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Concomitant calcium entry blockade and inhibition of the renin-angiotensin system: a rational and effective means for treating hypertension

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Key words: angiotensin-converting enzyme inhibitors, angiotensin II, antagonists, calcium antagonists, guidelines, hypertension, tolerability

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Abstract

Pharmacological treatment of hypertension is effective in preventing cardiovascular and renal complications. Calcium antagonists (CAs) and blockers of the renin-angiotensin system [angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists (ARBs)] are widely used today to initiate antihypertensive treatment but, when given as monotherapy, do not suffice in most patients to normalise blood pressure (BP). Combining a CA and either an ACE-inhibitor or an ARB considerably increases the antihypertensive efficacy, but not at the expense of a deterioration of tolerability. Several fixed-dose combinations are available (CA + ACE-inhibitors: amlodipine + benazepril, felodipine + ramipril, verapamil + trandolapril; CA + ARB: amlodipine + valsartan). They are expected not only to improve BP control, but also to facilitate long-term adherence with antihypertensive therapy, thereby providing maximal protection against the cardiovascular and renal damage caused by high BP.

Introduction

Hypertension still represents worldwide a leading cause of mortality and a main modifiable risk factor for cardiovascular, cerebrovascular and renal diseases.^{1,2} Despite major efforts directed over the last decades to screen and treat patients with raised blood pressure (BP), the control of hypertension remains often inadequate, both in industrialised and in economically developing countries.³ There is unequivocal evidence that antihypertensive treatment is effective in protecting against the classical complications of hypertension.^{4,5}

There is currently available a broad choice of BP lowering agents. Most of them belong to the classes of thiazide diuretics, β -blockers, calcium antagonists (CAs), angiotensin-converting enzyme (ACE) -inhibitors and angiotensin (Ang) II receptor blockers (ARBs). Notably, such agents allow the achievement of strict BP control in only a fraction of hypertensives when given as monotherapy.⁶ The co-administration of two or more drugs acting by different mechanisms is indeed required in the majority of patients to normalise both systolic BP (SBP) (< 140 mmHg) and diastolic BP (DBP) (< 90 mmHg), as

observed in all recent interventional trials with pre-defined target BP.^{7–11} Two-drug, fixed-dose combinations are becoming more and more attractive because they not only provide a favourable efficacy-tolerance profile, but also simplify treatment, facilitating thereby the long-term persistence on the prescribed treatment.^{12,13} Such preparations are considered in recent hypertension guidelines as a valuable option to initiate antihypertensive therapy, especially in patients with BP \geq 160 mmHg for SBP and/or \geq 100 mmHg for DBP, or in those with high or very high total cardiovascular risk.^{14,15}

Drugs that interrupt the renin-angiotensin system (RAS) and CAs have been shown to reduce hypertensive target organ damage and to have documented benefits in prospective, randomised outcome trials carried-out in hypertensive patients. Combining these two types of agents appears therefore particularly appealing. This urged us to review the experience accumulated with CAs co-administered with an ACE-inhibitors or an ARB, given either individually as monosubstances or associated in fixed-dose combinations.

Antihypertensive efficacy and tolerability of calcium antagonists, ACE-inhibitors and ARB

There are three major classes of CAs available for clinical use: verapamil is a phenylalkylamine derivative, diltiazem a benzothiazepine derivative, and nifedipine the prototype of the dihydropyridine derivatives.¹⁶ All these agents act by blocking the transmembrane calcium influx in vascular and myocardial cells through L-type channels. The various types of CAs can be more or less selective for the vasculature and the heart. Verapamil has the greatest chronotropic and inotropic depressant actions, whereas the dihydropyridines exert more effect on vascular smooth muscle cells. Diltiazem has an intermediate action, being less potent than verapamil in the heart and less potent than dihydropyridines in blood vessels. A few years ago a classification of CAs based on clinical pharmacologic properties was proposed.¹⁷ According to the selected criteria CAs may be subdivided into first-generation drugs (instant release formulations of verapamil, diltiazem and

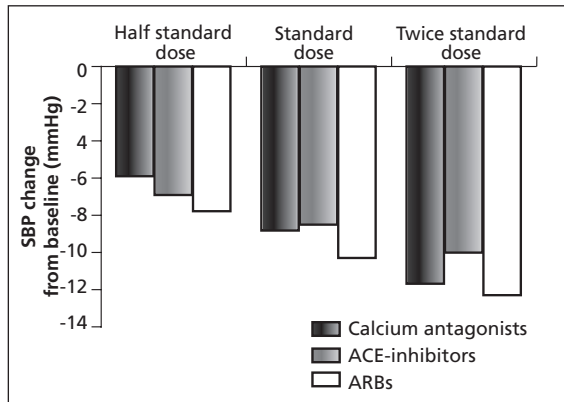


Figure 1
Placebo-adjusted reductions in SBP induced by increasing doses of a calcium antagonist, an ACE-inhibitor or an ARB.¹² ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; SBP = systolic blood pressure.

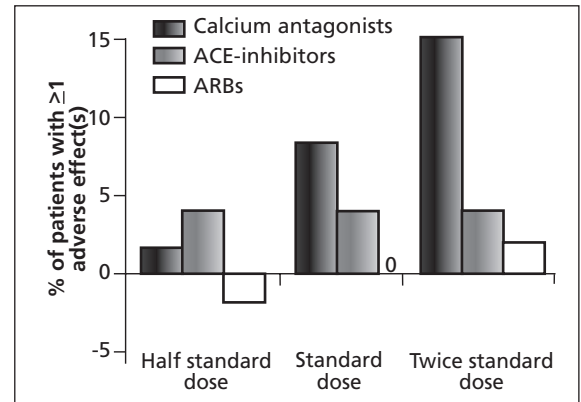


Figure 2
Percentage of patients having developed ≥ adverse effect(s) during treatment with a calcium antagonist, an ACE-inhibitor or an ARB.¹² ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

nifedipine), second-generation drugs compounds developed to improve the pharmacokinetic profile (slow-release formulations containing verapamil, diltiazem, nifedipine, felodipine, isradipine), and third generation dihydropyridines (amlodipine, lacidipine, lercanidipine), which are characterised by a slow onset, a long duration and a slow offset of action. Amlodipine has a long plasma half-life, whereas lacidipine and lercanidipine, because of their high lipophilicity, have a long receptor binding half-life.

CAs are potent vasodilators. They have a clear dose-dependent BP-lowering effect, as illustrated by the results of a meta-analysis of randomised double-blind, placebo-controlled trials, including 209 groups of hypertensive patients on CA therapy (figure 1).¹² The placebo-corrected reduction of SBP induced by calcium entry blockade averaged 10.3 mmHg (95% CI: 8.3–9.3) with a standard dose, smaller using half a standard dose (5.9 mmHg, 95% CI: 5.2–6.6) and larger using twice a standard dose (11.7 mmHg, 95% CI: 11.0–12.3). A dose-dependent decrease in BP was also observed in 217 groups of hypertensive patients treated with an ACE-inhibitor: the placebo-adjusted fall in SBP reached 8.5 mmHg (95% CI: 7.9–9.0) with a standard dose, 6.9 mmHg (95% CI: 6.1–7.8) with half a standard dose, and 10.0 mmHg (95% CI: 9.5–10.4) using twice a standard dose. A similar dose-dependency of the placebo-corrected mean SBP response was seen in 125 groups of hypertensive patients having received an ARB (standard dose, 10.3 mmHg, 95% CI: 9.9–10.8; half a standard dose, 7.8 mmHg, 95% CI: 7.1–8.6); twice a standard dose: 12.3 mmHg, 95% CI: 11.7–12.8).

As already pointed out, the antihypertensive efficacy of CAs, as well as that of ACE-inhibitors and ARBs is dose-dependent. With regard to the

tolerability, however, a clear-cut dose-dependency exists only for CAs. This is illustrated in figure 2, based on the same meta-analysis quoted above.¹² The percentage of patients with one or more adverse effects attributable to a CA averaged 8.3 (95% CI: 4.8–11.8) with a standard dose, compared with 1.6 (95% CI: -3.5–6.7) using half a standard dose and 14.9 (95% CI: 9.8–20.1) using twice a standard dose. The dose-response curve was flat for both the ACE-inhibitors and the ARBs, the latter exhibiting a placebo-like tolerability. The commonest symptoms of CAs, i.e. flushing, ankle oedema, headaches and palpitations are caused by the drug-induced vasodilation.¹⁸ Dry cough is the main problem encountered during ACE-inhibitor treatment, and is presumably due to the accumulation of peptides physiologically inactivated by ACE.¹⁹

There was some concern raised several years ago about the long-term safety of CAs.²⁰ In particular, it was thought that these drugs might increase the risk of myocardial infarction and cancer among hypertensive patients, but recent interventional morbidity-mortality trials have attested to the safety of CAs in this respect.^{7,9-11}

Position of calcium antagonists, ACE-inhibitors and ARBs in the treatment of hypertension

There is ample evidence today that CAs, ACE-inhibitors and ARBs have a positive impact on the cardiovascular, cerebrovascular and renal outcomes of hypertensive patients.^{4,21} No wonder therefore that these drugs are considered today as first-line medicaments for the management of hypertensive patients.^{14,15,22} According to the National Institute for Health and Clinical Excellence (NICE) in UK and the British Hypertension Society guidelines, the age and the ethnicity of patients are helpful in guiding the choice of the initial therapy.²² Older patients and

Table 1
Preferred indications of calcium antagonists, ACE-inhibitors and ARBs as first-line antihypertensive therapy (modified from ref. 15).

	CA		ACE-inhibitors	ARB
	ND	D		
Subclinical organ damage				
- Left ventricular hypertrophy	+	+	+	+
- Asymptomatic atherosclerosis	+	+	+	
- Microalbuminuria			+	+
- Renal dysfunction			+	+
Clinical events				
- Previous stroke	+	+	+	+
- Previous myocardial infarction			+	+
- Angina pectoris	+	+		
- Heart failure			+	+
- Atrial fibrillation				
Recurrent			+	+
Permanent	+			
- Peripheral artery disease	+			
- Renal failure/proteinuria			+	+
Condition				
- Isolated systolic hypertension	+	+		
- Metabolic syndrome	+	+	+	+
- Diabetes mellitus			+	+
- Pregnancy		+		
- Blacks	+	+		

Key: CA = calcium antagonist; ND = non-dihydropyridine; D = dihydropyridine; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

black patients of any age should receive preferably a CA, whereas younger patients are more likely to respond favourably to an ACE-inhibitor or an ARB. A joint initiative between the European Society of Hypertension and the European Society of Cardiology has led very recently to an update of recommendations regarding the management of high BP.¹⁵ In table 1 are shown the principal indications of CAs, ACE-inhibitors and ARBs as initial therapy. They are based on a large number of convincing observations made in well designed and controlled trials. It is however beyond the scope of the present review to comment on the evidence supporting the use of some antihypertensive drugs versus others in the individual hypertensive patient. CAs, ACE-inhibitors and ARBs are easy to use, which represents a major advantage in everyday practice. These agents have very few compelling contra-indications (grade 2 or 3 atrioventricular block for non-dihydropyridine CAs; pregnancy, hyperkalaemia and bilateral renal artery stenosis for ACE-inhibitors and ARBs; angioneurotic oedema for ACE-inhibitors), and can therefore be administered to nearly all hypertensives, either as single agents or in combination with other classes of agents and possibly with each other,

though the precise role for this has not yet been established.

Effects of calcium antagonists, ACE-inhibitors and ARBs on sympathetic nerve activity

There exists a close interplay between the renin-angiotensin and the sympathetic nervous system in the regulation of the cardiovascular system. The interactions are bidirectional, each system reinforcing the activity of the other one when stimulated. This occurs at different sites.²³ For instance, Ang II binds to receptors located on sympathetic nerve endings to facilitate norepinephrine release and, postsynaptically, enhances the contractile response to α -adrenergic receptor stimulation. Circulating Ang II may also reach brain stem cardiovascular centres through areas devoid of a tight blood-brain barrier, thereby increasing sympathetic efferent activity. On the other hand the stimulation of β -adrenergic receptors triggers the release of renin from renal juxtaglomerular cells. Actually, hyperactivity of the RAS and/or the sympathetic nervous system is known to contribute importantly to the development and the maintenance of high BP in patients with essential hypertension.^{24,25} Another issue deserves

to be mentioned: any BP-lowering intervention is expected to trigger, beyond a certain point, a reflex increase in sympathetic nerve activity and, via a reduction of renal perfusion, stimulation of renin secretion. It is therefore crucial to discuss here the impact of CAs, ACE-inhibitors and ARBs on sympathetic drive which, if increased, may limit their antihypertensive efficacy, accelerate heart rate and augment myocardial oxygen demand, and might be harmful in some cases, especially in the presence of coronary heart disease.²⁶ A reflex activation of the sympathetic nervous system in response to a drug-induced BP reduction may represent not only a factor limiting the antihypertensive efficacy of the pharmacological intervention, but also have a detrimental effect on the development of complications associated with hypertension.

The effects of CAs on sympathetic nerve activity has been examined in a meta-analysis of 63 trials involving 1,252 hypertensive patients.²⁷ Dihydropyridine and nondihydropyridine CAs were evaluated separately, taking also into account their duration of action (short-acting versus long-acting compounds) and the duration of treatment (single dosing versus long-term administration). Acutely, the BP response to the short-acting CAs was accompanied by an acceleration of heart rate and an increase in plasma norepinephrine levels that was significantly greater with dihydropyridines than with nondihydropyridines. The changes in heart rate and plasma norepinephrine induced by the short-acting compounds were significantly attenuated during long-term calcium entry blockade compared with the first dosing. Considering the long-acting CAs, nondihydropyridines tended to decrease, and dihydropyridines to increase (only slightly) heart rate and plasma norepinephrine during prolonged treatment. Based on these observations both long-acting dihydropyridine and nondihydropyridine CAs appear to have a minimal impact on sympathetic nerve activity during chronic treatment. This claim is supported by the results of a trial in which 43 hypertensive patients were randomised to receive for eight weeks amlodipine, 5 mg/day, or a slow-release preparation of either verapamil (240 mg/day) or nifedipine (40 mg/day).²⁸ The three CAs lowered BP to a similar extent. Notably, none of the compounds increased muscle sympathetic nerve activity measured by microneurography. Heart rate decreased slightly, albeit not significantly, in the three arms. Regarding plasma norepinephrine levels, there was no evidence for a treatment effect during the course of the study. There are therefore good reasons for using preferentially long-acting rather than short-acting CAs.

A hallmark of blockers of the RAS is their ability to lower BP without usually inducing consistent changes in heart rate and plasma

catecholamines.^{29,30} Chronic blockade of the RAS might have an inhibitory effect on muscle sympathetic nerve activity.³¹ The lack of reflex heart rate acceleration during blockade of the renin axis could also be partly due to an increase in vagal tone.^{32,33}

Rationale for co-administering a calcium antagonist with a blocker of the RAS

Enhanced antihypertensive efficacy

The combination of a CA with an ACE-inhibitor or an ARB is more effective in lowering BP than prescribing any of these agents as monotherapy. This is because of the interference of CAs and blockers of the RAS with different pressor mechanisms. Notably, the counter-regulatory response of the sympathetic nervous system to the vasodilation induced by calcium entry blockade is buffered by concomitant blockade of the RAS. Unlike selective arterial vasodilators CAs have a natriuretic effect, which may contribute to render BP maintenance Ang II-dependent.

Several trials have confirmed the superior antihypertensive efficacy of CAs-ACE-inhibitors and CAs-ARBs combinations versus corresponding monotherapies.³⁴⁻⁴⁰

The first fixed-dose combination containing a CA and a blocker of the RAS was based on verapamil (180 mg) and the ACE-inhibitor trandolapril (2 mg).³⁵ In a multicentre, prospective, randomised, double-blind, cross-over study the BP fall was significantly greater ($p < 0.001$) using the combination (-20/-15 mmHg), compared to both trandolapril (-14/-11 mmHg) and verapamil (-13/-11) monotherapy.

An ACE-inhibitor (benazepril)-dihydropyridine (amlodipine) fixed-dose combination was also developed. To this end a multicentre, double-masked, randomised, parallel-group study was performed.³⁴ A total of 308 hypertensive patients (all white) were allocated to a once-daily, 8-week treatment with either benazepril 20 mg, amlodipine 5 mg, benazepril 20 mg/amlodipine 5 mg, or placebo. The placebo-corrected BP reduction averaged 12.4/6.7 mmHg with benazepril, 16.2/8.8 mmHg with amlodipine, and 24.7/13.2 mmHg with the combination. The BP response to benazepril/amlodipine was of similar magnitude in patients < 65 and in those ≥ 65 years of age, as well as in men and in women. The BP response rate (proportion of patients having achieved a DBP < 90 mmHg or a ≥ 10 mmHg decrease from baseline in DBP) was significantly greater ($p \leq 0.005$) in the benazepril/amlodipine group (87.0%) than in the benazepril (53.3%), amlodipine (67.5%) and the placebo group (15.8%). Fixed-dose combinations containing a CA and an ARB have recently become available, such as that associating valsartan and amlodipine. The most

Table 2

Mean BP reductions (mmHg) induced by an 8-week once-daily, treatment with different doses of amlodipine and valsartan given alone or in combination (from ref. 40).

		Amlodipine doses, mg		
		0	2.5	5
Valsartan doses, mg	0	7.3/7.1	12.4/9.3	15.1/11.5
	40	11.8/10.1	15.5*/10.8	19.6**/14.6**
	80	12.9/9.7	17.0**/13.4**	20.8**/14.5**
	160	15.1/11.0	16.7*/13.3**	19.5**/14.2**
	320	15.7/13.4	18.3*/14.2**	22.7**/15.9**

BP = blood pressure; * = $p < 0.05$ versus the same dose of valsartan monotherapy; ** = $p < 0.05$ versus the same dose of amlodipine monotherapy.

appropriate doses of the two components were established in a multicentre, randomised, double-blind, placebo-controlled, parallel-group trials.⁴⁰ In one study, 2,478 hypertensive patients received for eight weeks either amlodipine 2.5 or 5 mg once-daily, valsartan 40, 80, 160 or 320 mg once-daily, the combination of amlodipine 2.5 or 5 mg with valsartan 40, 80, 160 or 320 mg once daily, or placebo. Table 2 depicts the BP reductions observed in the various treatment groups. There was a clear dose-dependent BP-lowering effect of both monotherapies. It also appeared that the co-administration of the two drugs was significantly more effective, whatever the dosages of the two combined agents, than the same dose of monotherapies.

Combination therapy has the potential to normalise BP in more patients than single agents, accounting for the growing interest in fixed-dose combinations, not only as second-line but also as initial therapy. It appears indeed easier to control BP by combining a CA with an ACE-inhibitor or an ARB than by titrating the doses of monotherapies.^{39,42}

As already mentioned, combination therapy is required in most hypertensive patients in order to normalise both SBP and DBP. It is therefore important to know more about the comparative antihypertensive efficacy of CA+ACE-inhibitors/ARB combinations and other types of combinations. Diuretics are generally considered the drugs of choice to add to blockers of the RAS when needed to achieve target BP. In fact, however, administering together a CA with an ACE-inhibitor or an ARB is as effective as a thiazide combined with an ACE-inhibitor or an ARB.⁴³⁻⁴⁸ For instance, 130 hypertensive patients were randomised to receive for six weeks in a double-blind fashion once-daily treatment with either a combination of amlodipine, 5–10 mg, and valsartan, 160 mg, or a combination of lisinopril, 10–20 mg, and hydrochlorothiazide (HCTZ), 12.5 mg.⁴⁸ The two types of combinations were equally effective in lowering BP, as shown in

figure 3. At completion of the trial, 67.2% of patients had their BP < 140/90 mmHg when on amlodipine and valsartan, versus 56.1% of patients allocated to lisinopril and HCTZ. Also of note, the co-administration of a calcium antagonist with a blocker of the RAS allows the achievement of a similar BP reduction as the combination of a β -blocker and a diuretic.^{45,46} To be kept in mind however is the fact that different antihypertensive combinations, even if they appear to provide equivalent BP reductions in groups of patients, may not necessarily have the same antihypertensive efficacy in the individual patient.

Preserved tolerability

As already discussed, the incidence of adverse effects increases dose-dependently during calcium entry blockade.¹² This is especially true for dihydropyridines as these agents are potent vasodilators. An important feature of both ACE-inhibitors and ARBs is their capacity to preserve, or even improve, the safety profile of CAs. For instance, the reflex increase in heart rate possibly occurring during treatment with dihydropyridines, which might manifest itself by palpitations, is prevented by concomitant blockade of the RAS.⁴⁹ One might also expect reductions in CA-associated constipation (verapamil) and flushing and headache (dihydropyridines), because lower doses of the CAs are generally needed when these vasodilators are used in combination with a blocker of the RAS.^{34,36,40}

A common and troublesome side-effect of CAs is ankle oedema.⁵⁰ Mechanistically, the development of lower extremity oedema during calcium entry blockade is not due to fluid retention as CAs have a natriuretic activity, but involves a rise in intracapillary pressure (as a consequence of a selective diminution of the precapillary arteriolar tone), with an ensuing net leak of fluid into the interstitium. Notably, blockers of the RAS reduce the lower extremity oedema caused by CAs,^{34,40,51} most likely because of their ability to dilate not only the arterial vascular bed, but also the venous capacitance vessels. This is illustrated by the results

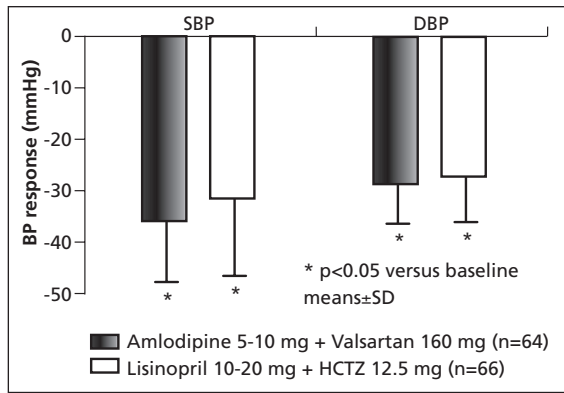


Figure 3
BP response to a 6-week treatment with a combination of amlodipine and valsartan, or lisinopril and HCTZ (from ref. 48). BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure; HCTZ = hydrochlorothiazide.

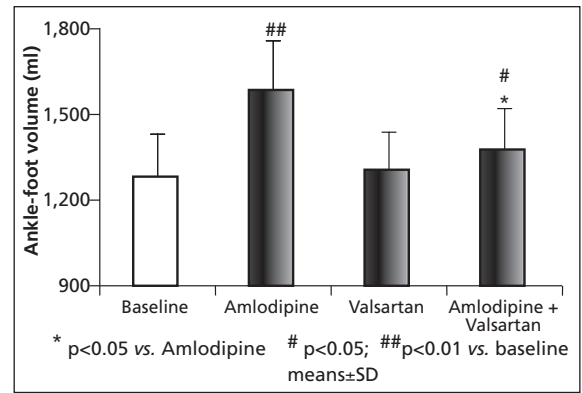


Figure 4
Ankle-foot volume measured in hypertensive patients before (baseline) and after six weeks of treatment with amlodipine, valsartan, and the combination of amlodipine and valsartan. The different treatments were given according to a cross-over design (from ref. 52).

of a study in which the ankle foot volume was determined by the principle of water displacement in 130 hypertensive patients randomised to a 6-week treatment, according to a cross-over design, with either an ARB (valsartan 160 mg/day), a CA (amlodipine 10 mg/day), or a combination of the two (valsartan 160 mg/day + amlodipine 10 mg/day).⁵² The BP response was significantly greater with the combination (-22.9/-16.8 mmHg) than with the monotherapies (valsartan: -14.5/-10.2 mmHg, amlodipine: -16.9/-12.9 mmHg). Figure 4 depicts the ankle foot volume measured at the beginning and again at the end of each treatment period. This volume was significantly smaller during the co-administration of the ARB and the CA compared with the CA monotherapy.

Improved adherence to therapy

There are now available a number of fixed-dose combinations containing a blocker of the RAS and a CA. Such preparations are likely to normalise BP in most hypertensive patients, but without altering adversely their quality of life. Because of their convenience for the patients, fixed-dose combinations are therefore expected to facilitate long-term adherence to antihypertensive therapy.⁵³ This hypothesis has been verified by analysing retrospectively the adherence to a once-daily, fixed-dose combination (amlodipine + benazepril), given for a minimum of 12 months, compared with a drug regimen consisting of an ACE-inhibitor and a dihydropyridine CA prescribed separately.⁵⁴ The medication adherence, defined as the medication possession ratio, was significantly ($p < 0.001$) better in the group of patients ($n = 2,754$) receiving the fixed-dose combination (80.8%) than in those ($n = 2,978$) taking an ACE-inhibitor and a CA as separate components (73.8%). Interestingly, this better adherence with therapy was associated with a significantly lower annual cost of cardiovascular-related care per patient.

Metabolic effects

Hypertension is frequently associated with other cardiovascular risk factors, in particular dyslipidaemia, insulin resistance and type 2 diabetes, leading to a further increase in the overall cardiovascular risk. It appears therefore highly desirable to lower BP whenever possible with drugs devoid of adverse impact on lipid and glucose metabolism. Both CAs and blockers of the RAS are neutral with regard to low-density lipoprotein- and high-density lipoprotein-cholesterol levels.^{55,56} CAs are also neutral in terms of glucose homeostasis,⁵⁵ whereas blockers of the RAS have the advantage of improving insulin sensitivity and of preventing or delaying the occurrence of new onset diabetes.^{57,58} Notably, in patients with metabolic syndrome, the combination of an ACE-inhibitor (trandolapril) and a CA (verapamil) has been shown to significantly reduce, over a 12-month period, the risk of new onset diabetes (incidence=11.0%) compared with a combination of an ACE-inhibitor (lisinopril) and HCTZ, a diuretic known to impair insulin sensitivity (incidence=26.6%).⁵⁹ Thus, the association of a CA with an ACE-inhibitor or an ARB is particularly appealing, not only to lower BP, but also to prevent the deterioration of metabolic indices, and even to ameliorate them.

Combined therapy with a calcium antagonist and a blocker of the RAS: what has been learned from randomised morbidity-mortality trials?

The International Verapamil-Trandolapril Study (INVEST)

A total of 22,576 hypertensive patients with documented coronary heart disease, aged 50 years or older, were randomly assigned to either a CA-based regimen (verapamil sustained release, 240 mg/day) or a β -blocker-based regimen (atenolol, 50 mg/day).⁹ To achieve the

BP goals (< 140/90 mmHg, or < 130/85 mmHg in the presence of diabetes or renal impairment) the CA could be combined with trandolapril, 2 mg (using a fixed-dose combination containing verapamil, 180 mg, and trandolapril, 2 mg), and the β -blocker with HCTZ, 25 mg/day. There was the possibility to double the doses if needed, and then to add HCTZ, 25 mg/day, in the CA group, or trandolapril, 2 mg/day, in the β -blocker group if still required. After 2 years, the target BPs were reached in 71.7% and 70.1% of patients on the verapamil- and atenolol-based strategy, respectively. At 24 months, in the CA group, 81.5% of patients were taking verapamil, 62.9% trandolapril, and 43.7% HCTZ. In the β -blocker group, 77.5% received atenolol, 60.3% HCTZ, and 52.4% trandolapril. No significant difference was noted in cardiovascular outcomes between the two treatment strategies. This was also true when considering only the 6,400 patients with diabetes at entry in the trial.⁶⁰ Interestingly, according to a recent analysis, the better the BP control during the trial, the better the protective effect of the antihypertensive treatment.⁶¹ Another relevant finding was that treatment with the verapamil-trandolapril combination attenuated the risk for developing diabetes compared with the co-administration of atenolol and HCTZ.⁶²

The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA)

This prospective trial included 19,257 hypertensive patients, aged 40–79 years, who had at least three other cardiovascular risk factors in addition to high BP.⁶³ These patients were randomly allocated to either amlodipine, 5–10 mg/day, or atenolol, 50–100 mg/day, with the aim to lower BP below 140/90 mmHg in the absence of diabetes, and below 130/90 mmHg in the presence of diabetes. To achieve these targets the second-line therapy consisted of perindopril, 4–8 mg/day, in the amlodipine-based regimen, and bendroflumethiazide, 1.25–2.5 mg/day, in the atenolol-based regimen. The mean follow-up was 5.5 years. BP values were lower throughout the trial by an average of 2.7/1.9 mmHg in the CA group versus the β -blocker group. At completion of the study 60% of all patients without diabetes had reached the BP targets, compared with 32% of those with diabetes. Most patients were taking at least two antihypertensive agents as only 15% and 9% of patients were still on monotherapy in the amlodipine and atenolol group, respectively. The main finding was a 23% reduction of fatal and non-fatal stroke ($p=0.0003$) in the amlodipine \pm perindopril treatment group compared to the atenolol \pm bendroflumethiazide group. This superiority of the CA-based regimen could be accounted for only partially by a greater BP-lowering effect.⁶³ Conceptually, different antihypertensive drugs, for a similar effect on brachial BP, might have a different impact on arterial stiffness and influence thereby the timing

and the magnitude of pressure wave reflections and, ultimately, central aortic pressure.⁶⁴ In fact, the amlodipine-based regimen appeared to be more effective than the atenolol-based regimen in reducing central BP, which possibly contributed to its better protective effect against stroke.⁶⁵ Finally, it is noteworthy that the incidence of new onset diabetes was reduced by 30% ($p<0.0001$) in the amlodipine- versus the atenolol-treatment strategy.

The Avoiding Cardiovascular events through COMBination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial.

The ACCOMPLISH trial is still ongoing.⁶⁶ It consists of a randomised, double-blind trial aimed at comparing the effects of two types of antihypertensive drug combinations on cardiovascular outcome of patients with high-risk hypertension. A total of 10,704 patients aged > 60 years were allocated to a single-tablet combination containing either amlodipine and benazepril (5/40 mg) or benazepril and HCTZ (40/12.5 mg). The doses could be increased, and other drugs be added (excluding ACE-inhibitors and CAs) in order to lower BP below 140/90 mmHg, or even further in patients with diabetes or renal insufficiency. At the end of the treatment adjustment period (month 6), the overall BP control rate was impressive, at 73%, considering that only 37% of participants had their BP < 140/90 mmHg at entry, even if virtually all were at that time on antihypertensive treatment (97%), and despite the fact that the majority (74%) were on two or more drugs.⁶⁷ Notably, only 26% of patients were receiving add-on treatment at month six.

Conclusions

The co-administration of two antihypertensive agents with different mechanisms of action is required in most hypertensive patients in order to normalise both SBP and DBP. CAs, ACE-inhibitors and ARBs are widely used today as first-line antihypertensive agents. A number of controlled interventional trials have demonstrated their efficacy in preventing the vascular, cardiac and renal complications of high BP.⁴⁵ CAs and blockers of the RAS are substantially more effective in lowering BP when combined than when given as monotherapy and without deterioration of the patient's quality of life. The use of fixed-dose combinations is currently gaining increasing acceptance and is even considered as a valuable first-line option according to the latest guidelines.^{14,15} Fixed-dose combinations allow a rapid and sustained BP control, and have been shown to improve long-term adherence with antihypertensive therapy. The availability of fixed-dose combinations containing a CA and an ACE-inhibitor or an ARB is expected therefore to facilitate the management of hypertension in the community and to have a positive impact on cardiovascular and renal outcome.

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