approaches to fluid overload refractory to LD monotherapy, with a Level of Evidence: C (expert opinion only) (2,50,64). A total of 5 sources were cited in support of this recommendation (12,15,26,41,56), none of which included a placebo-controlled trial; 1 was a randomized trial without placebo control (41).

Use of CDT requires weighing the known risks and potential benefits, summarized in Table 3. Based on the available literature, general recommendations can be made regarding prudent use of CDT in heart failure patients, similar to previously published recommendations about use of metolazone (46). Suggested considerations regarding CDT are summarized in Table 4. CDT is only appropriate for patients with gross fluid overload refractory to optimized doses of intravenous LD, especially in patients with chronic decompensated systolic heart failure and impaired renal function. Adequate doses of LD can be defined as 160 to 320 mg/day intravenous furosemide in divided doses or by continuous infusion; this was the usual dose range used in studies of CDT. Carefully selected patients with advanced, refractory, or end-stage (stage D) systolic heart failure may be candidates for outpatient CDT as a means to prevent recurrent hospitalization for fluid overload, although this approach is not well-studied and requires close follow-up (2,34,37,50,64). CDT should not be used in patients with peripheral edema due to local effects such as venous stasis rather than total-body fluid overload due to a sodium-retaining state. CDT is not an established or recommended approach to hypertension control in the absence of gross fluid overload (59). CDT is only expected to be effective in patients with diuretic resistance due to distal tubule hypertrophy from chronic LD exposure, and other causes of diuretic resistance should be carefully excluded.

Initiation of CDT should be done with careful observation and frequent monitoring of renal function and electrolytes. An equivalent dose of any TD should be effective (Table 5); longer-acting agents (e.g., metolazone) may be more useful for 2 to 3 times weekly dosing. A starting dose

Table 3 Potential Benefits and Adverse Effects of CDT

Potential Benefits	Potential Adverse Effects
Overcoming diuretic resistance	Hypokalemia
Relief of fluid overload + edema	Worsening renal function/azotemia
Weight loss	Hyponatremia
Low drug cost	Hypochloremic metabolic alkalosis
Symptomatic improvement	Hypotension
Decrease in systemic congestion	Hypovolemia/dehydration
Diuresis in chronic renal failure	Worsening hepatic encephalopathy
Improved ventricular function	Cardiac arrhythmias/ectopy
Hospital discharge	Hypomagnesemia
Prevention of readmission	Hyperuricemia

CDT = combination diuretic therapy.

Table 4 Important Considerations Regarding CDT

- Addition of thiazide-type diuretics can induce diuresis in patients refractory to massive loop diuretic doses
- Combination of loop + thiazide-type diuretics can be effective in patients with advanced chronic kidney disease
- Synergistic effects of thiazide-type diuretics on diuresis appear to be a class effect seen with all drugs studied
- Potentially dangerous hypokalemia can develop with CDT, warranting close laboratory monitoring
- Reversible increases in serum creatinine may be seen but are not the rule; reductions in creatinine can occur as well
- Safety and effects on morbidity and mortality with CDT are unknown

CDT = combination diuretic therapy.

Table 5 Dosing and Duration of Action of TD

Thiazide-Type Diuretic	Equipotent Dose, mg	Maximum Daily Dose, mg	Duration of Action
Bendroflumethiazide*	2.5	20	12–24 h (up to 48 h)†
Chlorothiazide	250	1,000	6–12 h (up to 24 h)†
Chlorthalidone	12.5	100	24–72 h†
Hydrochlorothiazide	25	200	6–12 h (up to 24 h)†
Indapamide	2.5	5	36 h
Methylclothiazide	2.5	20	24 h
Metolazone	2.5	20	12–24 h (up to 48 h)†
Quinethazone*	25	200	12–24 h†

*Not currently available in the U.S. †Duration of action can prolong substantially in the presence of renal insufficiency or chronic dosing. Adapted, with permission, from Hunt et al. (2).
TD = thiazide-type diuretics.

equivalent to metolazone 2.5 mg daily is suggested; 2 to 3 times weekly dosing is preferred for outpatient use rather than daily dosing (64). TD dosing recommendations for CDT from the American College of Cardiology/American Heart Association guidelines include oral metolazone 2.5 to 10 mg once daily (or 2.5 to 5 mg once or twice daily), oral hydrochlorothiazide 25 to 100 mg once or twice daily, or intravenous chlorothiazide 500 to 1,000 mg once or twice daily (2). For inpatients, the initial dose can be repeated or doubled each day in order to achieve desired diuresis, recognizing that TD tend to accumulate with repeated dosing in patients with impaired renal function, potentially leading to accelerating diuresis. A more aggressive regimen starting with 10 mg of metolazone daily with close monitoring and a treatment course limited to only 3 days appears to be safe and effective (41), resulting in a mean weight loss of ~5 kg over 5 to 6 days. When patients are on very high LD doses, halving the LD dose when a TD is added may reduce the risk of adverse effects. An aldosterone antagonist can improve natriuresis (21) and reduce hypokalemia (25) when added to CDT. Additionally, chronic aldosterone antagonist therapy can reduce mortality in outpatients with advanced heart failure receiving LD monotherapy (65).

Future Studies and End Points

Given the uncertainties regarding the balance of safety and clinical benefit, CDT should be subjected to a pragmatic clinical trial in fluid-overloaded inpatients with acute decompensated heart failure or outpatients with advanced chronic heart failure. The strategy of adding a TD to ineffective LD therapy could be compared with placebo or increasing LD doses using safety and morbidity/mortality end points such as days alive and free from hospitalization. Such a trial would allow clinicians to decide if and when to use this potentially powerful and potentially risky therapy that is currently recommended by major heart failure guidelines based on expert opinion. The National Heart, Lung, and Blood Institute's Heart Failure Network could provide the infrastructure to answer these questions, as demonstrated by the recent DOSE trial.

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