Fifty Years of Thiazide Diuretic Therapy for Hypertension

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Background: The use of thiazide diuretics has decreased over the past 30 years despite data from many well-controlled clinical trials demonstrating that the use of these agents as monotherapy or in combination with other antihypertensive agents will reduce blood pressure and decrease cardiovascular as well as cerebrovascular events.

Methods: We reviewed clinical and experimental data on thiazide diuretics since their introduction in the late 1950s.

Results: The results of thiazide-based therapy in young and old are consistently positive despite concerns about some metabolic changes, eg, insulin resistance or hypokalemia, that may occur.

Conclusion: We conclude that these agents are safe, effective, and well tolerated and should continue to be used either as monotherapy or with other medications in the management of hypertension.

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Thiazides and thiazide-like diuretics have remained a cornerstone in the management of hypertension for more than half a century since their introduction in 1958. Very few agents used for the treatment of any disease can boast such staying power, which is a testament both to the efficacy and safety of these compounds and to the relevance of salt and volume control in the management of essential hypertension. On the 50th anniversary of the entry of thiazide diuretics into the antihypertensive armamentarium, it is fitting to review (1) the history of the discovery and development of these medications; (2) the important intervention trials documenting their role either as monotherapy or in combination with other medications in the prevention of cardiovascular (CV) disease; and, finally, (3) the possible few limitations to the use of diuretics and insights into a future with possibly improved compounds with related actions.

HISTORY OF THE DISCOVERY AND DEVELOPMENT OF DIURETICS

Until 1937, the only effective available diuretics were intravenous or intramuscular mercurial agents, which were difficult to use; their use was restricted mostly to patients with heart failure. Despite knowledge that sodium restriction was helpful in lowering blood pressure (BP), there were few physicians who considered prescribing these medications. In 1937 and 1938, research on the mechanism of acidemia produced by sulfonamides demonstrated that they also had a diuretic effect, and oral diuretic therapy became conceivable. Seven years later, the development of the carbonic anhydrase inhibitor acetazolamide helped us to understand the mechanism for urinary acidification and diuresis in the renal tubules.

Therefore, Novello and Sprague and associates at Merck Sharp & Dohme decided to synthesize a large number of compounds in search of a better carbonic anhydrase inhibitor. In the process, they stumbled on chlorothiazide, which was, in fact, a sulfonamide as well as a carbonic anhydrase inhibitor. It was, however, a more potent diuretic that completely and unexpectedly distinguished itself from a carbonic anhydrase inhibitor by causing an increase in chloride rather than bicarbonate excretion. Much later, we came to understand that what chlorothiazide was doing was no longer just inhibiting carbonic anhydrase (a relatively irrelevant process in the action of thiazides) but rather inhibiting another transport system, ie, the sodium chloride cotransport system. It is interesting to speculate that had Beyer et al known that a better carbonic anhydrase inhibitor was neither necessary nor probably feasible be-
cause of the diuretic limitations of an agent acting on the proximal tubule (the carbonic anhydrase site of action), they would never have pursued this line of discovery and possibly would never have discovered thiazides.

Research efforts in the late 1950s were totally different from those in recent years. Serendipity played a major role. When one of us (M.M.) requested a supply of chlorothiazide from Merck Sharp & Dohme, it was for use in congestive heart failure. Within 2 weeks, after use in just a few patients, it became obvious that this compound lowered BP. In 1958, we called and requested a large supply from the clinical research head (John Beam, MD) and launched studies, without rigid protocols, power calculations, or predetermined numbers of patients, in parallel with similar studies by Freis et al,10; the results were often dramatic. Publications advanced thiazides as adjunctive therapy,2 failing to realize that diuretics might also be useful as monotherapy. We wonder whether this advance could have taken place this quickly if we had had to follow carefully drawn protocols that are now a part of any drug research program.

MECHANISM OF ACTION

Despite the dramatic results in BP lowering, the exact mechanism of action of the thiazide diuretics has not been definitely established. The initial decrease in BP results from diuretic-induced reduction in plasma volume and cardiac output (with a slight increase in peripheral resistance) is followed by a decrease in vascular resistance, perpetuating the lowered BP. The cardiac output returns to normal, but with a continuing slight decrease in plasma volume.8 The reduction in volume explains the ongoing increases in the activity of the renin-angiotensin system action. Tobian and Binion9 reasoned that the blood vessels of an individual with hypertension were “waterlogged” with excessive amounts of sodium and water, making them more susceptible to sympathetic nervous system stimuli; thiazides reversed this effect on the vessels, making them less sensitive to vasoconstrictive activity. While these explanations have experimental support, they are not definitive, and the precise mechanism of long-term action of thiazides remains unknown, except that a natriuretic effect initiates the process.

It is well known that approximately 30% to 40% of individuals in the United States are salt sensitive; ie, they respond to a high sodium intake with increases in BP and to sodium restriction with decreases in BP. Many of these individuals respond readily to thiazide diuretic therapy. Elderly and black individuals are generally more salt sensitive and respond better to therapy with thiazides than whites and younger individuals with hypertension. However, all ages and ethnic groups will respond to some extent with BP lowering.10

CURRENT ROLE OF DIURETICS IN THE PREVENTION OF CV EVENTS

The landmark randomized, controlled trial to prove that lowering of BP by medications caused a decrease in CV events associated with hypertension was the Veterans Cooperative Study,14 which was initiated 45 years ago in 1964, only 5 years after the development of thiazide diuretics. This trial established for the first time that antihypertensive intervention aimed at lowering BP in moderate to severe hypertension was beneficial, with remarkable decreases in the incidence of death, strokes, and other CV events in patients with diastolic BP levels above approximately 105 mm Hg. The drugs used were a combination of a thiazide diuretic, reserpine, and hydralazine hydrochloride. Drugs proved to decrease BP were subsequently approved, with evidence that such effect translates into decreases in CV events.

Subsequently, the Hypertension Detection and Follow-up Program extended this observation to mild and moderate hypertension.12 It demonstrated that a “stepped-care” approach, with diuretics as initial therapy, resulted in better BP reduction than referral to community medical therapy (“referred care”). A decrease in strokes, coronary heart disease events, and associated death was noted with a decrease in BP even in patients with what was then termed mild hypertension (diastolic BP, 90-104 mm Hg).

The Multiple Risk Factor Intervention Trial in high-risk men attempted to confirm the protective effect of BP lowering even in patients with less severe hypertension but did not clearly demonstrate such an effect.15 However, that trial, which compared intensive treatment of hypertension (but also smoking and cholesterol) with less intensive (usual care) treatment, unlike the Hypertension Detection and Follow-up Program, failed to achieve a meaningful difference in BP reduction between the 2 treatment arms. The lack of greater reduction in the intensive care group was probably attributable to improved management in the usual care group as the trial progressed over a long period of time; physician education improved the usual care treatment of patients with hypertension. An important observation is that the trial reported that mortality in both treated groups was considerably less than was predicted based on risk factor analysis; ie, both groups had risk factors modified with a decrease in CV events. The controversy about the many retrospective secondary analyses of the role of diuretics, hypokalemia, and the type and dosages of diuretics is beyond the scope of this review, but many of the findings suggesting a negative outcome in the intensive treatment group could have, as the investigators reported, occurred by chance.14

These trials and many subsequent ones relied on a diuretic as a major component of treatment. The simple conclusion is that the use of diuretics prevents CV events.15 All of these trials used diastolic BP as the end point for establishing BP targets. The first major blinded trial to address systolic hypertension was the Systolic Hypertension in the Elderly Program (SHEP),16 in which the primary purpose was to demonstrate that lowering systolic BP in patients with isolated systolic hypertension (at that time defined as systolic BP >160 mm Hg and diastolic BP <90 mm Hg) reduces strokes and other CV events. The
trial clearly demonstrated that BP reduction in elderly patients with isolated systolic hypertension reduced the incidence of stroke and major CV events. A stepped-care drug treatment regimen with low-dose chlorthalidone as step 1 medication was used.

Patients in the SHEP trial were older than in many other trials (mean age, 72 years). The controversy regarding the age at which the benefit of lowering BP no longer applies was addressed subsequently by the Hypertension in the Very Elderly Trial in patients older than 80 years. That trial, using the diuretic indapamide as initial therapy (with or without addition of an angiotensin-converting enzyme [ACE] inhibitor), reported that death and incidence of stroke, other CV events, and heart failure were reduced by lowering BP with a diuretic-based treatment.

Notwithstanding all of the positive evidence in favor of diuretics from many trials in older and middle-aged groups, the use of diuretics in the United States declined in the 1980s and 1990s as heavily promoted medications were introduced (Figure, A). The question remained, “Were these newer classes with different mechanisms of action any better in preventing CV outcomes with similar lowering of BP?” The blinded, randomized Antihypertensive and Lipid-Lowering Treatment of Hyper tension in the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure trial clearly demonstrated that BP reduction was as effective in reducing clinic BP as hydrochlorothiazide at 25 to 50 mg/d and may be more effective at lowering nighttime BP. In the SHEP trial, the dosages of chlorthalidone were 12.5 to 25.0 mg/d. There are also some data suggesting that the doses of hydrochlorothiazide used in some of the recent trials were too low. Many physicians are reluctant to use higher doses of hydrochlorothiazide because of concerns about metabolic problems.

It is not the purpose of this review to analyze all aspects of each trial with diuretics, but it is clear that the aggregate conclusion from these data is that diuretic use as monotherapy or as part of a treatment program has proved beneficial in reducing BP and CV events. The meta-analysis performed by the Blood Pressure Lowering Treatment Trialists’ Collaboration on 31 trials reported no evidence for differences between classes on major CV event prevention or any differ-
ence of their preventive effectiveness in older compared with younger patients.\textsuperscript{25,26}

While the possible metabolic effects of diuretics, especially hypokalemia and hyperglycemia, have been repeatedly emphasized in the literature,\textsuperscript{27} they appear to have been overemphasized and do not obviate the benefit of thiazide use.\textsuperscript{28-32} For example, in the SHEP trial, in which patients were treated with a chlorthalidone-based regimen, there was a more marked reduction in fatal and nonfatal myocardial infarctions (54% and 26%, respectively) and all-cause mortality in the diabetic patients compared with the nondiabetic patients (23% and 15%, respectively). The beneficial results of therapy with a diuretic were somewhat reduced, however, in patients whose potassium levels decreased to below 3.5 mEq/L (to convert to millimoles per liter, multiply by 1.0), but the outcome was still better than in the placebo group. There was a clear relationship between the doses of chlorthalidone and the degree of hypokalemia. The doses of chlorthalidone that are presently used result in less hypokalemia.

In ALLHAT, which compared 3 different classes of antihypertensive drugs, a diuretic-based chlorthalidone treatment program resulted in similar fatal and nonfatal myocardial infarction outcomes as an ACE inhibitor or a CCB-based treatment program despite the fact that new-onset diabetes was greater in the diuretic-based (11.6%) than in the ACE inhibitor–based (8.1%) or CCB-based (9.8%) treated patients. As noted, heart failure was less with diuretics than with CCBs, and the occurrence of stroke and heart failure was less with a diuretic than with an ACE inhibitor; the results did not differ in patients with diabetes or in patients with impaired baseline fasting glucose levels. Therefore, there is limited evidence at present to indicate that the metabolic effects of diuretic therapy at the dosages currently used are of major clinical significance.

However, despite abundant evidence that treatment with diuretics lowers BP and reduces CV events, the use of these agents has decreased over the past 3 decades, as shown graphically in the Figure (A shows the decline in diuretic use from 56% in 1982 to 27% in 1993,\textsuperscript{18} and B shows the global use of antihypertensive drugs in more recent years [IMS Health Inc, Norwalk, Connecticut]). Lack of promotion of diuretics or heavy promotion of other classes of drugs may have contributed to this decline\textsuperscript{31}; motivation by the desire to be up-to-date through the use of the newer modalities may also contribute.\textsuperscript{18} At least part of this phenomenon, however, may be related to the possible metabolic effects of thiazides and to the perception of physicians that these are of clinical significance. Clinical trial data, however, do not reflect this, especially when lower doses of these agents are used (chlorthalidone, 12.5-25.0 mg/d; or hydrochlorothiazide, 12.5-50.0 mg/d). Because the use of angiotensin II receptor blockers (ARBs) is associated with fewer metabolic effects while providing approximately the same BP-lowering efficacy, some physicians believe that these medications may represent better initial therapy.

It may be true that there are beneficial effects of antihypertensive medications other than their BP lowering, as in the case of ARBs or ACE inhibitors in patients with diabetic nephropathy. However, it should be remembered that in trials demonstrating benefit of the latter agents, not only in patients with nephropathy but also in patients with left ventricular hypertrophy, the use of diuretics had been necessary to lower BP in most patients.\textsuperscript{32} In the large TRIALISTS analysis, it was determined that therapies, based on several different drugs, were equally effective in reducing CV events except for heart failure, for which diuretics were more effective than other medications.\textsuperscript{23,26} At present, data clearly demonstrate that the degree of BP lowering is a more important determinant of outcome than the specific medication.\textsuperscript{33}

When diuretics are used in combination with other medications such as \(\beta\)-blockers, ARBs, or ACE inhibitors, BP lowering is greater and racial differences in response are reduced. For example, black patients do not respond to ACE inhibitor–based therapy to as great an extent when compared with diuretic-based treatment. When diuretics are administered with these agents, BP lowering is significantly greater and outcome is improved. In the PROGRESS Study\textsuperscript{34} in patients who had experienced a CV event, an ACE inhibitor alone did not prevent another event, but the use of a diuretic with the ACE inhibitor significantly reduced the incidence of a recurrence.

In general, the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure\textsuperscript{21} and many other guideline committees have suggested that a diuretic should be part of any multidrug regimen. A recent comparative trial (ACCOMPLISH)\textsuperscript{35} compared the outcome with an ACE inhibitor–diuretic combination with an ACE inhibitor–CCB combination and concluded that the second combination was more effective in reducing composite CV events, although there were no statistically significant differences in fatal and nonfatal strokes, heart failure, or CV deaths. The investigators concluded that an ACE inhibitor–CCB combination might be a better option than an ACE inhibitor–diuretic combination if the use of 2 drugs is indicated.

The ALLHAT data are consistent with the “BP lowering results in most, but not all, of the benefit” point of view.\textsuperscript{19} Black patients who showed a 3- to 5-mm Hg greater decrease in systolic BP with the use of diuretics compared with other drugs experienced fewer strokes. Heart failure events, however, were reduced more with the diuretic-based regimen than with the ACE inhibitor–CCB combination regardless of race, sex, or lack of significant differences in BP. In the UK Prospective Diabetes Study,\textsuperscript{10,37} in which results were similar with a \(\beta\)-blocker–diuretic and an ACE inhibitor–diuretic when BP levels were lowered equally, the BP achieved determined outcome, not the drugs used. Moreover, when BP control was not continued, the benefits of previously improved BP control were lost.\textsuperscript{57} While the debate may continue, preponderant evidence favors the achievement of a goal BP level as the most important factor in
determining outcome in most patients; diuretics are necessary to achieve goal BP in most hypertensive patients, whether used as monotherapy or in combination with other agents.48

Of current diuretics, the thiazide type is the one that is most frequently used in the treatment of hypertension except in the presence of renal dysfunction. When the serum creatinine level exceeds 2 mg/dL (to convert to micromoles per liter, multiply by 88.4) (or a glomerular filtration rate <50 mL/min), the thiazide type diuretic may become ineffective, and a loop diuretic should be used instead, both as a diuretic and as a BP-lowering agent. Loop diuretics are otherwise not used for initial therapy in hypertension because of their short duration of action. While there are some comparative outcome studies to support their BP-lowering efficacy, to our knowledge there are no long-term, well-controlled outcome studies.39 Of note, several other sodium-reabsorbing mechanisms remain for which inhibitors have not yet been developed; some of these may not cause as many of the adverse metabolic effects as thiazides. Some adverse effects, such as hyperuricemia, hypomagnesemia, hyperlipidemia, sexual dysfunction, and rare hypersensitivity reactions (owing to thiazide's sulfonamide moiety), are relatively infrequent with thiazide therapy, but hypokalemia and hyperglycemia have been of concern, particularly at higher dosages. Hyperglycemia associated with thiazide therapy is presumed to be at least partly due to hypokalemia.40 The increased incidence of new-onset diabetes is believed, by some investigators, to be of long-term clinical importance, despite the evidence from ALLHAT41 and the UK Prospective Diabetes Study36 refuting such belief. It has been suggested that the negative effects on glycemia may counteract some of the beneficial effects on BP and outcomes, but none of the trials to date have demonstrated any adverse effect, to our knowledge, perhaps because the duration of the trials has been too short (3-5 years). In a 14-year follow-up of the SHEP study, however, there was no adverse effect on outcomes despite the changes in glucose levels.42

THE FUTURE OF DIURETICS IN THE TREATMENT OF HYPERTENSION

If it is true that the decline in the use of available diuretics for the treatment of hypertension may in some way be related to the perception that metabolic effects may decrease their proved outcome benefits, then other metabolically neutral agents may be better choices. There may be a reason for developing other diuretics in the future. In addition to the fact that sodium-reabsorbing sites in the nephron, with potentially better patterns of electrolyte handling, may lead to better diuretic therapy, recent identification of rare mutations that affect both renal ion handling and BP provide new insights into the molecular mechanisms underlying the hypertensive trait.43 Therefore, in Gitelman syndrome, absence of the gene coding for the thiazide-sensitive sodium chloride cotransporter leads to absence of the cotransporter in the distal collecting duct in the kidneys.44 Cloning of this transporter provides an opportunity to develop highly specific diuretics, possibly nonthiazides, that would be devoid of metabolic adverse effects on lipids and glucose levels as well as the rare sulfonamide-related allergic reactions. In Bartter syndrome types 1, 2, and 3, deficits of the sodium-potassium-chloride cotransporter, the K+ channel ROMK, and the chloride channel CLCNKB, respectively,45,46 suggest that selective antagonists of these transporters and channels could be developed, with more potent diuretic potential and without the risk of hypokalemia. The hypertension observed in Liddle syndrome, in which there is overexpression of the epithelial sodium channel ENaC,46 as well as the converse, pseudohypoaldosteronism type 1, in which a deficit in ENaC is present, points toward possibilities for the development of selective antagonists that could be potassium sparing and more potent than the current ENaC inhibitor amiloride. Our increased understanding of the transport mechanisms in the kidneys, identification of the genes that code for these transporters, and recognition of genetic syndromes related to these genes that alter BP regulation may result in the development of even better diuretics in the future.

In conclusion, thiazide diuretics have stood the test of time for more than 50 years in the management of hypertension. Their use as monotherapy or in combination with other antihypertensive agents has resulted in dramatic decreases not only in cerebrovascular but also in CV events. Comparative data with other antihypertensive medications with different mechanisms of action indicate that diuretics are as, and in some instances more, effective in event reduction than other antihypertensive drugs. We hope that better understanding of the transport mechanisms in the kidneys and more recent advances in our understanding of the molecular mechanisms and genetic traits that underlie variations in BP in the population will lead to improved diuretics and, possibly, to improved treatment of hypertension.

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