



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Drugs of Choice in the Treatment of Hypertension Part 2

After review of the long term hypertension studies, including the epidemiologic and randomized placebo controlled drug trials, certain clinically important facts stand out:

- Risk of cardiovascular events correlates better with systolic than diastolic blood pressure.<sup>1</sup>
- Risk correlates better with blood pressures taken outside the doctor's office than with office blood pressures.<sup>2</sup>
- Blood pressure consistently decreases with placebo treatment (10/8 mm Hg).<sup>3</sup>
- The average additional blood pressure fall in the active treatment group is modest (11/6 mm Hg).<sup>3,4</sup>
- The average blood pressure fall with treatment in trials using low doses of just one drug (7-9.5/4-6.5mm Hg)<sup>5,6</sup> is similar to that obtained from an overview of trials using high doses of multiple drugs (11/6 mm Hg).<sup>3,4</sup>

These facts suggest the following ways to assist in managing your patients with hypertension:

- Put more emphasis on systolic and home blood pressures when making treatment decisions.
- Appreciate that some of the blood pressure lowering effect seen in the office is due to the placebo effect. In other words, no matter what you are prescribing, it is likely to appear efficacious.
- Realize that "pushing" the dose seldom improves the antihypertensive effect. Likewise, the dose can frequently be lowered in patients receiving high doses of antihypertensive drugs without changing the antihypertensive effect.

In Part 1 we summarized the published evidence demonstrating that if we want to be certain of reducing morbidity and mortality in our hypertensive patients, a low-dose thiazide diuretic is the best choice. However, we obviously need the use of more than one class of antihypertensive drugs. Beyond the thiazides, we have much less evidence of effectiveness in decreasing cardiovascular events. **We cannot assume that drugs which are equivalent in lowering blood pressure will prove to be equally effective in reducing morbidity and mortality.**



• **What is the evidence that beta blockers decrease morbidity and mortality in hypertensive patients?**

There are only two trials in which the effectiveness of beta blockers (propranolol<sup>3</sup> and atenolol<sup>7</sup>) can be compared with placebo. When the data from these trials are combined, there is a trend towards a reduction in the incidence of total stroke, log odds ratio, 0.77 (0.59-1.04), but little effect on total coronary events, 0.89 (0.71-1.13). The lack of effectiveness of atenolol based therapy in reducing coronary events corroborates that seen in other studies.<sup>8,9</sup> It may be that the high cardioselectivity of atenolol is not a desirable pharmacological action.

There are three trials<sup>3,7,10</sup> in which the effectiveness of beta blockers can be compared with thiazides. When the results of these trials are combined in a meta-analysis the patients receiving thiazide had a non statistically significant reduction in the incidence of stroke, 0.81 (0.58-1.14) and coronary events, 0.92 (0.74-1.14). In post myocardial infarction trials, non-selective beta blockers and high dose beta-1 selective blockers, but not oxprenolol or pindolol, beta blockers with high partial agonist (increased sympathomimetic) activity, reduce risk of reinfarction and mortality.<sup>11</sup> *With the evidence presently available, it is advisable when prescribing beta blockers to use a non-selective beta blocker in the lowest dose required to lower the blood pressure (see table).*



### •In what hypertensive patients is a beta blocker the drug of first choice?

To lower blood pressure in patients with angina pectoris a beta blocker is the drug of first choice. Although we do not have the evidence, it also seems reasonable to use a beta blocker as first choice in patients where the

drug can be used to treat more than the hypertension, eg. patients with frequent recurrent migraine or patients with sympathetic hyperactivity, resting tachycardia, and palpitations. Beta blockers should not be used in patients with asthma or other forms of obstructive airways disease.

**Table 1 Beta Blockers**

| Beta Blockers  | Trade name   | Usual Dosage Range                                   | Daily Cost ❖                                    |
|--|--|--|---|
| Propranolol*   | Inderal <sup>®</sup> , generic<br>Inderal <sup>®</sup> LA  | 20-120 mg BID<br>60-240 mg daily                     | \$0.08-\$0.24<br>\$0.47-\$1.66                  |
| Nadolol*   | Corgard <sup>®</sup> , generic   | 20-160 mg daily                                      | \$0.15-\$0.79                                   |
| Timolol*   | Blocadren <sup>®</sup> , generic   | 5-20 mg BID  | \$0.36-\$1.05                                   |
| Atenolol <sup>°</sup><br>Metoprolol <sup>°</sup>     | Tenormin <sup>®</sup> , generic<br>Betaloc <sup>®</sup> , Lopressor <sup>®</sup> , generic<br>Betaloc <sup>®</sup> SR, Lopressor <sup>®</sup> SR | 25-100 mg daily<br>25-100 mg BID<br>100-200 mg daily | \$0.20-\$0.66<br>\$0.26-\$0.48<br>\$0.41-\$0.71 |
| Acebutolol <sup>°Δ</sup><br>Oxprenolol* <sup>Δ</sup> | Sectral <sup>®</sup> , Monitan <sup>®</sup> .generic<br>Trasicor <sup>®</sup><br>Slow Trasicor <sup>®</sup>                                      | 100-400 mg BID<br>20-160 mg BID<br>80-320mg daily    | \$0.44-\$1.32<br>\$0.31-\$1.65<br>\$0.83-\$1.66 |
| Pindolol* <sup>Δ</sup><br>Labetalol* <sup>◇</sup>    | Visken <sup>®</sup> , generic<br>Trandate <sup>®</sup>   | 5-15 mg BID<br>100-400 mg BID                        | \$0.52-\$1.31<br>\$0.52-\$1.82                  |

\* non-selective; ° selective; Δ partial agonist; ◇ alpha blocker

### •In what hypertensive patients is an ACE inhibitor the drug of first choice?

ACE inhibitors have been clearly shown to prolong survival in patients with congestive heart failure.<sup>12</sup> They are therefore the obvious first choice in patients with hypertension and CHF. It is not established at the present time whether ACE inhibitors have a unique renal protective effect in diabetic nephropathy.<sup>13</sup>

A recent study suggests that ACE inhibitors increase the risk of hypoglycemia in treated diabetic patients.<sup>14</sup> There are no proven therapeutic differences between the ACE inhibitors; drug choice can be made based on convenience and cost. (See Table). The cost can be minimized by prescribing 1/4 or 1/2 tablets whenever possible. (e.g. 1/4 of a 20 or 40 mg tablet of quinapril costs \$0.23 a day).

**Table 2 ACE Inhibitors**

| ACE Inhibitors                          | Trade name  | Usual Dosage Range                                  | Daily Cost ❖  |
|---|---|---|---|
| Quinapril<br>Ramipril<br>Captopril      | Accupril <sup>®</sup><br>Altace <sup>®</sup><br>Capoten <sup>®</sup> , generic                | 5-40 mg daily<br>1.25-10 mg daily<br>12.5-50 mg BID | \$0.92<br>all tablets<br>\$0.72-\$1.01<br>\$0.45-\$1.19 |
| Perindopril<br>Benazepril<br>Cilazapril | Coversyl <sup>®</sup><br>Lotensin <sup>®</sup><br>Inhibace <sup>®</sup>                       | 2-8 mg daily<br>5-40 mg daily<br>1-10 mg daily      | \$0.68-\$1.28<br>\$0.61-\$1.64<br>\$0.65-\$1.69         |
| Lisinopril<br>Fosinopril<br>Enalapril   | Prinivil <sup>®</sup> , Zestril <sup>®</sup><br>Monopril <sup>®</sup><br>Vasotec <sup>®</sup> | 5-40 mg daily<br>10-40 mg daily<br>5-40 mg daily    | \$0.70-\$2.10<br>\$0.84-\$2.01<br>\$0.82-\$2.36         |

### •In what hypertensive patients is a calcium antagonist the drug of first choice?

At the present time there are no outcome studies which identify a group of patients who would specifically benefit from a calcium antagonist. It is clear that post MI patients with left ventricular dysfunction do worse with diltiazem than with placebo.<sup>15</sup> An overview of 31 placebo controlled trials submitted to the United States Food and Drug Administration<sup>16</sup> reported that patients receiving calcium antagonists had a 63% excess of cardiac events, as compared to placebo.

A recent unpublished but highly publicized study also suggests that patients receiving a calcium antagonist for hypertension have a significantly increased risk of myocardial infarction compared with patients receiving diuretics or beta blockers. Neither of these studies are definitive. They do, however, reinforce the message in this and the previous letter, and emphasize the need for prospective randomized controlled studies measuring morbidity and mortality. These trials are under way, but we cannot expect any results for 4 - 5 years.

**Table 3 Calcium Antagonists**

| CalciumAntagonists | Trade name                                  | Usual Dosage Range | Daily Cost ❖  |
|--------------------|---|--------------------|---------------|
| Diltiazem          | Cardizem <sup>®</sup> , generic             | 60 -120 mg BID,TID | \$0.77-\$2.32 |
|                    | Cardizem SR <sup>®</sup>                    | 60-180 mg BID      | \$1.50-\$3.60 |
|                    | Cardizem CD <sup>®</sup>                    | 120-300 mg daily   | \$1.35-\$2.98 |
| Verapamil          | Isoptin <sup>®</sup> , generic              | 80-160 mg BID,TID  | \$0.62-\$1.85 |
|                    | Isoptin SR <sup>®</sup> ,                   | 120 -240 mg BID    | \$2.07-\$3.08 |
|                    | Verelan <sup>®</sup>                        | 120-480 mg daily   | \$0.88-\$2.45 |
| Nifedipine         | Adalat <sup>®</sup> , generic               | 5 mg -30 mg BID    | \$0.55-\$1.27 |
|                    | Adalat PA <sup>®</sup>                      | 10-30 mg BID       | \$0.99-\$2.54 |
|                    | Adalat XL <sup>®</sup>                      | 30-90 mg daily     | \$1.00-\$2.56 |
| Felodipine         | Plendil <sup>®</sup> , Renedil <sup>®</sup> | 2.5-20 mg daily    | \$0.54-\$2.12 |
| Amlodipine         | Norvasc <sup>®</sup>                        | 5-10 mg daily      | \$1.33-\$1.94 |
| Nicardipine        | Cardene <sup>®</sup>                        | 20-40 mg TID       | \$1.85-\$3.70 |

**•In what hypertensive patients are second drugs useful ?**

From the large controlled studies of the treatment of mild hypertension it is clear that in at least 50% of patients the BP can be controlled with a thiazide alone. The additional drugs used in these studies, for patients not controlled with a thiazide include reserpine in three studies, methyldopa in two studies, hydralazine in two studies, and beta blockers in two studies. We thus can have some confidence in the effectiveness of these drugs used in combination with a thiazide. In patients with moderate to severe hypertension 3 to 4 drugs are often required to adequately control the blood pressure. We, therefore, are fortunate to have a wide armamentarium of drugs to choose from (see Tables).

**•Conclusion**

It is up to the clinician, through systematic therapeutic trials, to identify the drug(s) which are efficacious, well tolerated in low doses, convenient, and affordable to the patient and society. **We should use the drugs proven to reduce morbidity and mortality as much as possible, but occasionally we are forced to individualize and choose based on other factors.**

**Table 4 Alpha1 Blockers**

| Alpha1 Blockers | Trade name                       | Usual Dosage Range | Daily Cost ❖  |
|-----------------|----------------------------------|--------------------|---------------|
| Prazosin        | Minipress <sup>®</sup> , generic | 1-10 mg BID        | \$0.34-\$1.32 |
| Terazosin       | Hytrin <sup>®</sup>              | 1-20 mg daily      | \$0.64-\$2.94 |
| Doxazosin       | Cardura <sup>®</sup>             | 1-16 mg daily      | \$0.58-\$3.60 |

**Table 5 Central and Peripheral Sympatholytics**

| Central and Peripheral * Sympatholytics | Trade name                      | Usual Dosage Range   | Daily Cost ❖  |
|---|---------------------------------|----------------------|---------------|
| Reserpine*                              | Serpasil <sup>®</sup> , generic | 0.0625-0.25 mg daily | <<\$0.01      |
| Methyldopa                              | Aldomet <sup>®</sup> , generic  | 125 mg-1 g BID       | \$0.08-\$0.50 |
| Clonidine                               | Catapres <sup>®</sup> , generic | 0.05-0.3 mg BID      | \$0.20-\$1.06 |

**Table 6 Direct Vasodilators**

| Direct Vasodilators | Trade name                        | Usual Dosage Range | Daily Cost ❖  |
|---------------------|-----------------------------------|--------------------|---------------|
| Hydralazine         | Apresoline <sup>®</sup> , generic | 25-100 mg BID      | \$0.35-\$1.08 |
| Minoxidil           | Loniten <sup>®</sup>              | 2.5-40 mg daily    | \$0.34-\$2.96 |

❖ Average or lowest cost alternative (LCA) price in B.C., 1994.

### References

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16. Glasser SP, Clark PI, Lipicky RJ et al. *Exposing patients with chronic, stable, exertional angina to placebo periods in drug trials*. J. Amer. Med. Assoc. 1991;265:1550-1554.

### •What is the Therapeutics Initiative?

The Therapeutics Initiative was established in the Department of Pharmacology and Therapeutics to provide physicians and pharmacists with up to date, evidence based, practical information in the area of rational drug therapy. This organization is dedicated to effect an immediate and long term change in physician prescribing habits that will result in improved health care in the province of British Columbia.

The Initiative is also committed to evaluate the effect of all educational interventions on patterns of prescription writing utilizing the Pharmicare database and other sources of data.

The Therapeutics Initiative must be credible to the physicians and pharmacists in the province. For this reason, the Initiative was established in the University and made independent from the government and any other vested interest groups.

### Therapeutics Letters published to date:

- Letter 1, October 1994: *Treatment of Non Ulcer Dyspepsia in Adults: Common Questions about H<sub>2</sub> Blockers*.
- Letter 2, November 1994: *Definite Treatment of Peptic Ulcer Disease by eradication of Helicobacter Pylori (H. pylori)*.
- Letter 3, December 1994: *Treatment of Gastroesophageal Reflux Disease*.
- Letter 4, February 1995: *Should we be using NSAIDs for the treatment of Osteoarthritis and "Rheumatism"?*
- Letter 5, March 1995: *Anti-Infection Guidelines for Community-acquired Infections*.
- Letter 6, May 1995: *Medical Management of Ischemic Heart Disease: The Optimal use of Nitrates*.
- Letter 7, June 1995: *Drugs of Choice in the Treatment of Hypertension, Part 1*.
- Letter 8, July/August 1995: *Drugs of Choice in the Treatment of Hypertension, Part 2*.

**If you have any questions about the Therapeutics Initiative, or if you are missing a Therapeutics Letter please contact us at the numbers below.**