Choosing a First-Line Drug for Older Adults with Hypertension: An Evidence-Based Approach

Abstract

Choosing the optimal first-line drug for patients with hypertension must address a hierarchy of treatment goals: reduction in mortality and morbidity, efficacy in lowering blood pressure, ensuring tolerability, and minimizing cost. This article examines the evidence for the different classes of first-line antihypertensive drugs in light of these four goals. The evidence indicates that first-line low-dose thiazides are better than or equivalent to other antihypertensive drug classes for each of the goals of therapy in both people with hypertension in general and in older adults ≥ 60 years of age.

Keywords: hypertension, thiazide, first-line, older adults, evidence-based

Physicians face two critical decisions when treating a patient with elevated blood pressure: first, they need to decide when to start antihypertensive therapy; and second, they must decide what drug to prescribe first. In this article, I focus on the second issue and describe an evidence-based approach. As much as possible, I use randomized controlled trial (RCT) data from individuals at least 60 years of age. The importance of which drug is prescribed first is underappreciated. It has enormous potential consequences for patients and the health care system in four categories: optimizing a reduction in mortality and morbidity, optimizing the proportion of patients who will achieve a satisfactory blood pressure-lowering effect, ensuring the treatment is well tolerated to enhance compliance, and minimizing the cost to the patient and the health care system. The optimal

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first-line drug will be near the top choice for each of the categories. Below, I describe the best available evidence for each of these categories.

**Optimizing Reduction in Mortality and Morbidity**

The category of optimizing a reduction in mortality and morbidity is obviously the most important. If one class of first-line drugs is clearly better at reducing mortality and morbidity than other classes, that outweighs conflicting evidence in the other categories. To investigate mortality and morbidity, we need to look at systematic reviews studying first-line drugs versus placebo and no treatment, as well as systematic reviews studying first-line drug classes compared with each other in head-to-head RCTs.

A recent Cochrane systematic review provided the best available evidence for first-line drugs versus placebo or no treatment. It was based on 24 RCTs with 28 arms in over 58,000 people. Nineteen of the RCTs studied the effect of first-line thiazides. An early important observation was that outcomes were better for low-dose versus high-dose thiazides. Coronary heart disease events were reduced by low-dose thiazides (relative risk [RR] 0.72, 95% confidence interval [CI] 0.61–0.84) but not by high-dose thiazides (RR 1.01, 95% CI 0.85–1.20). This made it clear that low-dose thiazides were the best approach. The pooled data for first-line low-dose thiazides showed that they reduced total mortality (RR 0.89, 95% CI 0.82–0.97) and total cardiovascular events (all fatal and nonfatal stroke, myocardial infarction and congestive heart failure [CHF]) (RR 0.70, 95% CI 0.64–0.76). Results for the other classes of antihypertensive drugs showed that first-line beta-blockers in five RCTs reduced total cardiovascular events (RR 0.89, 95% CI 0.81–0.98) but not total mortality (RR 0.96, 95% CI 0.86–1.07). First-line angiotensin-converting enzyme (ACE) inhibitors in three RCTs reduced both total mortality (RR 0.83, 95% CI 0.72–0.95) and total cardiovascular events (RR 0.76, 95% CI 0.67–0.85). First-line calcium channel blockers (CCBs) reduced total cardiovascular events (RR 0.71, 95% CI 0.57–0.87) but not total mortality (RR 0.86 95% CI 0.68–1.09). From these data, the authors drew the following conclusion: “First-line low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust. First-line high-dose thiazides and

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**Key Point**

First-line low-dose thiazides reduce mortality and morbidity as well as or better than first-line high dose thiazides, or any of the other classes of antihypertensive drugs.
first-line beta-blockers are inferior to first-line low-dose thiazides.” Less robust means that we have less confidence in the effect estimates for the ACE inhibitors and CCBs, and this is reflected in the wider 95% confidence intervals for these estimates in comparison with the first-line low-dose thiazides.

Head-to-head trials of different first-line drug classes are a more direct way to compare the mortality and morbidity outcomes between different classes of drugs. First-line beta-blockers were compared with other classes of antihypertensives in a Cochrane systematic review. This review concluded that the available evidence does not support first-line beta-blockers for hypertension because of the trend towards worse outcomes with beta-blockers than with CCBs, renin angiotensin system inhibitors, or thiazide diuretics. Cochrane reviews to compare the other classes of drugs are in the protocol stage; therefore, it is necessary to search for reviews elsewhere.

The best non-Cochrane review investigating the comparison between first-line drug classes is the network meta-analysis done by Psaty et al. This analysis showed that no other class of antihypertensive was better than first-line low-dose thiazides for any outcome. Compared with CCBs, first-line low-dose thiazides reduced total cardiovascular events (RR 0.94, 95% CI 0.89–1.00) and CHF events (RR 0.74, 95% CI 0.67–0.81). Compared with ACE inhibitors, first-line low-dose thiazides reduced total cardiovascular events (RR 0.94, 95% CI 0.89–1.00) and CHF events (RR 0.88, 95% CI 0.80–0.96). This meta-analysis also confirmed the inferiority of first-line beta-blockers compared with thiazides as shown by the previous work, and added evidence showing the inferiority of first-line alpha-blockers as well. The network analysis was not able to illustrate any differences between first-line low-dose thiazides and angiotensin receptor blockers; however, there were only two small RCTs and no direct head-to-head comparison.

These two analyses thus provide strong mortality and morbidity evidence for the superiority of first-line low-dose thiazides over all the other classes of antihypertensives except for angiotensin receptor blockers. One limitation of these data for the present purpose is that they are based on RCTs that include people of all ages. Thus, it is reasonable to ask whether this result is likely the case in older adults. It is not possible to repeat...
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**Figure 1: Drug Therapy for Hypertension**

**Beta-blockers**

- stimulated ATP-dependent Ca²⁺ reuptake
- increased number of Ca²⁺ channels open allowing more Ca²⁺ into cell
- increased velocity of contraction with beta blockers
- heart beating more slowly with less force
- blood vessels dilate to improve blood flow

**ACE inhibitors**

- Angiotensinogen
  - renin
  - Angiotensin I
  - Angiotensin Converting Enzyme (ACE)
  - Angiotensin II
  - AT-1 and AT-2 receptors
    - vasoconstriction
    - aldosterone secretion
    - blood vessels dilate to improve blood flow

**Reduction of Blood Pressure**

Reduced blood pressure
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all these analyses in patients 60 years of age and over, however, the Cochrane systematic review of pharmacological treatment of hypertension in older adults has recently been updated.4 The updated review demonstrated that in 15 RCTs in >24,000 individuals with hypertension age 60 years or older, treatment with any first-line antihypertensive compared with no treatment reduced total mortality (RR 0.90, 95% CI 0.84–0.97) and total cardiovascular events (RR 0.72, 95% CI 0.68–0.77). I removed from these data all the RCTs that did not use first-line thiazides to obtain an estimate of the effect of first-line thiazides in older adults. This analysis showed that first-line thiazides reduced total mortality (RR 0.89, 95% CI 0.81–0.97) and total cardiovascular events (RR 0.68, 95% CI 0.62–0.75) in older adults (see Table 1). These relative risks are somewhat lower than the total and suggest that the results in older adults are, if anything, better for first-line thiazides than for other first-line drugs.

In the updated review of treatment in older adults, a subgroup analysis in people 80 and over was also done. This revealed that pharmacological therapy reduced total stroke events (RR 0.66, 95% CI 0.52–0.83) but not total mortality (RR 0.98, 95% CI 0.87–1.10). An exploration of the lack of effect on

### Table 1: First-line Thiazide Trials in Older Adults

<table>
<thead>
<tr>
<th>Trial</th>
<th>Thiazide</th>
<th>Number of patients</th>
<th>Average Age years</th>
<th>Mortality RR (95% CI)</th>
<th>Total cv events RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANBP</td>
<td>Chlorothiazide</td>
<td>582</td>
<td>64</td>
<td>NA</td>
<td>0.76 [0.49, 1.19]</td>
</tr>
<tr>
<td>Carter</td>
<td>any</td>
<td>48</td>
<td>69</td>
<td>0.92 [0.41, 2.06]</td>
<td>NA</td>
</tr>
<tr>
<td>EWPHE</td>
<td>HCTZ/triamterene</td>
<td>840</td>
<td>72</td>
<td>0.92 [0.76, 1.12]</td>
<td>NA</td>
</tr>
<tr>
<td>HYVET</td>
<td>indapamide</td>
<td>3845</td>
<td>84</td>
<td>0.82 [0.69, 0.99]</td>
<td>0.71 [0.57, 0.87]</td>
</tr>
<tr>
<td>HYVET P</td>
<td>bendrofluazide</td>
<td>852</td>
<td>84</td>
<td>1.29 [0.77, 2.16]</td>
<td>NA</td>
</tr>
<tr>
<td>Kuramoto</td>
<td>trichlormethiazide</td>
<td>91</td>
<td>76</td>
<td>1.07 [0.41, 2.80]</td>
<td>0.47 [0.16, 1.43]</td>
</tr>
<tr>
<td>MRCOA</td>
<td>HCTZ/amiloride</td>
<td>4396</td>
<td>70</td>
<td>0.97 [0.84, 1.12]</td>
<td>0.85 [0.73, 0.99]</td>
</tr>
<tr>
<td>SHEP</td>
<td>chlorthalidone</td>
<td>4736</td>
<td>72</td>
<td>0.88 [0.74, 1.05]</td>
<td>0.67 [0.59, 0.76]</td>
</tr>
<tr>
<td>SHEP P</td>
<td>chlorthalidone</td>
<td>551</td>
<td>72</td>
<td>1.11 [0.51, 2.46]</td>
<td>0.57 [0.32, 1.04]</td>
</tr>
<tr>
<td>VACoop</td>
<td>HCTZ</td>
<td>81</td>
<td>67</td>
<td>NA</td>
<td>0.41 [0.22, 0.76]</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>16002</td>
<td></td>
<td>0.89 [0.81, 0.97]</td>
<td>0.68 [0.62, 0.75]</td>
</tr>
</tbody>
</table>

HCTZ – hydrochlorothiazide, NA- not available, RR- relative risk, cv- cardiovascular

Key Point
Thiazides are better or as well tolerated as other classes of antihypertensive drugs.
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mortality leads to the one RCT that showed a reduction in mortality, Hypertension in the Very Elderly (HYVET).\(^5\) This trial stands out because of the treatment regimen that was used. Treatment started with a low dose of the thiazide-like diuretic indapamide at 1.5 mg daily. The addition of an ACE inhibitor, perindopril 2 mg daily with one increase to 4 mg daily, was the maximum drug therapy allowed. The designers of HYVET were very wise and experienced clinicians who appreciated the special vulnerability of this population. The conservative HYVET approach and starting with a first-line low-dose thiazide diuretic is now the standard for very old patients.\(^6,7\) Since mortality and morbidity evidence outweighs the other categories, I could stop here; however, it is worthwhile to briefly look at the evidence for the other categories.

**Optimizing Efficacy in Lowering Blood Pressure**

The second category, efficacy in lowering blood pressure, could present some advantages if one class were better than others. A systematic review to answer this question

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**Table 2: Average Daily Cost of Antihypertensive Classes in Canada**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Example</th>
<th>Approximate daily cost of starting dose for hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide</td>
<td>hydrochlorothiazide</td>
<td>$0.02 to 0.03</td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>indapamide</td>
<td>$0.20</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>atenolol</td>
<td>$0.40</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>ramipril</td>
<td>$0.60</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>amlodipine</td>
<td>$0.70</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>valsartan</td>
<td>$1.30</td>
</tr>
</tbody>
</table>

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*Key Point*

Thiazides are less expensive than other classes of antihypertensive drugs.
concluded that all classes of drugs lower blood pressure to approximately the same degree. However, the reviews by Psaty et al. and Wright both suggest that thiazides appear to reduce systolic blood pressure more for an equal reduction in diastolic blood pressure. The magnitude of greater blood pressure lowering is only about 2 mm Hg; however, this could be part of the reason for the better mortality and morbidity outcomes seen with thiazides and, once again, first-line thiazides appear to have an advantage.

Ensuring Tolerability
For the third category, the best measure of tolerability of first-line antihypertensive therapy is withdrawals due to adverse effects in head-to-head trials comparing one class of drug with another. When this was done, first-line thiazides were significantly better tolerated than beta-blockers, CCBs, and alpha-blockers and not significantly different from ACE inhibitors for this outcome.

Minimizing Costs
When it comes to the fourth and final category, cost of treatment, thiazides in general are the least expensive first-line antihypertensive drug in Canada and probably most countries in the world (see Table 2). The least expensive thiazide in Canada is hydrochlorothiazide.

Conclusion
In this evidence-based approach, all the evidence leads to using a low-dose thiazide as the first drug choice in most patients being started with drug therapy for hypertension. In my experience, there are very few patients for whom this is not possible—the rare exception being a patient with...
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problematic recurrent gout who is not receiving allopurinol. I believe that physicians should be aware of the least expensive low dose thiazide in their jurisdiction and prescribe that drug first-line to most of their patients with elevated blood pressure. If this approach were widely followed, we could expect improved morbidity and mortality outcomes, better blood pressure control, improved tolerability, and markedly reduced costs associated with treatment than is presently the case.

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References


Clinical Pearls

When starting a patient with hypertension on drug treatment, the least expensive low dose thiazide is the drug of first choice to optimize patient outcomes.