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# Monotherapy versus Combination Therapy as First Line Treatment of Uncomplicated Arterial Hypertension

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## Abstract

Mild to moderate hypertension still remains poorly controlled. This relates to multiple factors including low antihypertensive efficacy of single drug therapies, reluctance of primary care physicians to modify/titrate initially chosen therapy to obtain target blood pressure, and poor compliance with medication. Several guidelines for the treatment of high blood pressure now include combination therapy with low doses of 2 drugs as one of the strategies for the initial management of mild/moderate arterial hypertension. Evidence discussed in this article points to superior control of blood pressure by combinations of low doses of 2 drugs as compared with monotherapy in regular doses. This superior effectiveness of combined therapy relates to a better antihypertensive efficacy and higher response rates in the low range of doses as the result of complementary mechanisms of antihypertensive effects, better tolerance as a result of a lower rate of adverse effects in the low dose range, improved compliance from better tolerance and simple drug regimen, and lower cost. Whether increased use of fixed low dose combination therapies would translate to better control of arterial hypertension in the population and thereby further reduction of cardiovascular/cerebrovascular morbidity and mortality caused by hypertension remains to be assessed.

## 1. Initial Treatment of Uncomplicated Hypertension

### 1.1 Current Recommendations

Mild uncomplicated arterial hypertension represents about 75% of all cases of hypertension, and accounts for the largest proportion of cardiovascular morbidity and mortality caused by hypertension. As the blood pressure reaches levels of 140/90mm Hg, the risk for cardiovascular morbidity and mortality starts to increase steeply. Once the diagnosis of arterial hypertension is established, non-pharmacological measures and antihypertensive drugs need to be used.

Current recommendations for the initial treatment of mild uncomplicated hypertension by the International Society of Hypertension (ISH)/World Health Organization (WHO),[1] or national organisations such as the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC),[2] or the Canadian Hypertension Society,[3] emphasise, as the principal strategy, single drug therapy with stepwise dose increases and the addition of a second (and third) agent when high/maximal doses of single drug therapy fail to normalise the blood pressure, and to change the initially chosen drug if it is ineffective or not tolerated by the patient.

Combination drug therapy, including low doses of the 2 drug components, is only recently being highlighted.[1,2] There are several reasons for this change in focus, including better antihypertensive efficacy and higher response rates in the low range of doses as a result of complementary mechanisms of antihypertensive effects, better tolerance as the result of a lower rate of adverse effects in the low dose range, improved compliance from better tolerance and simple drug regimens, and lower cost.

### 1.2 Current Actual Management

Given the clear evidence for a hypertension-induced increase in risk for cardiovascular morbidity and mortality, the relative ease of diagnosis of hypertension, the availability of many drugs to lower blood pressure, and the evidence for a decrease in cardiovascular morbidity and mortality from normalising blood pressure by several classes of antihypertensive drugs, one would assume that most patients with hypertension would be aware of their condition, be on antihypertensive medication and have normal blood pressure. In contrast, recent surveys in Canada,[4] the US[2,5] and in many other countries[6-8] showed that only 50 to 60% of those with high blood pressure are aware of their disease, and only a minority of these have an adequately controlled blood pressure. Clearly, both better detection and better management of high blood pressure with antihypertensives are urgently needed.

Inadequate lowering of blood pressure with antihypertensive drug therapy can be attributed to several factors, including the multitude of pathophysiological mechanisms playing a role in the maintenance of high blood pressure and their heterogeneity among patients, failure of physicians to titrate/modify the first line therapy to reach the recommended target blood pressure, and patient compliance.

Single drug antihypertensive regimens address in general only one of the pathophysiological mechanisms contributing to the development/maintenance/progression of arterial hypertension. The role of a particular pathophysiological mechanism varies from patient to patient, and this probably explains the generally low response rates to single drug therapies. For example, in the Department of Veterans Affairs Cooperative Study on Antihypertensive Agents,[9] 1292 men with mild hypertension [diastolic blood pressure (DBP) 95-109mm Hg] were randomised to placebo, a diuretic (hydrochlorothiazide from 12.5 to 50 mg/day), a β-blocker (atenolol from 25 to 100 mg/day), an angiotensin-converting enzyme (ACE) inhibitor (captopril from 25 to 100 mg/day), a non-dihydropyridine calcium antagonist (diltiazem from 120 to 360 mg/day), an $\alpha_1$-blocker (prazosin 4 to 20 mg/day), or a centrally acting sympatholytic agent (clonidine from 0.2 to 0.6 mg/day). All drugs were started at the lowest dose, and titrated every 2 weeks to a target DBP of <90mm Hg. By the end of the titration period, of those on active treatment,

30, 19 and 51% were on the lowest, medium and highest dose of medication, respectively. Whereas all the drugs decreased blood pressure more than placebo, single drug therapy resulted in a decrease in DBP <90mm Hg at the end of titration period and below 95mm Hg at the end of one year (which is still considered mild hypertension) in only 40 to 60% of patients.

Similarly, in the HANE (Hydrochlorothiazide, Atenolol, Nitrendipine, Enalapril) study, response rates (defined as DBP <90 mmHg) to monotherapy with a diuretic (hydrochlorothiazide), β-blocker (atenolol), calcium antagonist (nitrendipine) or ACE inhibitor (enalapril) were only around 55%.[10]

Of interest, in both above quoted studies,[9,10] approximately 50% of responders to initially chosen monotherapy responded to the lowest doses.[9,10] An increase from low to regular dose resulted in target blood pressure being reach in approximately 20% of those not responding with low dose therapy.[9,10] Of those on the highest dose of medication, about 35% reached the target blood pressure.[9,10] This may suggest only a small additional improvement in antihypertensive efficacy with 'high' doses of single drug therapy.

Alternatively, those not responding to regular/high doses of monotherapy may represent individuals with the highest initial blood pressures requiring larger decreases to reach the target blood pressure. This was not analysed in the above quoted studies,[9,10] but it was in other studies. For example, in the Intervention as a Goal of Treatment (INSIGHT) study,[11] 6418 patients with hypertension were randomised to treatment with the calcium antagonist nifedipine GITS (gastrointestinal therapeutic system) 30 mg/day or the diuretic hydrochlorothiazide/amiloride 25/2.5 mg/day. The treatment target was blood pressure ≤140/90mm Hg, and/or fall in systolic blood pressure (SBP) by 20mm Hg and DBP by 10mm Hg. In those who did not respond to initial low dose single drug therapy, doubling of the initial dose was permitted after 2 weeks. Atenolol and enalapril were mandatory second drugs, started at week 4 in low doses of 25 mg/day and 5 mg/day, respectively. These low doses were increased to atenolol 50 mg/day and enalapril 10 mg/day in nonresponders. After 12 weeks of treatment, any other drug (with the exception of a diuretic or a calcium antagonist) could be added. At the end of the titration period (18 weeks), from 5669 patients still receiving randomised treatment, 68% were on a low or high dose of a single drug, 27% were receiving a second drug at low or high dose and 5% were receiving a third drug. The pattern of changes in blood pressure according to the final dose step showed that poor responders to monotherapy had higher baseline blood pressure, and that adding a second drug resulted in larger decreases in blood pressure than increasing the dose of the first line drug.

Studies such as those discussed here[9-11] used a parallel group design and do not test within patient differences in blood pressure response to different antihypertensive drugs. In general, cross-over trials on the antihypertensive efficacy of drugs acting by different mechanisms such as β-blockers, calcium antagonists, ACE inhibitors and diuretics show that it is difficult to predict if a given patient will be a responder or not to a given antihypertensive class.[12,13] Some patients respond to whatever antihypertensive drug and even to placebo, some respond exclusively to one antihypertensive drug class, and others remain hypertensive irrespective of the antihypertensive drug used. Exceptions to the limited predictability of the response to a given antihypertensive drug are few, such as plasma renin activity, race or age.

Another reason for the limited antihypertensive efficacy of single drug therapy relates to compensatory increases in other pressor mechanisms blunting the antihypertensive effect. For example, diuretic monotherapy is associated with activation of the renin-angiotensin system and consequent haemodynamic and renal effects which may blunt antihypertensive effects. In a study by Van Hoogdalem et al,[14] 16 patients with renovascular and essential hypertension received the diuretic furosemide 40mg twice daily for 3 days, resulting in negative sodium balance and bodyweight loss, and a significant rise in plasma renin activity. Blood

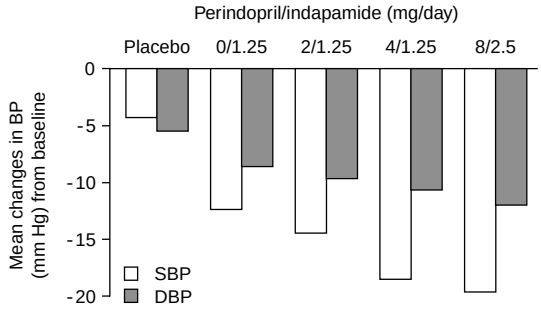


**Fig. 1.** Changes in systolic and diastolic blood pressure in response to different doses of perindopril and indapamide alone or in combination versus placebo in patients with mild moderate arterial hypertension. From Myers et al.[18] and personal communication (Myers and Leenen).

pressure, however, showed only small decreases and even increased in some. Decreases in blood pressure in response to an infusion of the angiotensin II antagonist, saralasin, were proportional to the increases in plasma renin activity induced by diuretic therapy,[14] indicating that diuretic-induced activation of the renin-angiotensin system contributes to the maintenance of high blood pressure. Thus, the antihypertensive effect of a given drug can be enhanced by targeting activated pressor mechanisms with another drug.

Addition of an ACE inhibitor, $AT_1$ receptor blocker or β-blocker to diuretic in low doses also counteracts diuretic monotherapy-induced activation of the renin-angiotensin system and results in decreases in blood pressure equivalent to or larger than those seen with a high dose of each drug alone.[15-21] For example, indapamide at a low dose of 1.25 mg/day decreases blood pressure only slightly more than placebo (fig. 1).[18] However, the addition of low doses of the ACE inhibitor perindopril (2 and 4 mg/day, respectively) significantly decreases blood pressure (fig. 1).[18] These decreases in blood pressure with the low dose combination of indapamide and perindopril were in extent similar to those seen on high dose of each drug alone (fig 1).[18] In another study, Chanudet et al[21] showed greater decreases in blood pressure with the combination of low doses of perindopril 2 mg/day and indapamide 0.625 mg/day compared to those seen with a regular dose of the $AT_1$ receptor blocker losartan 50 mg/day (fig. 2). Similarly, addition of a low dose of the β-blocker bisoprolol (2.5 mg/day) to low dose hydrochlorothiazide (6.25 mg/day) decreased blood pressure to a similar extent as observed with regular/high doses of hydrochlorothiazide or bisoprolol alone.

Whereas it is common practice to titrate drug therapy to the target blood pressure during clinical trials, this appears not to happen in primary care. Once primary care physicians initiate single drug antihypertensive therapy, they are unlikely to take action in response to poorly controlled blood pressure. For example, surveys in primary care centres in Spain[6] as well as in other Western European countries[7,8] showed blood pressure below 140/90mm Hg only in 15 to 45% of patients with hypertension who received treatment. However, in

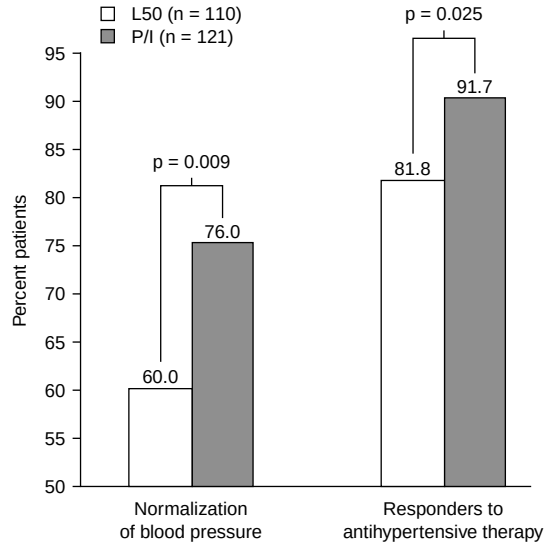


**Fig. 2.** Percentage of patients responding (BP < 140/90mm Hg and/or a decrease in supine DBP ≥ 10mm Hg and/or a decrease in supine SBP ≥ 20mm Hg) to antihypertensive therapy and with normalisation of BP (supine DBP < 90mm Hg) with perindopril 2mg/indapamide 0.625mg (P/1) versus losartan 50mg (L50) on per-protocol analysis (from Chanudet,[21] with permission). **BP** = blood pressure; **DBP** = diastolic BP; **SBP** = systolic BP.

only 13 to 16% of those with inadequate blood pressure control did physicians modify the antihypertensive therapy (fig. 3).[6] Similarly, over a 2-year period 40% of 800 men with hypertension at 5 Department of Veterans Affairs sites in New England had blood pressure at or higher than 160/90mm Hg despite an average of >6 hypertension-related visits per year.[22] Whereas physicians generally increased the frequency of the visits in response to high blood pressure in the office, they rarely titrated/modified therapy.[22] Consistent with these surveys, at the time of enrolment into the Hypertension Optimal Treatment study,[23] nearly 50% of the 19 193 patients were already receiving antihypertensive treatment. However, blood pressure control was still inadequate (average blood pressure 162 ± 18/99 ± 9mm Hg) in these patients.[23] Most of these patients (59%) were receiving single drug antihypertensive therapy.[23]

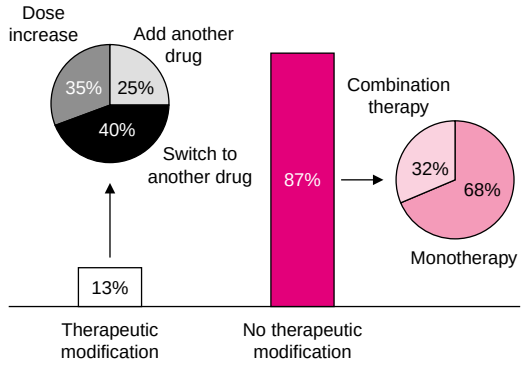


**Fig. 3.** Results of a survey of treatment strategies adopted by Spanish physicians for patients with inadequate blood pressure control. Therapy was modified in only 13% of these patients. Adapted from Coca.,[6] with permission.

## 2. Compliance with Antihypertensive Medication

Compliance can be defined as the extent to which a person's behaviour coincides with medical advice. Multiple factors affect compliance. These include cognitive, social and behavioural factors as well as aspects of the treatment *per se* such as adverse effects and the complexity of the regimen. In the following sections we discuss adverse effects which may contribute to poor adherence to single drug regimens in patients with mild arterial hypertension.

### 2.1 Overall Adherence to Antihypertensive Medication

Patients with uncomplicated mild arterial hypertension mostly 'feel well' and are advised to take antihypertensive medication which should prevent cerebrovascular/cardiovascular events years later. Caro et al.[24] recently reported that only 78% of adults in the province of Saskatchewan, Canada with newly diagnosed hypertension persisted with therapy at the end of 1 year and only 46% at the end of 4.5 years. Patients with newly diagnosed hypertension are more likely to discontinue their medication compared with those with an established diagnosis. For example, in the study by Caro et al.,[24] the adherence to therapy at the end of the first and fourth year was significantly ($p < 0.001$) better in those with established arterial hypertension (97% and 82%, respectively) compared with those with newly diagnosed disease.

This high discontinuation rate at this initial stage probably relates to a variety of factors including feeling 'better' without medication, poorly explained risk from arterial hypertension for cardiovascular/cerebrovascular morbidity and mortality, and overwhelmingly advertised negative adverse effects of antihypertensive drugs. As Martin Myers pointed out in his article *Compliance in hypertension: why don't patients take their pills?*: '…it may seem surprising that so many patients actually *do* take their medications as prescribed!'.[25]

### 2.2 Frequency of Adverse Effects with Low versus High Doses of Single Drug Therapy

One possible explanation for the reluctance of primary care physicians to titrate the dose of antihypertensive drugs to target blood pressure is the higher frequency of adverse effects seen with higher doses of antihypertensive drugs.[26] This concept is valid and based on basic pharmacology principles. The incidence of adverse effects such

as metabolic effects including hypokalaemia, hyperuricaemia, hyperglycaemia with diuretics,[15,27] peripheral oedema with calcium antagonists,[15,28-32] and cough with ACE inhibitors[18] increases with increasing dosages. For example, an increase in the dosage of hydrochlorothiazide from 6.25 to 25 mg/day significantly increases the incidence of hypokalaemia and hyperuricaemia and the extent of these metabolic changes is significantly larger with higher doses.[15] Some of these adverse effects may have a negative impact on cardiovascular morbidity and mortality. For example, in the Systolic Hypertension in the Elderly Program (SHEP), the decrease in SBP by the diuretic chlorthalidone resulted in a significant decrease in cardiovascular events, coronary events and strokes.[27] A recent sub-analysis showed that the benefit from the lowered SBP by chlorthalidone on cardiovascular morbidity only occurred in those who did not develop hypokalaemia and not in those who developed hypokalaemia ($[K^+]$ <3.5 mmol/L) (fig. 4).[27]

Given the fact that many of the adverse effects are dose-related, one may expect an improved 'safety' profile with low dose combination antihypertensive therapies over high dose monotherapies for the same antihypertensive efficacy (see section 3). However, combination therapy may imply an increase in the risk for dose-independent adverse effects such as allergic reactions of 2 drugs *versus* only 1.

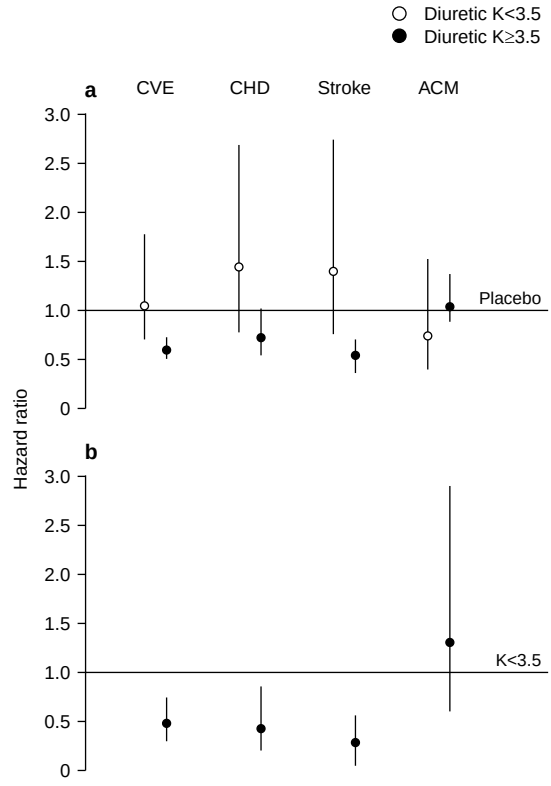


**Fig. 4.** Hazard ratio of cardiovascular events (CVE), coronary heart disease (CHD), stroke (S) and all-cause mortality (ACM) according to plasma potassium (K) level at 1 year in the Systolic Hypertension in the Elderly Program. (**a**) compared to placebo (n = 2003) and (**b**) within the diuretic group (K <3.5, n = 151; K ≥ 3.5, n = 1951). Numbers are mean hazard ratio (•) and 95% confidence interval. Potassium levels are in mmol/L.

## 3. Fixed Combination Therapies in the Initial Treatment

### 3.1 Rationale

Single drug antihypertensive therapies result in blood pressure control in at most 50-60% of patients. As discussed in sections 1 and 2, this relates to: (i) monotherapy affecting only one of many pathophysiological mechanisms involved in the maintenance of arterial hypertension; (ii) drug-induced compensatory hypertensive mechanisms; (iii) lack of intervention by physicians to increase/modify initially chosen medication despite inadequate blood pressure control; and (iv) poor compliance with medication by patients.

Combination therapy as recently recommended by ISH/WHO[1] and JNC VI[2] in the US as a first-line approach has several advantages over monotherapy, in particular better antihypertensive efficacy in low doses and therefore a lower incidence of adverse effects and better compliance.

### 3.2 Diuretic-Based Combinations

The response rate to diuretics is about 40% with low doses and may be up to 60% with regular and

high doses. However, this higher antihypertensive efficacy with regular and high doses is associated with increased incidence of adverse effects.

Activation of the renin-angiotensin system by diuretics counteracts their antihypertensive effects.[17] Thus, the addition of drugs such as ACE inhibitors, $AT_1$ receptor blockers or β-blockers, which block the diuretic-induced activation of the renin-angiotensin system or its effects, is a logical approach from an antihypertensive efficacy point of view. The other way around, the antihypertensive effect of ACE inhibitors[16,33,34] and $AT_1$ receptor blockers[17] can also be enhanced by combination with a diuretic even in patients with low-renin (volume-dependent) hypertension.[16,33,34] Similarly, a diuretic and a β-blocker in combination complement each other; the diuretic opposes the sodium and water retention caused by β-blockade,[35] while β-blockade blunts the volume depletion-induced hypertensive mechanisms such as sympathetic hyperactivity[36] and increase in plasma renin activity.[37]

Enhanced antihypertensive effects with low dose combination therapy have been documented in several studies for low dose combinations of a diuretic with an ACE inhibitor or a $AT_1$ receptor blocker.[16-21] For example, in a study by Chalmers et al.[19] 383 elderly patients (age 65-85 years) with mild to moderate hypertension or isolated systolic hypertension were randomised to once daily low doses of the ACE inhibitor perindopril 2mg and the diuretic indapamide 0.625mg in 1 tablet or placebo. After 12 weeks, all patients on combination therapy with perindopril/indapamide (n = 138) and patients with normalised blood pressure on placebo (DBP < 90mm Hg or SBP < 160mm Hg for isolated systolic hypertension; n = 61) were maintained on their regimen for an additional 48 weeks. Patients in the placebo group whose blood pressure was not normalised (n = 60) were switched to perindopril/indapamide combination therapy. During the first 12 weeks normal blood pressure was achieved in 96% of patients who received perindopril/indapamide. A total of 79% of patients who received perindopril/indapamide completed the study (60 weeks) with sustained normalisation of blood pressure. This high rate of normalisation of blood pressure on the combination of low dose of perindopril/indapamide was also reported by Chanudet et al[21] and clearly exceeds those seen with ACE inhibitor, $AT_1$ receptor blocker, or diuretic alone.[9,10,16,18]

The antihypertensive efficacy of diuretics in combination with β-blockers has also been assessed in several clinical trials.[15,38-40] For example, in a study by Frishman et al.[15] 512 patients with mild to moderate arterial hypertension were randomised to once daily treatment with the diuretic hydrochlorothiazide in doses of 0, 6.25 and 25mg, the β-blocker bisoprolol in doses of 0, 2.5, 10 and 40mg, and all possible combinations. The combination of low dosage hydrochlorothiazide 6.25 mg/day and very low to low dosage bisoprolol 2.5 to 10 mg/day resulted in response rates (defined as sitting DBP of 90mm Hg or lower or a decrease in sitting DBP from baseline of 10mm Hg or greater) in 61% and 85% of patients, respectively. This compares to response rates of 52% and 75% in patients randomised to high dosages of hydrochlorothiazide 25 mg/day and bisoprolol 40 mg/day alone.

Arterial hypertension may be associated with other conditions (such as insulin resistance/obesity/diabetes mellitus, dyslipidaemia etc.) which *per se* are risk factors for cardiovascular morbidity and mortality. Thus, besides the decrease in blood pressure, antihypertensive drugs should have at least a neutral (if not a positive) effect on these conditions. Indeed, metabolic adverse effects with (mostly high doses) antihypertensive drugs could offset the benefits in cardiovascular morbidity outcome from the lowered blood pressure (fig. 4).[27] In this regard, improved antihypertensive efficacy in the low range of doses in combination antihypertensive therapies also may be advantageous. Indeed, metabolic adverse effects such as hypokalaemia, hyperuricaemia and hyperglycaemia were lower for a given antihypertensive efficacy on combination therapies with a diuretic and an ACE inhibitor compared with therapy with a diuretic

alone.[16] In elderly patients with hypertension, combination therapy with low doses of the ACE inhibitor perindopril and the diuretic indapamide caused only mild hypokalaemia ($[K^+]$ = 3.1–3.3 mmol/L) in 13 patients out of 253 (compared with 1 out of 61 in the placebo group) and no significant changes in serum glucose levels compared with placebo.[21]

Similarly, in the study by Frishman et al,[15] for a given antihypertensive efficacy hydrochlorothiazide and bisoprolol in low combination were associated with significantly fewer dose-related metabolic adverse effects such as hypokalaemia, hyperuricaemia and hyperglycaemia than each drug when given alone. The low incidence of negative metabolic effects with low doses of hydrochlorothiazide and bisoprolol compared with therapy with each drug alone was quoted in the approval of this drug combination by Food and Drug Administration in the US: '[t]he pivotal consideration is that each of these agents (bisoprolol and hydrochlorothiazide) has both dose-dependent and dose-independent adverse drug reaction. In a given patient, the dose-independent risks of the combination of low-dose bisoprolol and low-dose hydrochlorothiazide might, therefore, be preferable to the dose-dependent risks associated with monotherapy that employs a higher dose of either agent'.[41] For a given antihypertensive effect, the incidence of adverse events associated with the combination of bisoprolol and hydrochlorothiazide such as decrease in libido, bronchospasm, depression, diarrhoea, dyspepsia and somnolence was either similar or lower compared with treatment with higher doses of each drug alone.[15] The highest withdrawal rate in this study was reported for the placebo group (14%) and for combination of bisoprolol and hydrochlorothiazide at higher doses (40 mg/day and 25 mg/day, respectively, 12%). Withdrawal rates in all other groups were 2-10%.[15]

### 3.3 Nondiuretic-Based Combinations

ACE inhibitors and calcium antagonists reduce peripheral vasoconstriction[42,43] and facilitate salt and water excretion[44,45] through different mechanisms and their antihypertensive effects could be additive to each other. Several studies assessed the antihypertensive efficacy of ACE inhibitors and calcium antagonists in combination.[46-49] For example, studies on the antihypertensive efficacy of monotherapy with the calcium antagonist amlodipine 2.5 to 5 mg/day or the ACE inhibitor benazepril 5 to 20 mg/day and all possible combinations of the 2 drugs showed that the low dose combination of amlodipine 2.5 mg/day with benazepril 5 to 10 mg/day decreased both SBP and DBP to similar extent as regular to high doses of amlodipine 5 mg/day and benazepril 20mg alone.[46] Whereas blood pressure control was reached in only half of the patients on amlodipine or benazepril alone, 87% of patients responded to combined therapy.[46] Similarly, enhanced antihypertensive efficacy has been reported for the ACE inhibitor trandolapril combined with the non-dihydropyridine calcium antagonist verapamil.[49]

The most common adverse effect associated with calcium antagonist monotherapy is peripheral oedema. The above combinations may reduce the peripheral oedema by a calcium antagonist in 2 ways: (i) through improved local haemodynamics (venodilation) in combination with an ACE inhibitor; (ii) by using lower doses of a calcium antagonist. In the above study,[46] the incidence of peripheral oedema with amlodipine monotherapy was 9.1% in women and 2.2% in men and decreased significantly in combination with the ACE inhibitor to 3.2% in women and 0.6% in men.

A β-blocker and calcium antagonist of the dihydropyridine type may complement each other in terms of antihypertensive effect (decrease in peripheral vascular resistance and cardiac output), but also in terms of tolerability. Calcium antagonists could ameliorate the unwanted adverse effects of β-blockers on peripheral circulation (e.g. in patients with peripheral vascular disease) and β-blockers may blunt baroreflex-mediated increases in sympathetic activity.

Several studies showed better antihypertensive efficacy for combinations of a calcium antagonist

and a β-blocker in low doses compared with each drug alone.[30,31,50-55] For example, in a study by Dahlof et al.,[50] 159 patients with mild hypertension were randomised to the calcium antagonist felodipine 10 mg/day, the β-blocker metoprolol 100 mg/day, or a combination of both in the same dosages for a 12-week treatment period. The response rate was defined as DBP <90mm Hg and was significantly better with combination (71%) than with felodipine (49%) or metoprolol (34%) alone. In another study by this group,[52] 58 patients with mild to moderate hypertension were randomised to low dose metoprolol (50 mg/day), low dose felodipine 5 mg/day, or a combination of above 2 drugs at the same dosages. Dose titration was performed after 6 weeks of active treatment (increase felodipine from 5 mg/day to 10 mg/day, metoprolol from 50 mg/day to 100 mg/day and similar increases for the combination of both drugs). The low dose combination of felodipine and metoprolol resulted in a positive response (DBP 24 hours after dose ≤90mm Hg) in 65% of patients. Corresponding numbers for low dose felodipine and low dose metoprolol alone were significantly lower. Moreover, the response rate with the low dose combination of felodipine and metoprolol (65%) was higher than with monotherapies titrated to regular doses (45% for felodipine and 40% for metoprolol).

In a study by Waeber et al,[52] patients with mild to moderate hypertension were randomised to either a low dose combination of felodipine 5 mg/day and metoprolol 50 mg/day, an ACE inhibitor enalapril 10 mg/day or placebo for 12 weeks (with the possibility of doubling the initial dose after 4 or 8 weeks if DBP remained >90mm Hg). In this study, 38% of patients receiving the combination required dose adjustment compared with 61% of those receiving enalapril. Overall response rates (defined as DBP ≤90mm Hg 24 hours after dose) was 72%, 49% and 30% for felodipine/metoprolol, enalapril and placebo, respectively.[52] For a given antihypertensive effect, the overall incidence of dose related adverse effects such as peripheral oedema with calcium antagonists was lower with the low dose combination with β-blocker compared with monotherapy.[30] The incidence of other adverse effects with calcium antagonists (headache and flushing) and β-blockers (fatigue and headache) appeared not to be affected by dosages.[30]

### 3.4 Fixed-Dose versus Extemporaneous Forms of Combination Therapy

Combination antihypertensive therapy can be administered in fixed or extemporaneous forms. It appears that fixed drug combinations have several advantages over extemporaneous combinations (table I). Fixed drug combinations are more likely to be based on sound additive benefits for blood pressure control, thus avoiding nonrational combinations (such as β-blocker + non-dihydropyridine calcium antagonist, β-blocker + ACE inhibitor etc.). However, only drugs with similar minimal duration of antihypertensive effect should be combined to assure a sustained effect on blood pressure over the dose administration interval. Moreover, fixed drug combinations provide enhanced simplicity of antihypertensive regimens allowing a de-

**Table I.** Advantages and disadvantages of treatment of hypertension with low dose combination therapy *versus* monotherapy

| | Monotherapy | Combination therapy | |
|---|---|---|---|
| | | extemporaneous | fixed |
| Response rate | low | high | high |
| Complexity of dose administration | simple | complex | simple |
| Titration flexibility | high | high | low |
| Adverse effects | medium | low | low |
| Compliance | medium | medium | high |
| Cost | medium | high | low |
| Overall blood pressure control | low | medium | high |

creased number of pill-bottles and of pills *per se*, which is associated with better compliance.[56] Last but not the least, the price of fixed drug combinations is lower than extemporaneous combinations. Two-drug therapy is more expensive in that there are 2 dispensing fees, the cost of titrating 2 drugs and the cost of the 2 drugs themselves. Fixed drug combinations involve only 1 dispensing fee and the drug price is typically less than if the 2 components were used separately.

On the other hand, extemporaneous combination therapies offer more flexibility in the titration process compared with fixed dose combinations. Given the evidence that this rarely happens and that absence of titration of monotherapy and/or addition of another drug is one of the major factors for inadequate blood pressure control in the population, this freedom appears to be only an academic rather than a practical advantage. Extemporaneous combination therapies also offer more flexibility in combining drugs with different duration of their antihypertensive effect (e.g. one drug once daily, another one twice daily). However, this 'advantage' appears counterproductive given the inverse relationship between compliance and complexity of dose administration regimen. Extemporaneous combinations also potentially offer better awareness by physicians and patients of possible drug interactions and specific adverse effects compared with fixed dose combinations where the components are 'hidden'. Whether this is clinically relevant remains to be assessed.

## 4. Conclusion

The control of arterial hypertension remains disturbingly inadequate. This relates to poor blood pressure lowering by single drug therapies *per se*, reluctance of primary care physicians to modify/titrate initially chosen therapy to target blood pressure and poor compliance with medication. Fixed low dose combination therapies appear to offer better initial antihypertensive efficacy and improved tolerability. This leads to a larger proportion of patients started on antihypertensive medication having blood pressure controlled (without further dose adjustments), titration without changes in the number of medications, fewer dose-related adverse effects and, potentially, improved compliance. Whether improved antihypertensive efficacy and a lower incidence of adverse effects with fixed low dose combination therapies as first line treatment of hypertension will translate in better control of arterial hypertension in the population and thereby in further reduction in cardiovascular/cerebrovascular morbidity and mortality remains to be assessed.

For those patients requiring larger decreases in blood pressure, fixed regular to high dose combination therapies offer the high end of the antihypertensive effect of combination therapy, but with a potentially higher incidence of dose-dependent adverse effects. One may speculate that the addition of a third drug in a low dose to fixed low dose combinations would overall (i.e. taking into account antihypertensive efficacy, incidence of adverse effects and compliance) outperform high dose combinations of 2 drugs.

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