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ORIGINAL ARTICLE

Verapamil SR/trandolapril combination therapy for the elderly hypertensive patient

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A total of 254 elderly hypertensive patients (71 men and 183 women aged between 63 and 92 years, diastolic blood pressure (DBP) 95–115 mm Hg inclusive) were treated with the fixed combination of verapamil SR/trandolapril following a 4-week single-blind placebo run-in period. Treatment was started with a response dependent 3-step dose titration period. All patients were initiated at dose step 1 (verapamil SR/trandolapril 120/0.5 mg o.d.) and if not normalised (DBP $<$90 mm Hg) titrated at 4-weekly intervals over dose step 2 (verapamil SR/trandolapril 180/1 mg o.d.) to dose step 3 (verapamil SR/trandolapril 180/2 mg o.d.) during the first 12 weeks. After 3 months of treatment all patients not normalised were excluded from further participation in the study. The total duration of the treatment period was 6 months. Routine safety investigations were performed prior, during and on completion of the treatment period. Verapamil SR/trandolapril was highly effective in reducing blood pressure. At individual last visit during active treatment (also taking the non-responders into account), the mean reduction in SBP/DBP was 21.9/17.1 mm Hg (95% CI 19.8–24.1/16.1–18.1 mm Hg), with most of this reduction occurring during the first 3 months of treatment. After 6 months, 81.9% of the patients enrolled showed normalisation of DBP ($<$90 mm Hg) and 85% were responders (normalisation and/or reduction in DBP by at least 10 mm Hg). Normalisation and responder rates appeared to be comparable when stratified by age subgroups (63–69, 70–79 and $\geqslant$80 years) and were all greater than 80%. Verapamil SR/trandolapril was very well tolerated and there was no evidence of any clinically relevant changes in routine laboratory safety variables or resting ECG. In conclusion, the fixed dose combination of verapamil SR/trandolapril is an effective and safe alternative treatment for the elderly hypertensive patient.

Keywords: verapamil/trandolapril combination therapy; elderly; essential hypertension; efficacy; tolerability

Introduction

Until recently, studies have focused on young and middle-aged hypertensive patients, due to a general reluctance amongst physicians for pharmacological intervention in elderly hypertensives. However, over the past decade, several major international, prospective, randomised studies[1,2] consisting of therapies such as beta-blockers and diuretics either alone or in combination, have demonstrated a reduction in cardiovascular mortality and morbidity with reduction in arterial blood pressure (BP). Cost–benefit analyses provided additional support for the importance of pharmacological intervention in elderly hypertensives.[3] However, as elderly patients are more likely to have end-organ damage, as evidenced by renal, hepatic or metabolic dysfunction, and concomitant cardiovascular disease such as coronary artery disease, left ventricular dysfunction, and diabetes,[4] alternative therapies such as angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists, may be more appropriate in management. Both ACE inhibitors and calcium antagonists offer distinct advantages over the use of diuretics and beta-blockers in the elderly: an excellent safety profile and a lack of undesirable metabolic,[5] renoprotective,[6] and cardioprotective effects.[7–11] Thus the combination of a calcium antagonist and an ACE inhibitor may prove particularly useful in the elderly hypertensive.

Verapamil SR (sustained release) is a highly effective and safe calcium antagonist which is recommended as first-line antihypertensive therapy in national and international guidelines.[4] Trandolapril is a long-acting, non-sulphydryl ACE inhibitor which has been shown to be highly effective and safe in mild to moderate hypertension.[12] The fixed combination of these agents (verapamil SR 180 mg and trandolapril 1 or 2 mg) has been shown to be highly effective in mild to moderate hypertension, with the magnitude of the BP reduction significantly superior to that with either monosubstance.[13] In addition, a fixed combination of lower doses of each monosubstance would be expected to minimise the

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potential risk of side effects. The aim of this study was to evaluate the efficacy and safety of verapamil SR/trandolapril combination therapy in various dosage combinations in elderly hypertensive patients.

Patients and methods

This was an open, non-comparative, multicentre study in elderly patients (≥65 years) with either newly diagnosed or unsuccessfully-treated stable mild to moderate hypertension (sitting diastolic BP (DBP) ≥95 and ≥115 mm Hg at the end of a 4-week placebo run-in period). Patients with malignant hypertension, congestive heart failure, severe bradycardia (<50 beats/minute), second and third-degree AV block, sick sinus syndrome, atrial fibrillation/flutter, cardiovascular disease requiring treatment, renal artery stenosis or renal transplantation, serum creatinine >1.8 mg/dl or >160 μmol/l, aortic stenosis, arterial occlusive disease (Fontaine stage II–IV), or a history of recent myocardial infarction (within 3 months), angioneurotic oedema, stroke, known hypersensitivity or intolerance to calcium antagonists or ACE inhibitors, orthostatic symptoms (decrease of systolic BP (SBP) >15 mm Hg), severe concomitant disorders and cerebral and peripheral perfusion disorders, or any other contraindications for either monotherapy, were excluded. Concomitant antihypertensive medication was not permitted. The study was approved by the Ethics Committee of the Landesärztekammer Rheinland-Pfalz and was conducted in accordance with the Declaration of Helsinki (Hong Kong revision, 1989). All patients gave written informed consent prior to entry.

Study design

The study was divided into three periods: a 4-week single-blind placebo run-in period (patients previously treated with antihypertensive drugs were started with a 2-week wash-out period prior to enrolment into the placebo run-in period), a 6-month open treatment period starting with a 3-step response dependent dose titration period, and a 2-week single-blind placebo wash-out period. Patients were seen at weeks 3 and 4 of the placebo run-in period, at 4-week intervals during the treatment period, and at the end of the 2-week placebo washout period (end of study).

BP and pulse rate were measured before the daily dose was taken on the morning of each visit (ie, approximately 24 h post-dose). BP was measured in the same arm throughout the study. Sitting BP was measured three times at 2-min intervals after the patient had rested for 10 min. All decisions about admission to the study and changes in treatment were based on the average of the three recordings. A single BP measurement was then made after the patient had stood for 2 min. SBP and DBP were taken as phase I and phase V respectively of the Korotkoff sounds in accordance with the guidelines of the Deutsche Liga zur Bekämpfung des hohen Blutdruckes. Radial pulse was measured over a 30-sec period.

The advice for lifestyle modifications was given at the discretion of the individual study physician. During the run-in period, all patients were treated with one placebo-capsule once-daily in the morning. At the end of the placebo run-in period inclusion/exclusion criteria were checked and in all eligible patients treatment was started. During the first 12 weeks of this period, the patients were titrated to their individual dose (dose step 1—verapamil SR/trandolapril 120/0.5 mg o.d.; dose step 2—verapamil SR/trandolapril 180/1 mg o.d.; dose step 3—verapamil SR/trandolapril 180/2 mg o.d.), in order to achieve a sitting DBP of less than 90 mm Hg. Treatment was initiated at dose step 1 and dosage was increased at 4-weekly intervals until satisfactory BP control was achieved. Dosage could be reduced if sitting DBP was less than 70 mm Hg on any visit, or less than 85 mm Hg on any two visits, during the titration period. Patients who did not respond to dose step 3 at the end of the 12-week titration period were subsequently withdrawn as non-responders. All other patients continued on treatment for a further 12 weeks. At the end of the 6-month treatment period patients completed a 2-week placebo wash-out period in order to confirm the treatment's effectiveness at lowering BP.

Physical examination including 12-lead resting ECG and routine laboratory parameters were performed at the start of the study (baselines), at the end of the treatment period and at the end of the 2-week washout period. In addition, routine laboratory parameters and 12-lead resting ECG were checked after 1 month on active treatment, and a 12-lead resting ECG were repeated after 3 months on active treatment. At each visit observed and spontaneously reported adverse events were recorded.

Patient's compliance was assessed by routine capsule counts on each visit and measurements of plasma concentrations of verapamil, trandolapril and trandolaprilat, the active metabolite of trandolapril after 3 and 6 months respectively. Trandolapril and trandolaprilat concentrations were determined by radioimmunoassay with specific antibodies as has been previously described.[14] Plasma concentrations of verapamil were determined by high performance liquid chromatography.[15]

Statistical analysis

The study was analysed in accordance with the intention-to-treat principal. All patients who received at least one dose of active treatment were included in the primary analyses. The primary efficacy criterion was normalisation of DBP, defined as a reduction in sitting DBP to less than 90 mm Hg. In addition, the reduction in sitting DBP and SBP relative to baseline (defined as the end of the placebo run-in period) and the overall BP response (defined as normalisation and/or reduction in DBP by at least 10 mm Hg) at 6 months, were determined.

As the study design may have biased the results (non-responders were titrated to the highest dose before withdrawal from the study), only descriptive analysis of the study results was undertaken. Mean values, standard deviations and two-sided 95% con-

fidence intervals (CI), or median values and the corresponding interquartile range, were calculated for DBP, SBP and pulse rate at each visit. In addition, the differences between baseline and month 6 as well as the difference between month 6 and the end of the wash-out period was calculated for SBP, DBP and pulse rate with 95% CI. The percentage of patients on each dose step showing normalisation and/or BP response at the end of the treatment period was calculated.

Safety data were analysed descriptively. The frequency and incidence of different adverse events, and patients withdrawn due to adverse events, were calculated.

Results

A total of 272 patients were enrolled into the placebo run-in period by 33 participating centres: 18 patients were excluded from entry into the active treatment period due to adverse events to placebo (4), intolerable increase of BP under placebo (3), ineligibility (4), or for other non-medical reasons mostly withdrawn of consent for further participation in the study (7). A total of 254 patients (including seven aged 63 and 64 years) were subsequently enrolled into the treatment period, details given in Table 1.

A total of 214 patients (84.3%) of the 254 patients in the study suffered from concurrent diseases. The most frequent concurrent diseases affected the musculoskeletal system (116 patients), the endocrine/immune systems (115 patients, mostly diabetes mellitus) and the circulatory system (82 patients). Concomitant medication (antihypertensives were not allowed) was used in 168 patients (66.1%). The number of concomitant medications per patient ranged from one to 10 drugs. One drug was given in 73 patients, two in 54 patients, three in 18 patients and four or more in 23.

Out of 254 patients, 23 patients had to be prematurely discontinued in the study due to adverse events. Two of these were during the 4-week single blind placebo run-in period and 21 patients were discontinued during the 6-month treatment period.

Table 1 Patient characteristics (n = 254)

Sex (M:F)	71:183
Age (yr)	72.9 (63–92)
63–69 (yr)	111
70–79 (yr)	97
>80 (yr)	46
Weight (kg)	73.6 (40–120)
Duration of hypertension (yr)	5.0 (0–32)
Severity of hypertension at baseline	
Mild (n)	178 (70%)
Moderate (n)	76 (30%)
Previous antihypertensive therapy (monotherapy: combination therapy) (n)	190 (129:61) 75%
Calcium antagonist (n)	69 (40:29)
ACE inhibitor (n)	59 (34:25)
Calcium antagonist + ACE inhibitor (n)	15

Values are mean (range) unless otherwise stated.
Severity of hypertension defined in terms of sitting DBP at the end of the placebo run-in period: mild <105 mm Hg; moderate ⩾105–114 mm Hg.

No patients were withdrawn during the final placebo wash-out period. Compliance with the treatment regimen (capsule count use of 80–120% of the estimated amount and detectable plasma levels of verapamil and trandolapril respectively) was generally good (over 90% at 3 months and 83% at 6 months).

Efficacy

BP remained stable with values of 170.9 ± 15.8/100.6 ± 6.5, 174.2 ± 15.1/102.6 ± 5.0 and 174.5 ± 16.1/102.5 ± 4.9 mm Hg at entry, after 2 weeks and at the end of the 4-week placebo run-in period, respectively. The body weight was 73.6 ± 12.4 kg at baseline and did not change during the treatment period (73.7 ± 12.5 kg after 6 months).

The combination of verapamil SR/trandolapril was highly effective in reducing BP. Over all doses, the mean reduction in sitting BP (SBP/DBP) at the last individual evaluable visit was 21.9/17.1 mm Hg (95% CI 19.8–24.1/16.1–18.1 mm Hg), with most of this response occurring during the first 3 months of treatment (mean reduction 21.4/15.8 mm Hg, 95% CI: 19.5–23.3/14.8–16.9 mm Hg). The BP increased during the 2-week placebo wash-out period, confirming the BP-lowering effect of treatment (Table 2). Changes in standing BP during the treatment and placebo wash-out period was comparable with those of sitting BP. There were no relevant changes in sitting or standing pulse rate during the three periods of the study (mean sitting pulse rate (beats/min): baseline 78.8 ± 8.8, mean change at end of treatment period –1.2 ±9.4; mean change from end of treatment to end of placebo wash-out period 1.8 ± 7.0).

At 6 months, 81.9% of patients showed normalisation of DBP and 85.0% were responders (Table 3). And nearly 75% of patients were on the two lower dose steps; 98 (38.6%) patients were on dose step 1 (verapamil SR/trandolapril 120/0.5 mg o.d.), 92 (36.2%) were at dose step 2 (verapamil SR/trandolapril 180/1 mg o.d.). Sixty-four (25.2%) patients were on the highest dose step (verapamil SR/trandolapril 180/2 mg o.d.). Hypertensives, who needed higher dose levels, had a higher initial mean BP. On the other hand, patients titrated to the highest dose level III responded with a smaller absolute BP decrease (15.8/13.7 mm Hg) as compared to hypertensives on the lower dose levels I and II (23.5/18.6 and 24.6/17.8 mm Hg, respectively; Table 2). Nine patients who did not achieve the target BP (<90 mm Hg diastolic) on dose step 3, were excluded from the study. Thus, as the study has been analysed using end-point data, data in the highest dose step group were biased by the inclusion of end-point data from non-responders. This accounts for the smaller reduction in BP in the highest dose step than in either of the two lower dose step treatment groups. Stratifying the efficacy data for age (63–69, 70–79, ⩾80 years) normalisation and responder rates for all three subgroups were comparable; all exceeded 80%.

Table 2 Mean sitting BP (mm Hg, ±s.d.) at baseline, during treatment with verapamil SR/trandolapril and at the end of the placebo wash-out period, for all doses and stratified for last administered dose

Assessment	*Verapamil SR/ trandolapril*		*Verapamil SR/ trandolapril*		*Verapamil SR/ trandolapril*		*Verapamil SR/ trandolapril*	
	Any (n = 254)		*120/0.5 mg (n = 98)*		*180/1 mg (n = 92)*		*180/2 mg (n = 64)*	
	n	*SBP DBP*	*n*	*SBP DBP*	*n*	*SBP DBP*	*n*	*SBP DBP*
Baseline	254	174.5 + 16.1 102.5 ± 4.9	98	172.9 + 15.8 102.0 ± 5.1	92	174.0 + 16.6 102.7 ± 4.4	64	177.9 + 15.6 103.1 ± 5.2
3 months	237	152.6 + 14.5 86.8 ± 6.4	89	148.6 + 13.6 83.5 ± 4.2	85	150.7 + 12.5 86.4 ± 4.4	63	161.0 + 15.0 92.1 ± 7.8
6 months	221	150.9 + 14.3 84.2 ± 5.0	84	148.5 + 12.9 82.9 ± 4.4	83	148.3 + 11.9 84.0 ± 4.1	54	158.9 + 16.9 86.6 ± 6.1
Last visit	251	152.7 + 17.0 85.5 ± 7.0	95	149.5 + 16.3 83.5 ± 4.6	92	149.3 + 12.5 84.8 ± 5.1	64	162.1 + 19.9 89.4 ± 10.2
Δ (95% CI)	251	−21.9(−24.1 to −19.8) −17.1 (−18.1 to −16.1)	95	−23.5(−26.8 to −20.2) −18.6(−19.9 to −17.3)	92	−24.6(−27.9 to −21.4) −17.8(−19.3 to −16.4)	64	−15.8(−20.8 to −10.7) −13.7(−16.4 to −11.0)
Wash-out	218	168.1 + 15.6 96.5 ± 5.7	84	168.5 + 15.2 96.6 ± 5.8	82	165.2 + 16.3 95.2 ± 4.9	52	172.1 + 14.5 98.4 ± 6.4

Δ = Decrease in BP defined as the mean change in SBP/DBP from baseline (end of placebo run-in period) to the last visit during the treatment period, with 95% confidence intervals (CI).

Table 3 Normalisation of BP and overall response (number of patients/total, %) after 3 and 6 months on active treatment, stratified according to the severity of hypertension at baseline

Dosage	*All patients (n = 254)*			*Mild hypertensives (n = 178)*			*Moderate hypertensives (n = 76)*		
	3 months	*6 months*	*Last visit*[a]	*3 months*	*6 months*	*Last visit*[a]	*3 months*	*6 months*	*Last visit*
Normalisation									
120/0.5 mg	85/104	82/84	90/98	59/71	58/59	65/71	26/33	24/25	25/27
180/1.0 mg	72/94	81/83	84/91	51/66	58/60	61/65	21/28	23/23	23/26
180/2.0 mg	24/39	45/54	45/62	16/26	30/34	30/39	8/13	15/20	15/23
All doses	181(71.3)	208(81.9)	219(86.2)	126(70.8)	146(82.0)	156(87.6)	55(72.4)	62(81.6)	63(82.9)
Overall response									
120/0.5 mg	94/104	83/84	95/98	63/71	58/59	68/71	31/33	25/25	27/27
180/1.0 mg	77/94	81/83	87/91	53/66	58/60	62/65	24/28	23/23	25/26
180/2.0 mg	29/39	52/54	54/62	16/26	33/34	33/39	13/13	19/20	21/23
All doses	200(78.7)	216(85.0)	236(92.9)	132(74.2)	149(83.7)	163(91.6)	68(89.5)	67(88.2)	73(96.1)

Normalisation of BP defined as a sitting DBP <90 mm Hg.
Overall BP response defined as normalisation of BP and/or a reduction in sitting DBP of at least 10 mm Hg.
Percentages calculated from the total number of patients per group or subgroup.
Last visit defined as the last patient evaluation on active study medication; [a]data missing for three patients with mild hypertension.

Tolerability and safety

One hundred and two patients reported 178 adverse events; 20 adverse events were considered by investigators to be treatment-related. In 41 of the adverse events a relationship was questionable and 105 adverse events were evaluated unrelated. Twelve adverse events were not assessed for relation to study medication. The profile of the adverse events reported are consistent with the monosubstances. The most commonly reported treatment-related adverse events were first-degree AV-block (six patients), headache (nine patients—one of these also had increased cough), vertigo (11 patients), cough or increase of cough (nine patients) and rash (four patients). All six patients with the first-degree AV-block continued in the study and there was no evidence of development of second or third-degree AV-block in any patient. None of the patients complained about clinically relevant orthostatic reactions during the treatment period. Most events were of mild to moderate severity and self-limiting.

Twenty-one patients were withdrawn due to adverse events during the treatment period. Fifteen of 21 were of non-serious degree and due to abdominal pain and other intestinal complaints (four patients), cough (3), chest pain (2), headache (2), hypertension (2), palpitation (1) and hot flushes (1). Six patients developed serious adverse events (hospitalisation due to joint disorder, acute deterioration of kidney functions, rash, hypertensive crisis and cerebral ischaemia, worsening of known bladder neoplasm and vertigo). However, only eight out of these 21 adverse events were considered by the

study physicians as causally related to the study drugs and only one of these were serious (female patient who developed rash covering the whole body 2 weeks after starting treatment with verapamil SR/trandolapril 120/0.5).

During the treatment period 82 of 178 adverse events (46.1%) occurred first at the lowest dose (verapamil SR 120 mg/trandolapril 0.5 mg); at the intermediate dose (verapamil SR 180 mg/trandolapril 1 mg) there were 73 adverse events (41.0%) which occurred for the first time and 23 (12.9%) at the highest dose group (verapamil SR 180 mg/trandolapril 2 mg). The different duration of treatment and the study design (dose titration, evaluation of only the first appearance of an adverse event) have to be considered when assessing the adverse events in the three dosages.

There were no consistent clinically relevant trends for changes in laboratory safety variables. One patient, who unfortunately continued her previous antihypertensive treatment (prazosin, diuretic, calcium antagonist, aldosterone antagonist) developed acute renal failure with serum creatinine 2.7 mg/dl and hyperkalaemia 7.1 (mol/l). The patient left the hospital with serum creatinine 1.32 mg/dl. Only one out of 13 patients with initial serum creatinine above normal increased by $\geqslant$0.3 mg/dl (ie, 0.4 mg/dl), whereas four out of 251 patients with normal values increased by 1.8, 0.65 and 0.3 (two patients) mg/dl during the study.

Discussion

In our study, the mean BP remained stable during the 4-week placebo period, thus excluding a major placebo effect during the run-in and the subsequent treatment period. During the treatment period BP was decreased from 174.5/102.5 mm Hg to 152.6/86.8 mm Hg, ie, by 21.9/17.1 mm Hg. In the 218 patients who entered the 2-week placebo washout period, the mean BP rose from 152.7/85.5 mm Hg to 168.1/96.5 mm Hg, ie, by 15.4/11.0 mm Hg. Thus, the BP reduction related to active treatment lies between 21.9 and 15.4 mm Hg systolic and 17.1 and 11.0 mm Hg diastolic, respectively. Normalisation of DBP ($<$90 mm Hg) was achieved in 81.9% of patients at the end of 6 months' treatment, and 85% were responders ($<$90 mm Hg and/or reduction of at least 10 mm Hg). Treatment response was not influenced by age range (normalisation rates were greater than 80% in each age subgroup). In other studies,[16–18] the fixed combination of verapamil SR/trandolapril has been shown to be significantly more effective than either monocomponent administered alone.

The importance of studies in the elderly has been pointed out many times and lately by Bugeja[19] and colleagues. Those aged over 65 comprise 14% of the population in most industrialised countries, yet they consume a third of all drugs. Ample evidence indicates that, even in healthy elderly people, aging impairs the way the body handles drugs. In ill elderly people those changes can be exaggerated considerably.[20] They have co-existing medical problems — in our study over 84% suffered concurrent diseases — for which they are likely to be taking other potentially interacting drugs. In the middle of the trial they are also more likely to suffer an infarct of the heart or brain or simply to die, thus they are not 'ideal' subjects for drug development process. Not surprisingly, therefore, trial designers are often reluctant to enrol many truly elderly patients. Questions remain whether such studies should be performed under premarketing testing or should it be postmarketing process, as in our study. However, the possibilities remain to evaluate the efficacy and safety (toxicity) with age-related differences, particularly unexpected differences may emerge in side effects when a drug is used routinely by large numbers, eg, hypertensive elderly treated with thiazide diuretics and risk of starting treatment for gout was significantly increased for thiazide doses of 25 mg/day.[21]

A cumulative percentage of withdrawals due to adverse events were observed in the MRC-trial in 17.1% of men and 12.8% of women on the diuretic bendrofluazide and in 15.5% and 18.0% on the beta-blocker propranolol during 5 years, respectively, ie, on average approximately 3.2% per year.[22] Similar rates between 2.9% and 4.5% per year were reported in other trials lasting between 2.1 to 7 (mean 4.7) years involving younger as well as elderly hypertensive patients.[2] However, as commonly observed, most withdrawals occur early in the trial. In the MRC trial, the rate during the first 6 months was approximately 6% to 7%. In the present trial only eight (3.2%) patients were withdrawn due to drug-related adverse reactions. Thus combination of verapamil SR/trandolapril was very well tolerated. The profile of side effects was consistent with the profile of adverse effects of each monosubstance. There was no evidence of any increase in any type of adverse effect in combination. In particular, the incidence of cough (3.5%), a well known side effect with ACE inhibitor therapy, was comparable with that reported in other studies with trandolapril[12,23] and other ACE inhibitors.[24,25] There was no evidence of any clinically relevant deterioration in renal function on verapamil SR/trandolapril combination therapy.

The single tablet formation of the two drugs (trade names Tarka®, Knoll Ag, Ludwigshafen; Ocadrik®, Udramil® and Ziaxel®, Hoechst Marion Roussel, Bad Soden, Germany), the first fixed combination of a calcium antagonist with an ACE inhibitor, is already marketed in the European Community. According to traditional concepts the use of fixed combinations is judged with reservations. However, the inherent advantage of combination therapy of any kind is the improvement of BP control and the reduction of adverse effects by neutralisation of counterregulatory mechanisms and through lower dosage requirements of the components.[26,27] Furthermore, compliance to therapy is improved and cost of treatment is reduced. All antihypertensive combinations with constituents of different mechanisms have an additive BP-lowering effect. There are several pharmacologic rationales for combining a calcium antagonist with an ACE inhibitor such as improved renoprotective[28,29] and cardioprotective effects.[30] In addition,

calcium antagonists and ACE inhibitors have been shown in practice to be useful drugs for the treatment of hypertension, coronary heart disease, tachyarrhythmias, congestive heart failure, or diabetic nephropathy and are amongst the most frequently prescribed drugs worldwide. Because of the many advantages of combination therapy it has been recommended even as the initial step of antihypertensive therapy in place of single-substance therapy at the onset of treatment.[26,27]

To conclude, a prescriber can do little to modify age-related physiological changes in trying to minimise the likelihood that an older person will develop drug toxicity, but creating optimal drug regimen, that meet the complex needs of elderly people requires thought and careful planning, eg, considering alternative drugs that might be safer in terms of the risk of adverse effects in older people. Our study is a step in that direction. The fixed combination of verapamil SR/trandolapril is a useful alternative treatment for elderly patients with mild to moderate hypertension, as it has been shown to be effective and well tolerated in our study.

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Participating centres

The German Hypertension Study Group comprised the following investigators: W Behrens (Wennigsen), GR Blumenberg (Leer, Brassat), S Brühl (Walluf), P Bügge (Obernkirchen), M O'Connally (Schwabach-Wolkersdorf), G Dienhart-Schneider (Beckingen), K Engels (Augsburg), U Geibel (Kirchhain), I Gurdan (Leutershausen), H Harmening (Osnabrück), H Hauer (Emskirchen), J Helmbrecht (Bochum-Harpen), WA Herrmann (München), F Hertrich (Lebach), W Hüttner (Neuwied), H-D Kalek (München), J Kuhlmann (München), A Müller (Klingenmünster), G Orlovius (Mannheim), M Reifl (Nürnberg), W Roeckl (München), D Roeder (Amberg), L Romming and W Romming (Fürth), Schardt (Würzburg), D Schneider (Battenberg), R Schneider (Lübeck), W Spitzbarth (Osnabrück), H Vahle (Amberg), H-J Vandenesch (Essen-Stadtwald), K Wissing (Riegel), R Woitke (Amberg), V Ziegler (Schramberg), A Zuber (Peiting).

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