REVIEW

Diuretics for Hypertension: A Review and Update

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This review and update focuses on the clinical features of hydrochlorothiazide (HCTZ), the thiazide-like agents chlorthalidone (CTDN) and indapamide (INDAP), potassium-sparing ENaC inhibitors and aldosterone receptor antagonists, and loop diuretics. Diuretics are the second most commonly prescribed class of antihypertensive medication, and thiazide-related diuretics have increased at a rate greater than that of antihypertensive medications as a whole. The latest hypertension guidelines have underscored the importance of diuretics for all patients, but particularly for those with salt-sensitive and resistant hypertension. HCTZ is 4.2–6.2 systolic mm Hg less potent than CTDN, angiotensin-converting enzyme inhibitors, beta blockers, and calcium channel blockers by 24-hour measurements and 5.1 mm Hg systolic less potent than INDAP by office measurements. For reducing cardiovascular events (CVEs), HCTZ is less effective than enalapril and amlodipine in randomized trials, and, in network analysis of trials, it is less effective than CTDN and HCTZ-amiloride. Combined with thiazide-type diuretics, potassium-sparing agents decrease ventricular ectopy and reduce the risk for sudden cardiac death relative to thiazide-type diuretics used alone. A recent synthesis of 44 trials has shown that the relative potencies in milligrams among spironolactone (SPIR), amiloride, and eplerenone (EPLER) are approximately from 25 to 10 to 100, respectively, which may be important when SPIR is poorly tolerated. SPIR reduces proteinuria beyond that provided by other renin angiotensin aldosterone inhibitors. EPLER also reduces proteinuria and has beneficial effects on endothelial function. While guidelines often do not differentiate among specific diuretics, this review demonstrates that these distinctions are important for managing hypertension.

Keywords: amiloride; blood pressure; chlorthalidone; eplerenone; hydrochlorothiazide; hypertension; indapamide; potassium-sparing diuretics; sodium chloride symporter inhibitors; spironolactone.

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With the advent of chlorthiazide in 1958, thiazide diuretics quickly became a key component in the management of hypertension.[1] Just 9 years later in 1967, the publication of the landmark, randomized trial in US veterans demonstrated that hydrochorothiazide, reserpine, and hydralazine lowered "terminating events" (cardiovascular events (CVEs), hospitalizations, and sudden death) by more than 95% and undercut in glaring fashion the lingering concept that very high blood pressure (BP) (115–129 mm Hg diastolic pressure) was a normal physiologic process required for adequate tissue perfusion.[2] Meanwhile, spironolactone (SPIR) was being developed in the 1950s, and triamterene and amiloride were approved for use in 1964 and 1967, respectively.

In 2012, 12% of US adults were prescribed a diuretic, and the relative increase in prescriptions from 1999 through 2012 was 1.4, which is identical to that of antihypertensives as a whole (Figure 1).[3] Prescriptions for thiazide and thiazide-like diuretics have increased at an even greater rate (relative increase 1.7). Thiazide and thiazide-like diuretics are the second most commonly prescribed class of antihypertensive agents. Thus, diuretics continue to be widely used for the management of hypertension.

Salt-sensitive hypertension is present when, following sodium loading, its deprivation and removal lead to a drop in systolic blood pressure (SBP) of 10 mm Hg or more. Possible methods for recognizing salt-sensitive hypertension in routine clinical practice include use of genetic markers,[4] BP response to amiloride analogues,[5] and measures obtained from 24-hour ambulatory monitoring,[6] but none of these methods has achieved wide acceptance and general use. Thus, clinicians rely on studies demonstrating that there is a higher prevalence of salt-sensitive hypertension in Blacks, the obese, the elderly, and some diabetics.[7]

Although diuretics may be particularly valuable in such patients, it should be remembered that, irrespective of salt-sensitive status, large meta-analyses have shown that low-dose diuretics compared to other antihypertensives have demonstrated superiority and have the most evidence available.[8,9] Thus, most recent guidelines continue to recommend thiazide-related diuretics as first-line agents for all patients with hypertension (Table 1). Here, we summarize their essential features (Tables 2 and 3), review their impact on CVEs (Table 4), and report on recent clinical studies.

HYDROCHLOROTHIAZIDE

The inferiority of hydrochlorothiazide (HCTZ) to thiazide-like diuretics and to other antihypertensive classes of medications has been recently reviewed in some detail.[18,35,36]

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The structure of HCTZ and its site of action differ from thiazide-like diuretics (Figure 2). HCTZ has a less than 24-hour duration of action and is less potent than indapamide (INDAP), chlorthalidone (CTDN), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and calcium channel blockers by 4.2–6.2 mm Hg SBP.[18,35]

HCTZ was less effective in preventing CVEs compared to enalapril in the ANBP2 trial, to amlodipine in the ACCOMPLISH trial, and to CTDN and HCTZ-amiloride in network analyses of trials (Table 4). HCTZ has been shown to be similar to CTDN in producing gout and hypokalemia.[37,38] In patients with hypertension and diabetes, HCTZ is inferior to INDAP in improving endothelial function and longitudinal strain.[39] HCTZ is inferior to SPIR in improving coronary flow reserve.[40]

In spite of these observations, in 2013 HCTZ was the 12th most commonly prescribed drug in the US with 50 million prescriptions (not including fixed-dose combinations),

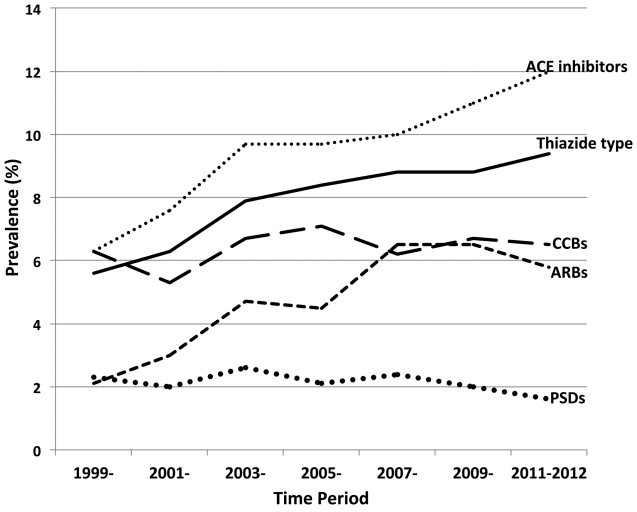

Figure 1. Trends in antihypertensive drug prescriptions in US adults from Kantor *et al.*[3] Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; PSDs: potassium-sparing diuretics; thiazide type, thiazide and thiazide-like diuretics.

and it is paradoxical that there has never been a placebo-controlled trial testing HCTZ's efficacy in reducing CVEs. However, it should not be forgotten that HCTZ-triamterene and HCTZ-amiloride have been demonstrated to be effective in reducing CVEs compared to placebo (Table 4). (Because the rationale in favor of potassium-sparing combinations is a strong one, we view these preparations as distinct from HCTZ itself, an approach which differs from a recent meta-analysis.[41])

In passing we wish to note that, at conventional doses, there is not a specific relationship between the serum half-life of a diuretic and its biologic potency that is above and beyond the primary action of the diuretic in question. An extended serum half-life of one or the other of these drugs is only as relevant as the achieved concentration remaining above the threshold for drug effect. Furthermore, the antihypertensive effect of thiazide-related diuretics can be reduced by concomitant administration of nonsteroidal anti-inflammatory agents, which block vasodilatory prostaglandin synthesis and therein negatively impact renal sodium handling.

CLORTHALIDONE

The distribution of CTDN into red blood cells creates a reservoir leading to a 2- to 3-day duration of action. For reducing CVEs, CTDN was more effective than HCTZ in network analysis. In the ALLHAT trial, CTDN was more effective than lisinopril for reducing CVEs and more effective than amlodipine in preventing congestive heart failure. See Table 4.

While concerns have often been raised regarding CTDN's tolerability, in the ALLHAT trial, control of BP after 5 years in the CTDN, amlodipine, and lisinopril arms was 68, 66, and 61%, respectively.[29] Further, at the 12.5–25 mg doses of CTDN, safety concerns stemming from hypokalemia and hyperglycemia appear to be unwarranted.[42,43] Hyponatremia is more common with CTDN than HCTZ but not at equipotent doses, and, perhaps more importantly, the incidence of hyponatremia for both medications is very strongly age related.[44] In the 22-year follow-up of the SHEP trial, those randomized to the CTDN arm (with or without atenolol)

Table 1. The latest guidelines and thiazide-type diuretics

Guideline (year issued)	Average patient	Blacks	Elderly
Australia (2012)[10]	1st line	Not specified	Not specified
Canada (2015)[11]	1st line	Thiazide or CCB	Not specified
Europe (2013)[12]	1st line	Not specified	Not specified
International/ASH (2014)[13]	1st line	Thiazide or CCB	Not specified
JNC8 (2014)[14]	1st line	Thiazide or CCB	Not specified
United Kingdom (2011)[15]	ACEi/ARB>>CCB>>ThiazLikea[a]	CCB >> INDAP or CTDN	CCB >> INDAP or CTDN
Resistant HTN (2008)[16]	CTDN, 1st line	NA	NA
Soc on HTN in Blacks (2010)[17]	NA	CTDN, 1st line	NA

Abbreviations: ASH, American Society of Hypertension; CCB, calcium channel blocker; CTDN, chlorthalidone; HTN, hypertension; INDAP, indapamide; JNC8, The Eighth Joint National Committee; NA, not applicable; Soc on HTN, Society on hypertension.
[a]ThiazLike: CTDN or INDAP.

Table 2. Indications, contraindications, and adverse effects for diuretics

Subclass	Indications	Contraindications	Adverse effects
Thiazides	Nephrogenic diabetes insipidus, mild edema, renal calcium stones	Hypersensitivity to sulfa agents and gout	Orthostatic hypotension. ↓ Na^+, K^+, Mg^+. Metabolic alkalosis. Increased serum calcium, uric acid, glucose, cholesterol, and triglycerides. Erectile dysfunction and lithium accumulation
"Thiazide-like" agents (e.g., chlorthalidone and indapamide)	Hypertension and resistant hypertension	Ditto	Ditto
Potassium-sparing pteridines: triamterene and amiloride	*Pteridine derivatives*: hypertension with K^+ and/or Mg^+ loss, Liddle's syndrome	Hyperkalemia (K > 5 mmol/l), concomitant use of ACEIs or ARBs (relative), advanced renal failure, pregnancy (particularly triamterene)	Increased serum K^+, Cl^-, and H^+. Nausea, flatulence, and skin rash with amiloride or triamterene; nephrolithiasis with triamterene. Gynecomastia and decreased libido in men with spironolactone
Aldosterone antagonists: pironolactone and eplerenone	*Aldosterone antagonists*: hypertension with K and/or Mg loss, resistant hypertension, primary aldosteronism and other mineralocorticoid excess, CHF		
Loop diuretics (furosemide, torsemide)	*For hypertension when GFR ≤ 30 ml/min*	Sufa allergies, gout, pregnancy	Electrolyte abnormalities and metabolic abnormalities as for thiazides[a]

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CHF, congestive heart failure; GFR, glomerular filtration rate.

[a]Low-dose torsemide (2.5–5 mg) produces not detectable effects on electrolytes, glucose, and lipids (and yet yields an antihypertensive effect comparable to thiazides).

Table 3. Diuretic duration of action, dose (mg), and effect on SBP (mmHg) and serum potassium (mEq/L)[18,19]

Diuretic	DOA (hours)	Dosage forms	Dose	Comparator	SBP change	Serum K change
HCTZ	8 < 24	12.5, 25, 50	25	Placebo	−9.5	0.3
CTDN	48–72	25	6.25–25	HCTZ 12.5–50	−3.0 to −10.1	−0.1
INDAP	24–34	1.25, 2.5, 5.0	1.25–5	HCTZ 12.5–50	−5.1	−0.1
TRIAM/HCTZ	<24/8 < 24	37.5/25, 50/25, 75/50	(TRIA below)	(TRIA below)	(TRIA below)	(TRIA below)
AMIL/HCTZ	24+/8 < 24	5/50	(AMIL below)	(AMIL below)	(AMIL below)	(AMIL below)
SPIR/HCTZ	24–34/8 < 24	25/25	(SPIR below)	(SPIR below)	(SPIR below)	(SPIR below)
TRIAM	<24	50, 100	50, 100	Placebo	−1.9	0.26
AMIL	24+	5	2.5–40	Placebo	−5.0 to −15.2	0.37
SPIR	24–34	25, 50, 100	25–400	Placebo	−7.6 to −24.8	0.43
EPLER	24+	25, 50	25–400	Placebo	−5.7 to −16.9	NA
Furosemide	4–6	20, 40, 80	10–80	Placebo	Less than thiazides[20]	NA
Torsemide	12	5, 10, 20, 100	10–100	Placebo and INDAP	Comparable to thiazides[21,22]	None

Abbreviations: AMIL, amiloride; CTDN, chlorthalidone; DOA (hours), duration of action in hours; EPLER, eplerenone; HCTZ, hydrochlorothiazide; INDAP, indapamide; SBP, systolic blood pressure; SPIR, spironolactone; TRIAM, triamterene.

had a gain in life expectancy free from cardiovascular death of 145 days ($P = 0.012$), while there was a smaller shortening of life from noncardiovascular deaths by 40 days ($P = 0.20$) although statistical power for this outcome was less than 45%. The overall gain in total survival was 105 days ($P = 0.073$).[45,46] Recently, it has been shown that, compared to lisinopril, CTDN was more effective in reducing visit-to-visit variability, which is a strong risk factor for cardiovascular disease.[47,48]

INDAPAMIDE

As with CTDN, the thiazide-like diuretic, INDAP, acts on the distal convoluted tubule more proximally than does

Table 4. SBP, baseline, decline, and relative risk for interventions with a diuretic at step 1 vs. placebo or other drug comparator for total mortality, cardiovascular events, coronary artery disease, and cerebrovascular accident

Diuretic, study (reference)	*N* setting	SBP baseline	SBP decline[a]	Step 1 intervention	Step 1 comparator (mg)	Outcome as relative risk				
						TM	CVEs	CAD	CVA	CHF
HCTZ										
OSLO[23]	785, men without CVD	155	−17	HCTZ 50	Nonplacebo control	1.07	0.82[b]	1.44	0/7**	0/1
ANBP2[24]	6,083. Australian practices	168	0	HCTZ, dose per MD[c]	Enalapril, dose per MD	1.11	1.14@	1.11	1.18	1.14
ACCOMPLISH[25]	11,506. US and Nordic countries	145.3	+0.9	Benazepril 20–40 + HCTZ 12.5–25	Benazepril 20–40 + amlodipine 5–10	1.11	1.25***		1.19	1.04
Network analysis[26]	50, 946. ACCOMPLISH, ANBP2, and ALLHAT	NA	NA	HCTZ 25	CTDN 12.5–25	1.06	1.27***		1.04	1.30*
Network analysis[18]	17, 827. ACCOMPLISH and INSIGHT	NA	NA	HCTZ 12.5–25	AMIL 2.5/ HCTZ 25		1.39**		1.32	2.27
CTDN										
SHEP[27]	4,736. United States	170.3	−12.4	CTDN 12.5–25	Placebo	0.87	0.68***	0.75*	0.64***	0.46***
ALLHAT[28]	24,335. North American centers	145	−2.4	CTDN 12.5–25	Doxazosin 2–8	0.93	0.83***	0.97	0.79**	0.56***
ALLHAT[29]	24,309. Otherwise as above	146	−2.2	CTDN 12.5–25	Lisinopril 10–40	1.00	0.91***	0.95	0.87**	0.84***
ALLHAT[29]	24,303. Otherwise as above	146	−1.1	CTDN 12.5–25	Amlodipine 2.5–10	1.04	0.96	1.00	1.08	0.72***
SHELL[30]	1,882. Italian practices	178.2	+1.2	CTDN 12.5–25	Lacidipine 4–6	0.81	0.99	1.18	1.04	0.83
INDAP										
PATS[31]	5,682. Chinese practices	154	−5 to −6	INDAP 2.5 (only 1 step)	Placebo	0.92	0.77**	1.19	0.73**	
AMIL-HCTZ										
MRC[32]	4,396. Age 65–74, European general practices	185	−14 to −3 to 0[d]	AMIL 2.5/HCTZ 25 AMIL 2.5/HCTZ 25	Placebo Atenolol 60e[e]	0.84, 0.82	0.65***, 0.72**	0.56***, 0.62**	0.69*, 0.82	
INSIGHT[33]	6,321. Europe and Israel	174	0	AMIL 2.5/ HCTZ 25	Nifedipine 30		0.90	1.69	0.90	0.46*
TRIAM-HCTZ										
EWPHE[34]	840. Age 60+, Europe	183	−22	TRIAM 50/ HCTZ 25	Placebo	0.91	0.72[f]	0.62[f]	0.57	0.63

Abbreviations: ABs, alpha blockers; AMIL, amiloride; BBs, beta blockers; CAD, coronary artery disease; CCBs, calcium channel blockers; CHF, congestive heart failure; CTDN, chlorthalidone; CVA, stroke; CVD, cardiovascular disease; CVEs, cardiovascular events; HCTZ, hydrochlorothiazide; NA, not available; SBP, systolic blood pressure; TM, total mortality; TRIAM, triamterene.

[a]Declines are comparator arm vs. the intervention arm.

[b]95% confidence limits 0.46–1.44.

[c]HCTZ was the recommended diuretic and enalapril the recommended angiotensin-converting enzyme inhibitor, but the clinician was free to choose.

[d]The atenolol arm declined less than the AMIL-HCTZ arm in 1 year by about 3 mm Hg systolic and then became identical to the AMIL-HCTZ decline after 2 years.

[e]Reduction of CVEs from AMIL/HCTZ relative to atenolol was not provided in the MRC report. We have calculated relative risks and *P* values based on the number of events and persons at risk in each arm. Our calculation for the point estimate for all CVEs agrees with the ratio of rates given in Table 2 of that report.

[f]These outcomes exclude nonfatal events.

@*P* = 0.05. *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$.

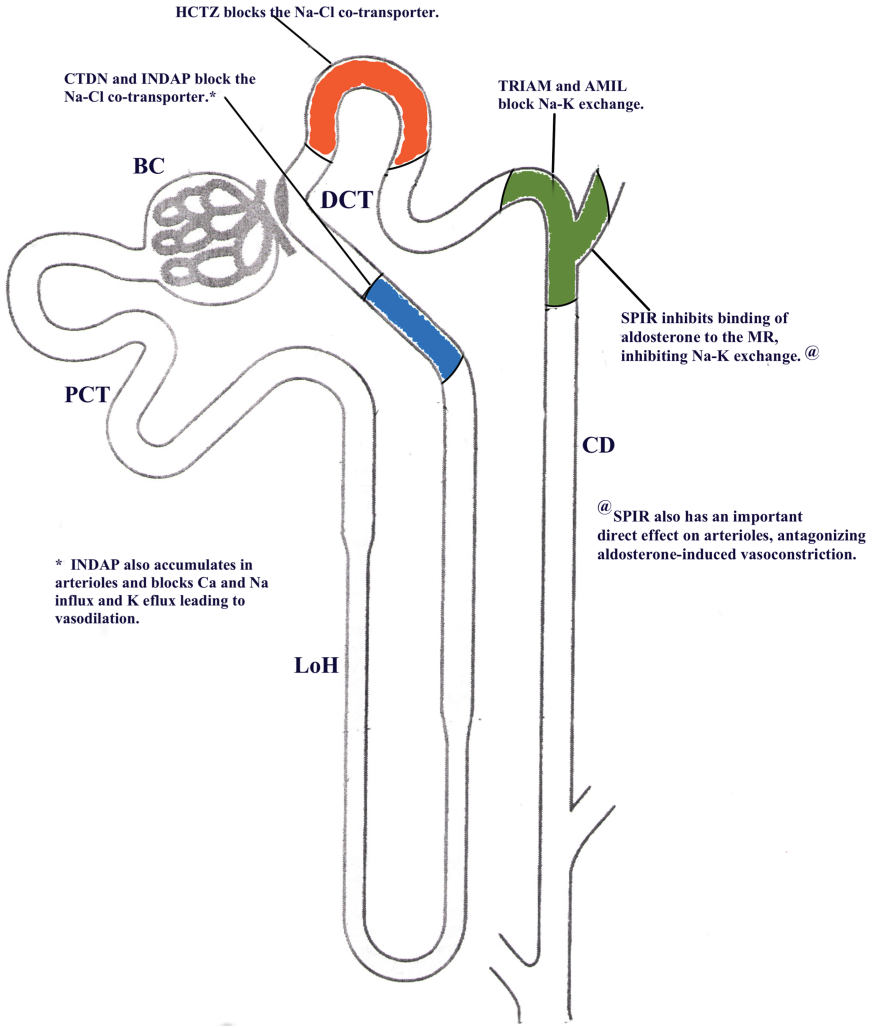

Figure 2. Sites and mechanisms of action for thiazide-related and potassium-sparing diuretics. All effects on electrolytes take place on the lumenal side of the epithelial cell, while SPIR leads to reduction in Na–K exchange on the interstitial side as well. AMIL, amiloride; BC, Bowman's capsule; CD, collecting duct; CTDN, chlorthalidone; DCT, distal convoluted tubule; INDAP, indapamide; LoH, loop of Henle; MR, mineralocorticoid receptor; PCT, proximal convoluted tubule; SPIR, spironolactone; TRIAM, triamterene. From Roush *et al.*[18]

HCTZ (Figure 2). In addition to its diuretic effects, INDAP acts to lower SBP via a calcium antagonist–like vasorelaxant effect,[49] and its potency is 5 mm Hg systolic greater than that of HCTZ.[35] The PATS trial demonstrated that, in stroke patients, INDAP at 2.5 mg was superior to placebo in reducing CVEs by 23% (Table 4). In 3 settings, the value of adding INDAP to perindopril for preventing cardiovascular disease has been demonstrated: following stroke,[50] in the elderly,[51] and among diabetics.[52] Relative to HCTZ, INDAP was superior in improving microalbuminuria in diabetics, reducing left ventricular mass index, inhibiting platelet aggregation, and reducing oxidative stress.[18] Further, INDAP's ability to reduce left ventricular hypertrophy is superior to enalapril.[18] Unlike other thiazides and CTDN, INDAP appears to have no impact on glucose or lipid metabolism.[35] In the United States, INDAP is available for $4 per month in discount pharmacies. A recent editorial has suggested that INDAP might be viewed as the best thiazide/thiazide-like diuretic.[36]

POTASSIUM-SPARING DIURETICS: OVERVIEW

As compared with potassium supplements, potassium-sparing diuretics are more effective in maintaining serum and intracellular levels of potassium.[19] Both observational and randomized trial data have highlighted the potential of thiazide and thiazide-like diuretics (generally at higher doses) to cause ventricular ectopy and sudden death and for the addition of potassium-sparing diuretics to avert it.[19] SPIR, eplerenone (EPLER), amiloride, and triamterene are all valuable, and the latter 2 drugs have been successfully combined with HCTZ to reduce CVEs relative to placebo (Table 4). In resistant hypertension, both SPIR and amiloride (up to 10 mg and with HCTZ) have demonstrated utility overall.[53–56]

A recent meta-analysis of 44 trials has clarified the dosing of these drugs and may foster the use of these underutilized agents.[19] Doubling the dose of AMIL, SPIR, and EPLER decreases SBP on average by 2.3 mm Hg. When SPIR given at, say, 25 mg is poorly tolerated, approximately equivalent

potency can be achieved from EPLER 100 mg or AMIL 10 mg. At the commonly used lower doses, SPIR and AMIL elevate serum potassium by 0.14–0.29 mEq/l.

SPIRONOLACTONE

Clinical features of SPIR have recently been summarized.[18,19] SPIR has 2 antihypertensive sites of action: (i) at the mineral corticoid receptor in the kidney around the junction of the distal convoluted tubule and collecting duct where it inhibits sodium–potassium exchange and (ii) on receptors in the arterioles, where it antagonizes aldosterone-induced vasoconstriction (Figure 2). Evidence for the latter mechanism is supported by a 6–8 mm Hg reduction in diastolic and mean pressure (but not for SBP) from SPIR in patients with end-stage renal disease.[57] While the potency of SPIR in resistant hypertension has often been cited as exceeding 20 mm Hg systolic, its placebo adjusted effect more likely approximates 9 mm Hg.[53,54] Although often given twice daily, once daily dosing of SPIR has led to nighttime declines in SBP as great or greater than daytime.[54]

SPIR has never undergone adequate testing for efficacy in reducing CVEs in unselected hypertensives but does reduce total mortality and sudden death in advanced heart failure.[58] Furthermore, in hemodialysis patients, it has been recently shown that SPIR at 25 mg, while having no effect on BP, decreased the primary outcome of cardiovascular death and hospitalization for CVEs by 60% (95% CI: 19%–80%), $P = 0.017$, with fewer numbers of coronary and cerebrovascular events in the SPIR-treated group.[59] (The low incidence of significant hyperkalemia in this trial (2%) is also consistent with a recent meta-analysis of hemodialysis patients.[60]) Nonblood pressure–related benefits of SPIR are further suggested by recent data showing SPIR's ability to reduce proteinuria by 61% in proteinuric kidney disease,[61] to reduce albuminuria by 60% in type 1 diabetics,[62] to normalize left ventricular hypertrophy in primary aldosteronism and low renin hypertension,[63] and to prevent CTDN-induced sympathetic activation and insulin resistance in hypertensive patients.[64]

EPLERENONE

In a recent meta-analysis, compared to other antihypertensives, EPLER caused a 1.5 mm Hg greater reduction in SBP but similar rates of hyperkalemia.[65] EPLER improves endothelial function in patients with hypertension.[66] As noted above, dose equivalency is approximately 100 mg of EPLER to 25 mg of SPIR.[19]

LOOP DIURETICS

As chronic kidney disease transitions from stage 3 to 5, particularly with extracellular fluid volume expansion, loop diuretic therapy becomes the preferred diuretic therapy for management of hypertension. Loop diuretics are less effective than thiazide-type drugs in reducing BP in the nonedematous patient as has been shown in a recent Cochrane analysis reporting the SBP/diastolic BP reduction of several loop diuretics in primary hypertension.[67] This Cochrane analysis did not show any within-class difference among the several loop diuretics reported; however, the evidence quality in these studies was low with a high likelihood of publication bias.[67] The antihypertensive effect of low-dose loop torasemide is improved with nighttime administration.[68]

CONCLUDING COMMMENTS

Diuretics are a popular, heterogenous class of antihypertensives with several decades of clinical application. However, their antihypertensive and beneficial effects can be thwarted in many circumstances, such as by concomitant administration of nonsteroidal anti-inflammatory agents as noted above. Dietary factors can also be very important. Excess salt ingestion blocks the antihypertensive effect of diuretics, perhaps by countering volume depletion and reduction in cardiac output, an "acute" phase which may be required for the longer-term, "chronic," vasodilatory phase associated with diuretic administration.

In large-scale clinical studies, the ability to reduce CVEs is well documented for CTDN, INDAP, amiloride-HCTZ, triamterene-HCTZ, and, in the context of congestive heart failure and end-stage renal disease, SPIR. Selection of the appropriate medication and dose optimizes the administration of diuretics in a variety of circumstances, particularly salt-sensitive hypertension, which is prevalent in the obese, the elderly, and black patients. In the setting of low renin hypertension, diuretics elevate renin in a dose-dependent manner and, therefore, would be expected to enhance the efficacy of angiotensin-converting enzyme inhibitors and aldosterone receptor blockers. Diuretics are critical in the management of resistant hypertension, which affects approximately 5% of all adults and is a major contributor to morbidity and mortality. Potassium-sparing diuretics are probably underutilized. The number of salt-sensitive patients (i.e., the obese and elderly) is increasing, and the SPRINT trial supports an SBP target of less than 120 mm Hg in many patients.[69] Thus, it is likely that diuretics will become even more prominent in the management of hypertension.

DISCLOSURE

The authors declared no conflict of interest.

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