

# Choosing a first-line drug in the management of elevated blood pressure: What is the evidence?

## 1: Thiazide diuretics

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### Abstract

ELEVATED BLOOD PRESSURE IS ASSOCIATED WITH an increased risk of cardiovascular illness and death. Efforts to reduce that risk have led to recommendations for a wide array of nondrug and drug therapies. Choosing the optimal first-line drug for hypertensive patients should address a hierarchy of treatment goals: decrease in morbidity and mortality associated with hypertension, decrease in blood pressure, lack of effect on patients' quality of life, dosing convenience and low cost. This article examines the evidence for thiazide diuretics as a class of first-line antihypertensive drugs in light of these treatment goals. The evidence indicates that low-dose thiazides are preferable to high-dose thiazides and that low-dose thiazides are better than or equivalent to other antihypertensive drugs for each of the goals of therapy.

**T**hiazide diuretics were originally used to treat patients with edema. When it was subsequently discovered that these drugs also reduce blood pressure, they became the starting point in standard stepped-care antihypertensive therapy. As a result, a thiazide was the first-line drug in most of the early trials designed to assess whether antihypertensive therapy decreases morbidity and mortality.

### What is a thiazide diuretic?

Thiazides are classified by their chemistry and their specific pharmacological effect on the kidney. They act within the lumen of the distal tubule to block the electroneutral sodium-chlorine ion ( $\text{Na}^+\text{-Cl}^-$ ) cotransporter. Chlorthalidone is usually grouped with the thiazides because it has the same pharmacological effect on the kidney even though it is chemically different. The precise mechanism by which thiazides reduce blood pressure is unknown. Consistent evidence obtained with several different thiazides suggests that the benefits of this class of drugs in treating hypertension are common to all its members (i.e., a class effect). However, these class benefits cannot be assumed to occur with other diuretics, which have different pharmacological effects on the kidney and other tissues: potassium-sparing diuretics, aldosterone antagonists, loop diuretics and other diuretics (Table 1).

### What is the evidence that thiazide diuretics reduce cardiovascular morbidity and mortality?

A large number of reviews of the effectiveness of antihypertensive therapy have been published. The two most comprehensive are the overall review by Collins and associates<sup>1</sup> and the review of therapy in elderly people by Mulrow and colleagues.<sup>2</sup> The best estimate of the effectiveness of thiazides as first-line therapy can be determined from the trials in which a thiazide was compared with placebo or no treatment. In the case of thiazides, the number of trials is sufficient not only to provide this type of estimate but also to allow comparison of low-dose therapy (starting dose less than 50 mg hydrochlorothiazide [HCTZ] daily) with high-dose therapy (starting dose 50 mg or more HCTZ daily). Two recent systematic reviews<sup>3,4</sup> have demonstrated that both low-dose and high-dose thiazide regimens have a beneficial

*Review*

*Synthèse*

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impact on the rates of total stroke, total cardiovascular events and total mortality, but only low-dose thiazide regimens reduce the rate of coronary artery disease events. In the more recent systematic review<sup>4</sup> the relative risk of total coronary artery disease events for all 16 thiazide trials compared with no drug therapy was 0.84 (95% confidence interval [CI] 0.75–0.95), 1.00 (CI 0.84–1.19) for the 11 high-dose trials (weighted mean thiazide dose 90 mg HCTZ) and 0.71 (0.60–0.84) for the 5 low-dose trials (weighted mean dose 26 mg HCTZ). These trials included adult men and women of all ages and represent strong evidence for the effectiveness of low-dose thiazide regimens as first-line therapy. The morbidity and mortality evidence for other classes of first-line antihypertensive drugs compared with placebo or no therapy was either lacking or not as robust as that for thiazides.<sup>4</sup>

In the same systematic review,<sup>4</sup> trials directly comparing different classes of antihypertensive drugs were also appraised and pooled. Five trials directly comparing thiazides with  $\beta$ -blockers and 2 trials directly comparing thiazides with calcium-channel blockers (CCBs) met the criteria for inclusion (randomized controlled trials of at least 1 year's duration and designed to measure morbidity and mortality rates). The meta-analysis of these trials showed no statistically significant differences among the classes, but the trend was toward better outcomes with the thiazides. These comparative data will appear in subsequent articles presenting the evidence for the other antihypertensive drug classes.

## How efficacious are thiazide diuretics in reducing blood pressure?

In the recent systematic review<sup>4</sup> the magnitude of reduction in blood pressure was also compiled in the various trials. The weighted net reduction in systolic and diastolic pressure for trials of high-dose thiazide regimens (15/7 mm Hg) as compared with untreated controls was very similar to same values for trials of low-dose thiazide regimens (16/6 mm Hg). This result suggests that, in terms of reducing blood pressure, there is no advantage to using a higher dose, especially when it is considered that high-dose thiazide regimens appear to be associated with less effectiveness in reducing coronary artery events. The magnitude of blood pressure reduction with thiazide regimens compared favourably with either  $\beta$ -blocker regimens (reduction in blood pressure of 10/6 mm Hg) or CCB regimens (10/5 mm Hg).<sup>4</sup>

However, the effect of thiazides relative to other classes of drugs is best assessed in direct comparisons in randomized trials. I was able to identify 8 randomized trials comparing thiazides with  $\beta$ -blockers,<sup>4,7</sup> 5 comparing thiazides with CCBs,<sup>4,7</sup> 3 comparing thiazides with angiotensin-converting enzyme (ACE) inhibitors<sup>5-7</sup> and 2 comparing thiazides with  $\alpha$ -adrenergic blockers.<sup>5,6</sup> Meta-analysis demonstrated that the effect of all 5 classes of drugs in reducing diastolic blood pressure was similar. In contrast, the decrease in systolic blood pressure was statistically signifi-

**Table 1: Dosing and cost of diuretics for the treatment of hypertension**

Diuretic drug	Examples of trade names	Usual daily dose	Daily cost,* cents
<b>Thiazide and thiazide-like</b>			
Hydrochlorothiazide (HCTZ)	Hydrodiuril, generic	12.5–25 mg	0.3–0.6
Chlorthalidone	Hygroton, generic	12.5–25 mg	0.5–1.0
Bendroflumethiazide	Naturetin	1.25–2.5 mg	7–13
<b>Potassium-sparing</b>			
Triamterene	Dyrenium	25–50 mg	10–20
Amiloride	Midamor	2.5–5 mg	15–30
Spironolactone	Aldactone, generic	25–100 mg	7–22
<b>Combination</b>			
HCTZ (25 mg) and triamterene (50 mg)	Dyazide, generic	1/2–1 tablet	3–5
HCTZ (50 mg) and amiloride (5 mg)	Moduret, generic	1/4–1/2 tablet	5–10
HCTZ (25 mg) and spironolactone (25 mg)	Aldactazide, generic	1/2–1 tablet	5–9
<b>Loop</b>			
Furosemide	Lasix, generic	20–40 mg	0.7–0.8
Ethacrynic acid	Edecrin	25–50 mg	17–34
Bumetanide	Burinex	0.5–1 mg	21–42
Torsemide	Demadex	1.25–2.5 mg	11–22
<b>Other†</b>			
Metolazone	Zaroxolyn	1.25–2.5 mg	8–16
Indapamide	Lozide, generic	1.25–2.5 mg	16‡–32

\*Mean drug cost to BC Pharmacare in 1999; prices may be different in other provinces.

†These drugs have some different pharmacological actions from those of the thiazide class.

‡Lower value shown represents cost if half of a 2.5-mg tablet is prescribed.

cantly greater for thiazides than for  $\beta$ -blockers (difference of  $-2.2$  mm Hg [CI  $-2.7$  to  $-1.6$  mm Hg]), CCBs (difference of  $-1.5$  mm Hg [CI  $-2.6$  to  $-0.3$  mm Hg]) and ACE inhibitors (difference of  $-3.5$  mm Hg [CI  $-5.2$  to  $-1.9$  mm Hg]). The difference between thiazides and  $\alpha$ -adrenergic blockers in reduction of systolic blood pressures was not statistically significant (difference of  $-1.8$  mm Hg [CI  $-3.8$  to  $0.2$  mm Hg]).

### How efficacious are thiazide diuretics in reducing left ventricular hypertrophy?

Regression of left ventricular hypertrophy as assessed by echocardiography is sometimes used as a surrogate measure of efficacy of antihypertensive drugs. In a meta-analysis of the effects of randomized trials of monotherapy, there were no significant differences in comparisons of thiazides with ACE inhibitors, CCBs and  $\beta$ -blockers in reduction of left ventricular mass index after adjustment for duration of treatment.<sup>8</sup>

### Do thiazide diuretics and other drugs differ in tolerability?

It was also possible to pool the results from the direct comparisons that recorded withdrawals due to adverse events.<sup>4,5,7</sup> The frequency of such withdrawals was significantly lower for thiazides than for  $\beta$ -blockers (6 trials,  $0.7$  [CI  $0.6$ – $0.8$ ]), CCBs (4 trials,  $0.7$  [CI  $0.5$ – $0.9$ ]) or  $\alpha$ -adrenergic blockers (1 trial,<sup>5</sup>  $0.1$  [CI  $0.04$ – $0.4$ ]). Thiazides also had a lower rate of withdrawals than ACE inhibitors (2 trials,  $0.6$  [CI  $0.3$ – $1.2$ ]), but this difference was not statistically significant.

The probable reason that physicians do not prescribe thiazides is concern about the potential metabolic consequences (specifically, hypokalemia, hyperuricemia, hyperlipidemia and hyperglycemia). This concern dates back to outcomes from the use of high doses for this class of drugs. In fact, the occurrence of hypokalemia may explain why the incidence of coronary artery disease did not decline with high-dose thiazide regimens. When the recommended low-dose regimens have been used, the incidence of hypokalemia has been small (e.g., 1% of patients in the Systolic Hypertension in the Elderly Program [SHEP] study<sup>9</sup> had a potassium ion level below  $3.2$  mmol/L). Hypokalemia is easily detectable (by means of a single measurement after 1–2 months of therapy) and can usually be managed by adding a potassium-sparing diuretic if the  $K^+$  level is below  $3.5$  mmol/L. Potassium supplements are not recommended because they are inconvenient and expensive. The increases in uric acid seen with thiazide therapy are without consequence in most patients.<sup>9</sup> However, thiazides should not be used in patients who experience recurrent gout with thiazide therapy. The small increase in total cholesterol and triglycerides observed with thiazide therapy in some studies was not observed in the Treatment of Mild

Hypertension (TOMH) Study<sup>6</sup> and is unlikely to be of clinical significance, given the substantial benefits of low-dose thiazide therapy in terms of reducing coronary artery disease and stroke. The potential hyperglycemic effect of thiazides was not seen in the TOMH study<sup>6</sup> (which used chlorthalidone at  $15$  mg/day) and occurred to only a minor degree in the SHEP study<sup>9</sup> (which used chlorthalidone at up to  $25$  mg/day). In the SHEP study 12% of patients had type 2 diabetes; these patients experienced the same relative risk reduction for major cardiovascular events (34%) as the nondiabetic population (34%); absolute risk reduction was twice as great in the diabetic patients (10%) as in the nondiabetic patients (5%).<sup>10</sup> The only diabetic patients in whom thiazides should be avoided are those who have experienced significant worsening of glucose control during a therapeutic trial of a low-dose thiazide.

### Do thiazide diuretics have advantages in terms of convenience or cost?

The preferred regimen for long-term preventive therapy is once-daily dosing, and the recommended regimen for thiazides and thiazide-like drugs is once-daily administration in the morning. In addition, thiazides have significant cost advantages over all other classes of antihypertensive drugs (the daily costs of other classes of drugs will be provided in subsequent articles). HCTZ is the least expensive of the diuretics available in Canada (Table 1). HCTZ is marginally preferable to chlorthalidone because of its availability in scored 25-mg tablets (the smallest tablet size for chlorthalidone is  $50$  mg) (see Table 1 for correct doses), and HCTZ is marginally less expensive than chlorthalidone.

### Conclusion

The evidence indicates that low-dose thiazide regimens are preferable to high-dose thiazide regimens for the management of elevated blood pressure. Doses above the equivalent of  $25$  mg of HCTZ are seldom necessary or justifiable. The fact that excessive doses may negate some of the beneficial effects of the drug may also prove true for other classes of antihypertensives.

The evidence also shows that low-dose thiazide regimens are equivalent to or better than other classes of drugs for each of the specific goals of therapy. Therefore, the best first-line therapy for the management of most patients with hypertension is a low-dose thiazide regimen. The exceptions to this recommendation will be discussed in subsequent articles.

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