

# Combination therapy for hypertension

## Introduction

Hypertension affects more than one tenth of the adult population in Hong Kong.<sup>1</sup> In fact, using the latest recommended cut-off points for systolic blood pressure of 140 mm Hg and diastolic blood pressure of 90 mm Hg,<sup>2</sup> the prevalence of hypertension in Hong Kong adults is close to 20%. The apparent increase in the prevalence of hypertension in recent years is largely due to increased recognition of isolated systolic hypertension and its associated risks.

## Ideal blood pressure

The Hypertension Optimal Treatment (HOT) study failed to show any significant differences in outcomes for target diastolic blood pressures of less than 80, 85, or 90 mm Hg, but did at least show that a target of 80 mm Hg is safe.<sup>3</sup> More than one drug is frequently needed to decrease the blood pressure to this level, however. For high-risk groups such as patients with diabetes or nephropathy, the target blood pressure has been reduced to a lower level. In the UK Prospective Diabetes Study (UKPDS), tight blood pressure control, rather than glycaemic control, was responsible for reducing the incidence of macrovascular complications.<sup>4</sup> Patients with diabetes in the HOT study also benefited from lower target blood pressures despite small differences in the achieved blood pressure values among the randomised groups.<sup>3</sup>

In the Heart Outcomes Prevention Evaluation (HOPE) study, patients treated with an angiotensin converting enzyme inhibitor (ACEI) had a lower cardiovascular event rate even if they were normotensive.<sup>5</sup> It is generally believed that ACEIs have a protective effect beyond blood pressure reduction. An alternative possibility is that lowering the blood pressure by a small amount for people at high cardiovascular risk is beneficial, even for normotensive people. This leads to the new hypothesis that instead of treating patients whose blood pressure exceeds a certain level, blood pressure should be lowered for all people who are at risk from strokes and heart attacks.<sup>6</sup>

## Blood pressure control in reality

While the prevalence of hypertension in the community is alarming, more disturbing is how badly blood pressure is controlled in patients who are known to be hypertensive. Given the relationship between raised blood pressure and stroke risk, good control of blood pressure is crucial for stroke prevention.<sup>7</sup> In Hong Kong, as in the US, blood pressure is effectively controlled in no more than 50% of patients.<sup>2,8</sup>

Why is blood pressure so poorly controlled? The reasons include disease severity, patient factors, doctor factors, and drug-related factors. As hypertension is usually

asymptomatic and complications such as stroke, heart attack, and heart and kidney failures usually appear only after time, patients are unlikely to present with characteristic symptoms. Treatment does not bring immediately obvious benefits to patients and involves inconvenience, medication side-effects, and expense, all of which influence compliance. Treatment failure may also be due to suboptimal drug therapy, with low doses, inappropriate or wrong dose schedules, or suboptimal use of therapeutic options (monotherapy or combination therapy).

## Synergism

Currently available antihypertensive drugs are similar in their overall effectiveness in lowering blood pressure. The response to different agents varies from person to person, however.<sup>9,10</sup> To effectively control blood pressure, the clinician may increase the drug dose or change to another drug.

There are non-empirical ways of predicting response, such as using renin measurements<sup>11</sup> or the 'Cambridge ABCD rule'.<sup>9</sup> Plasma renin can be measured,<sup>11</sup> usually in a research clinic setting—as a simple rule of thumb, younger and older patients can be assumed to have high or low renin levels, respectively.<sup>9</sup> The high renin form of hypertension is more responsive to drugs that block the renin angiotensin system, whereas the low renin form is more responsive to diuretics and calcium channel blockers. Nevertheless, these strategies only serve to select the best monotherapy for a patient. A survey of the utilisation of antihypertensive drugs in the Hypertension Clinic at Queen Mary Hospital showed that 60% of patients were taking more than one antihypertensive agent.<sup>12</sup> Rather than combining drugs on an empirical basis, there are rational combinations of drugs with different and complementary modes of action that should be considered. Examples of recognised combinations include diuretics and  $\beta$ -blockers,<sup>13</sup> diuretics and ACEIs,<sup>14</sup> diuretics and angiotensin receptor blockers (ARBs),<sup>15</sup> and ACEIs and calcium channel blockers.<sup>16</sup>

The combination of a diuretic and a blocker of the renin angiotensin system such as an ACEI or an ARB is synergistic in terms of efficacy. In terms of side-effects, combination therapy is also better. For example, diuretics stimulate the renin angiotensin system and can cause hypokalaemia in up to 50% of patients.<sup>17</sup> This is reduced by the addition of an ACEI or ARB.<sup>14,15</sup> In general, the enhanced antihypertensive efficacy of synergistic combinations allows lower doses of ingredient drugs with fewer dose-dependent adverse effects.

## Evidence-based therapy

Most of the early hypertension trials employed diuretics in combination with another agent, usually a potassium-

sparing diuretic or a  $\beta$ -blocker.<sup>18,19</sup> Thiazide diuretics were rarely given on their own because of the risk of hypokalaemia or because of the improved blood pressure-lowering effect when given in combination with other drugs. Diuretics have been well-tested for stroke prevention and are recommended in all hypertension treatment guidelines.<sup>2,20</sup>

A recent landmark trial, the Perindopril Protection against Recurrent Stroke Study (PROGRESS), showed that strokes are prevented more often in patients taking a combination of indapamide and perindopril than in those taking perindopril alone.<sup>21</sup> The unique factorial design of the study allowed statistical comparison of the combination of indapamide and perindopril with perindopril alone. The superior results of the combination were shown by the lower blood pressure values achieved. Another recent landmark trial, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, showed that losartan prevented cardiovascular events, mostly strokes, better than atenolol.<sup>22</sup> Less than one tenth of patients in this trial were receiving monotherapy. Hydrochlorothiazide was the add-on medication. Although these trials purported to show that ACEIs and ARBs prevent strokes, in clinical practice a diuretic should also be included in the regimen, as in these trials.

### Improved compliance and economy

Better efficacy and a lower incidence of side-effects with effective combination therapy should enhance compliance. Compliance decreases with the number of tablets taken daily, however.<sup>23</sup> Therefore, if more than one antihypertensive is used, there may be a place for fixed-dose combinations, which have the advantage of improved compliance, fewer tablets for the patient to take, and less room for dosing error. Compliance with other non-antihypertensive drugs may also improve, especially for elderly people who are taking multiple medications. In some countries, fixed-dose combinations are cheaper than prescribing the two drugs separately, both in terms of acquisition costs and patients' drug bills. For the pharmacy, there are fewer drug items to dispense, therefore enhancing efficiency and accuracy. Fixed-dose combinations do have some disadvantages, however, in that there is less scope for titration, and ascertaining the ingredient drug responsible for certain side-effects is problematic. Also, there are some patients for whom monotherapy is sufficient.

### Conclusions

The advantages of combination therapy for hypertension include better blood pressure control through the utilisation of synergistic combinations, decreased incidence of side-effects, improved patient compliance, and increased economy and efficiency. Many clinical trials of hypertension have concentrated on comparison between specific agents. The time has come to test combinations of antihypertensive drugs. The use of logical, empirical combinations is now supported

by accumulated evidence from clinical trials. New guidelines on the management of hypertension are likely to emphasise tight blood pressure control, especially for those patient with a high cardiovascular risk who are taking combinations of antihypertensive drugs.

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