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Combining renin-angiotensin-aldosterone system blockade with diuretic therapy for treatment of hypertension

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Abstract

The rationale for using angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) in combination with thiazide diuretic therapy has centred formerly around antihypertensive synergy and counter-balancing adverse metabolic effects, particularly on potassium homeostasis. However, two recent landmark clinical trials that included high-risk hypertensive patients have now provided an evidence base for this form of combination therapy by demonstrating the efficacy of perindopril/indapamide and losartan/hydrochlorothiazide in reducing vascular morbidity and mortality, a proportion of the benefit being unaccounted for by blood pressure reduction alone. Several unresolved issues remain concerning class effects versus specific drug effects, optimal dosing, potential differences in efficacy between ACE-I and ARBs, whether elderly mild hypertensives benefit from this form of combination therapy, and the possibility that the optimal regimen may be a triple combination of ACE-I, ARB and thiazide diuretic. These issues will be resolved by ongoing and future major endpoint trials in hypertension.

Introduction

Exactly a quarter of a century ago, Ondetti and co-workers completed their development of the first angiotensin-converting enzyme (ACE) inhibitor, captopril, heralding a new therapeutic era in cardiovascular medicine.¹ The importance of neuro-humoral systems, and of the renin-angiotensin-aldosterone system (RAAS) in particular, as a target for drug therapy, was underscored by a series of landmark placebo-controlled trials that demonstrated the mortality and morbidity benefits of ACE inhibition in all functional grades of chronic heart failure (CHF).² Because of the greater difficulty in conducting major endpoint trials in the field of hypertension, comparable data have been slower to accumulate in this arena. However, the situation has now changed with the recent publication of two multicentre trials, the LIFE³ and PROGRESS⁴ studies, that included high-risk hypertensive patients and used as active treatment, respectively, the angiotensin II (Ang II) AT₁-receptor blocker (ARB), losartan, and the ACE inhibitor (ACE-I), perindopril. In each study, for optimal blood pressure (BP)-lowering, antagonism of the RAAS was frequently combined with diuretic

therapy. Accordingly, this particular form of combination therapy is the subject of the present review, which will focus on: 1) the theoretical and practical basis for combining a drug that modulates the RAAS with a diuretic for treatment of hypertension; 2) the new evidence provided by the LIFE and PROGRESS trials regarding this combination regimen; and, 3) the unresolved questions that remain.

Rationale for combination therapy – general

Several key principles underlie the use of combination antihypertensive therapy.

- A fundamental tenet in the treatment of hypertension, that the greater the reduction in BP (at least down to a certain level), the better the outcome, was confirmed by the Hypertension Optimal Treatment (HOT) trial, which found that the ideal diastolic BP (DBP) to minimise cardiovascular events was 82.6 mmHg, and to reduce cardiovascular mortality was 86.5 mmHg.⁵ Combination drug therapy gives additive or synergistic antihypertensive responses, and such effects are frequently required to achieve target BP levels. Thus, among patients in the HOT trial for whom the DBP target was 85 mmHg, 68% of patients required combination therapy, rising to 74% for patients in whom the DBP target was 80 mmHg.⁶
- It has long been appreciated that hypertension is a multifactorial condition, being a complex interplay of genetic and environmental factors that results in multiple patient phenotypes.⁷ This heterogeneity means that hypertensive patients differ markedly, and unpredictably, in their responsiveness to different therapeutic agents, and combination therapy increases the likelihood of an optimal BP-lowering response.⁸
- Side-effects resulting from antihypertensive therapy are often dose-related, and are therefore more likely to occur with a strategy of simply increasing the dose of a single drug to achieve greater BP-lowering. The judicious use of particular classes of drugs in combination not only avoids this, but one agent may also reverse disturbances of homeostasis resulting from the other.

Rationale for specifically combining RAAS antagonism and diuretic therapy

ACE-I and ARBs exert their antihypertensive responses via multiple diverse mechanisms, including effects on circulating Ang II, the tissue RAAS, the sympathetic nervous system, the renal vasculature and nephron, and, in the case of ACE-I, but not ARBs, effects on the kinin system.⁹ The principal mechanism by which thiazide diuretics lower BP results from their natriuretic action, by inhibiting sodium reabsorption primarily in the distal renal tubule. Loop diuretics are infrequently used for their antihypertensive effects because the BP-lowering response to these agents is less predictable and the marked diuresis they promote is inconvenient. Also, their interactions with ACE-I, particularly captopril, are complex and remain incompletely understood.¹⁰

In general, monotherapy with ACE-I, ARBs or thiazides results in effective BP-lowering in 35–70% of patients, depending on dosage and definitions used.¹¹

A large number of studies have demonstrated that the antihypertensive efficacy of ACE-I (or ARBs) and thiazide diuretics in combination are significantly better than with each agent as monotherapy.^{12–16} Several mechanisms are important:

- In hypertensive patients with low circulating renin, notably black patients, the response to ACE-I monotherapy is sometimes poor,¹⁷ but both the antihypertensive response and effects in reducing/reversing left ventricular hypertrophy (LVH) are improved by combination therapy with ACE-I and thiazide diuretics.^{13,18}
- The BP-lowering capacity of thiazide diuretic monotherapy is limited by reactive hyper-reninaemia. By offsetting this secondary activation of the RAAS, and by potentiating natriuretic effects of thiazides, the addition of ACE-I/ARBs improve the antihypertensive response.¹¹
- Thiazide diuretics, particularly in higher doses, exert a counter-regulatory effect on potassium homeostasis, promoting potassium loss in the distal tubule. By attenuating Ang II-mediated aldosterone release, thereby shifting electrolyte balance towards potassium retention, ACE-I and ARBs redress this balance.¹¹
- Thiazide diuretics cause or exacerbate a number of adverse metabolic responses, including hyperuricaemia, hyperglycaemia and insulin resistance. These unwanted effects are offset by ACE inhibition.¹¹

Dosage

In achieving a significant BP-lowering response, adding a thiazide diuretic to standard dose ACE-I/ARB has been shown to be more efficacious than increasing the dose of the ACE-I/ARB.^{14,15} However, high doses of an ACE-I or ARB may be necessary for optimal effects on the tissue RAAS. This will be discussed further below.

Although there is a small body of literature suggesting that high-dose thiazide diuretic therapy leads to significantly greater BP-lowering than low

Table 1 Perindopril/Indapamide combination therapy: effects on diastolic blood pressure and serum potassium.

	Reduction in diastolic blood pressure (mmHg)	% of patients with serum K ⁺ <3.4 mmol/L
Placebo (n=77)	-5.5	0
Perindopril 4 mg + Indapamide 1.5 mg (n = 78)	-13*	2.6**
Perindopril 4 mg + Indapamide 2.5 mg (n = 71)	-13.5*	16.9*

* p<0.001 vs. placebo
** p = not significant vs. placebo

doses,¹⁹ it is generally accepted that the antihypertensive dose-response curve to thiazide diuretics, either as monotherapy or in combination, is flat, but that adverse effects, including hypokalaemia, occur more frequently with higher doses.

Chrysant *et al.*, in a multicentre trial of 505 mild-to-moderate hypertensive patients, found that low-dose hydrochlorothiazide (12.5 mg) decreased BP as effectively as a higher dose (25 mg) when added to lisinopril, 10 mg.²⁰ Similar findings have been observed for hydrochlorothiazide, 12.5 mg or 25 mg, in combination with candesartan (2–16 mg).¹⁵

Data concerning the newly available combination preparation of perindopril plus indapamide also illustrate this well. Although the dose of indapamide in the PROGRESS trial, discussed below, was 2.5 mg, the findings shown in Table 1 have led to Coversyl PlusTM being introduced into clinical practice as a combination of perindopril, 4 mg, with a lower dose (1.25 mg) of indapamide.

Two practical points of note are first, that thiazide diuretic therapy, alone or in combination, may take 6–12 weeks to become fully effective,²¹ and secondly, that a low-sodium diet can improve the antihypertensive efficacy of an ACE-I/ARB in combination with thiazide diuretic therapy.²²

Disadvantages of combination therapy with thiazide and ACE-I or ARB

Compliance

Poor compliance with prescribed drug therapy is a problem shared by all antihypertensive treatment combinations. This can be minimised by use of fixed-dose combination preparations, such as the perindopril/indapamide preparation described above.

First-dose hypotension

This is more typically associated with the initiation of ACE-I/ARB in CHF, but can also occur in the setting of hypertension, particularly when there is significant secondary activation of the RAAS. It can be minimised by avoiding diuretic-mediated intravascular depletion.

Renal dysfunction

It is well recognised that renal hypoperfusion and azotaemia may result from initiating either ACE-I or ARB in the presence of occult bilateral renal artery stenosis, which leads to a precipitous drop in glomerular filtration pressure. However, arguably there is a more frequent mechanism accounting for intraglomerular hypotension and renal dysfunction. This is simultaneous inhibition of both Ang II-mediated efferent arteriolar vasoconstriction and prostaglandin-mediated renal afferent arteriolar vasodilatation due to concomitant therapy with ACE-I (or ARB) and non-steroidal anti-inflammatory drugs, in the context of RAAS activation resulting from diuretic-mediated hypovolaemia.²³ This is a particular problem to be vigilant for and to avoid in elderly patients.

Landmark trials of combining RAAS modulation with diuretics in hypertension

Previous multicentre trials in hypertension have suggested that newer antihypertensive agents, including ACE-I, are not superior in terms of effects on either BP or clinical endpoints to long-established treatments, such as thiazides or β -blockers.^{24,25} Thus, thiazide diuretics have often been used as first-line agents, and ACE-I or ARBs as the 'add-in' agents. However, this strategy has now been challenged by the findings of the LIFE and PROGRESS trials, supplemented by the favourable results of many other recent clinical trials of ACE inhibition or AT₁-receptor blockade in the setting of ischaemic heart disease,²⁶ chronic renal disease,^{27,28} and other conditions, notably diabetes mellitus,^{29,30} that frequently coexist with hypertension (Table 2). Collectively, this large body of evidence now indicates that modulation of the RAAS should increasingly be considered as a first-line component of antihypertensive drug regimens.

The LIFE study³

This recently published trial was a double-masked randomised evaluation of losartan, 50–100 mg, versus atenolol, 50–100 mg, in 9,193 high-risk hypertensive patients (DBP 95–115 mmHg, systolic BP (SBP) 160–200 mmHg, with ECG voltage criteria for left ventricular hypertrophy [LVH]). To attain target BP in either group, hydrochlorothiazide, 12.5 mg, with or without additional antihypertensive drugs, was added to first-line therapy in approximately 60% of patients. In either group, the target DBP of 90 mmHg was achieved in 89% of patients, and the target SBP of 140 mmHg in just under half the patients. There was no significant difference in mean BP attained in either group (102.2 mmHg *vs.* 102.4 mmHg).

Over a mean follow-up interval of 4.8 years, a 13% relative risk reduction in the primary composite endpoint of cardiovascular mortality, stroke and non-fatal myocardial infarction (MI) was observed in the losartan \pm hydrochlorothiazide group, as compared with the atenolol \pm hydrochlorothiazide group ($p=0.021$), accounted for primarily by a 25% reduction in fatal or non-fatal

stroke ($p=0.001$). This marks the first time a difference of this magnitude has been observed between two active treatment regimens in a hypertension trial. The reduction in the primary endpoint in diabetic patients was even more marked (24%).³¹ The measured reduction in LVH was also more prominent in the losartan-treated group ($p<0.0001$).

In the STOP trial,³² β -blockers, with or without thiazide diuretics, were compared with placebo. In keeping with the recognised benefits of β -blockers in primary and secondary prevention of ischaemic heart disease, this class of drug yielded a 50% reduction of the composite endpoint of cardiovascular morbidity and mortality in STOP, with an event rate similar to that seen in the atenolol-treated group in LIFE. This indicates that the 13% reduction of the primary endpoint by losartan in LIFE is an additional benefit, over and above the established benefits of β -blockade.

Notably, in addition to the superior efficacy of the losartan \pm hydrochlorothiazide versus the atenolol \pm hydrochlorothiazide combination, discontinuation of treatment as a result of drug-related adverse effects was also significantly less common in the former group ($p<0.0001$), indicating the greater tolerability of the losartan \pm hydrochlorothiazide combination.

The PROGRESS study⁴

This study evaluated 6105 patients with a history of stroke or transient ischaemic attack within the preceding five years, approximately 50% of whom were hypertensive (DBP ≥ 90 mmHg and/or SBP ≥ 160 mmHg). In addition to standard antihypertensive therapy, patients were treated with either placebo, or additional active treatment with perindopril, 4 mg and, on a flexible, discretionary basis, the thiazide-related indoline diuretic agent, indapamide, at a dose of 2.5 mg (administered to 58% of patients).

'Active' treatment decreased BP by a mean of 9/4 mmHg as compared with 'placebo', associated with a 28% reduction in recurrent stroke ($p<0.0001$). Similar reductions in stroke were observed in hypertensive and non-hypertensive subgroups. Combination therapy with perindopril and indapamide reduced BP by 12/5 mmHg and stroke risk by 43%, while perindopril alone reduced BP by 5/3 mmHg and produced no significant reduction in the risk of stroke. In this latter group, patient numbers were comparatively low and confidence intervals wide, raising the possibility of a Type II error. However, the differences in therapeutic efficacy between combination and single drug therapy were consistent with the differences in BP reduction achieved and the direct evidence from randomised trials in other groups of patients that more intensive BP-lowering confers greater reduction in risk of stroke. However, the reduction in cardiovascular mortality with the perindopril-based regimen was twice as great as that expected by BP-lowering alone, in accordance with the benefits of the ACE-I, ramipril, in the secondary prevention of ischaemic heart disease that were observed in the HOPE trial.^{26,30}

In terms of tolerability, there was a slight but

Table 2 Glossary of multicentre clinical trials referred to in this review.

Study acronym	Expanded title	Reference no. (year)
ABCD	Appropriate Blood Pressure Control in Diabetes	29 (1998)
ABCD-2V	Appropriate Blood Pressure Control in Diabetes Part 2 with Valsartan	33 (ongoing)
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial	47 (ongoing)
EUROPA	European trial on reduction of cardiac events with Perindopril in stable coronary Artery disease	37 (ongoing)
HOPE	Heart Outcomes Prevention Evaluation	26,30 (2000)
HOT	Hypertension Optimal Treatment	5 (1998)
IDNT	Irbesartan Diabetic Nephropathy Trial	27 (2001)
LIFE*	Losartan Intervention For Endpoint reduction in hypertension	3 (2002)
MRC	Medical Research Council trial of treatment of hypertension in older adults	39 (1992)
ONTARGET	ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial	38 (ongoing)
PEACE	Prevention of Events with Angiotensin Converting Enzyme inhibition	36 (ongoing)
PROGRESS*	Perindopril Protection Against Recurrent Stroke Study	4 (2001)
RENAAL*	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan	28 (2001)
SCOPE*	Study on COgnition and Prognosis in the Elderly	44 (ongoing)
SHEP	Systolic Hypertension in the Elderly Program	40 (1991)
STOP-Hypertension	Swedish Trial in Older Patients with Hypertension	32 (1991)
STOP-Hypertension 2	Swedish Trial in Old Patients with Hypertension-2	24 (1999)
Syst-Eur	Systolic Hypertension in Europe Trial	41 (1997)
VALUE*	Valsartan Antihypertensive Long-term Use Evaluation	34 (ongoing)

* denotes clinical trial providing evidence for combination therapy with ACE inhibitor or angiotensin receptor blocker and thiazide or related diuretic for treatment of hypertension.

significantly greater number of patients discontinuing study treatment in the 'active' versus 'placebo' group (23% *vs.* 21%, $p=0.02$), the difference accounted for by discontinuation for cough (2.2% *vs.* 0.4%) and for hypotension (2.1% *vs.* 0.9%).

Unresolved issues relating to combination therapy with ACE-I or ARB and thiazide diuretics

Both the LIFE and PROGRESS trials demonstrate the benefits of RAAS modulation in combination with a thiazide or related agent in improving vascular morbidity and mortality in patients with hypertension. However, these two trials, as with all important studies, raise a number of further questions:

- Were the findings in LIFE specific to a losartan-based regimen or are they applicable to all ARBs? Unlike other ARBs, losartan is uricosuric, a potentially favourable property in a combination regimen that includes a thiazide diuretic. However, it is improbable that this alone would result in additional efficacy of losartan over other ARBs. Nonetheless, there are significant pharmacokinetic differences between ARBs, and an intriguing question is whether the use of a long-acting agent such as telmisartan might result in even greater benefit.³³ The issue of 'class effect' will, to some extent, be clarified by the ongoing VALUE trial which compares, in 14,400 high-risk hypertensive subjects, the reduction in cardiovascular morbidity/mortality with valsartan 80–160 mg \pm hydrochlorothiazide 12.5 mg, *vs.* amlodipine 5–10 mg \pm hydrochlorothiazide 12.5 mg.³⁴

- Should combination therapy with thiazide diuretic and ACE-I or ARB routinely incorporate ACE-I/ARB in high dose, even if the BP target is attained at lower dose? A conventional strategy, as reflected in current British Hypertension Society guidelines,³⁵ is to prescribe a low-dose thiazide diuretic in combination with low-to-moderate doses of ACE-I/ARB, because this may afford the optimal balance between BP-lowering and side-effects. For example, in the LIFE study, the study treatment algorithm incorporated adding hydrochlorothiazide to losartan, 50 mg, before increasing the dose of losartan to 100 mg.³ However, it is becoming increasingly clear that the efficacy of RAAS modulation is not solely dependent on BP reduction; there is additional benefit over and above any effect on BP control, as seen in LIFE and PROGRESS, and in other studies in the setting of vascular disease, notably the recent HOPE trial.^{26,30} Further confirmation of this is awaited from other primary/secondary prevention (PEACE,³⁶ EUROPA,³⁷ ONTARGET³⁸) and hypertension (VALUE,³⁴ ABCD-2V³³) trials of ACE inhibition and/or AT₁-receptor antagonism. The 'additional' efficacy of these two drug classes is thought to be attributable to blockade of the vascular tissue-based RAAS, which is achieved optimally by high-dose ACE inhibition/AT₁-receptor blockade. In LIFE, only 50% of patients in the losartan group were treated with the higher dose (100 mg), and although the results of the study were impressive, events in the losartan cohort were still frequent. The question is raised as to whether these events could be

5. the intriguing question of whether the optimal regimen for both BP-lowering and tissue-based vascular protection is a triple combination of ACE-I, ARB and thiazide diuretic.

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