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International Journal of Cardiology 100 (2005) 199–206

International Journal of Cardiology

www.elsevier.com/locate/ijcard

MORE—MOexipril and REgression of left ventricle hypertrophy in combination therapy A multicentric open label clinical trial

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Received 6 January 2004; received in revised form 15 March 2004; accepted 5 May 2004

Abstract

Aim: To evaluate the effect of ACE inhibitor moexipril if added to combination therapy in patient with poorly controlled hypertension.
Patients: Four hundred twenty patients with hypertension treated with monotherapy or two dug combination without an ACE inhibitor or AII antagonist and with blood pressure ≥140/90 mm Hg.
Design: Single-blind, multicenter, open, with a double-blind echocardiographic examination.
Methods: Basic cardiological examination including echocardiography was performed before including into the study. If the patient fulfilled inclusion criteria, ACE inhibitor moexipril was added to the therapy and uptitrated according to BP values. BP measuring, clinical examination, and basic laboratory were performed every month, echocardiography was repeated after 6 months.
Results: Sitting BP decreased from 161.43±12.84/96.72±7.74 mm Hg to 135.87±9.98/82.36±5.83 mm Hg (p<0.0001), heart rate from 73.08±9.87 to 69.80±7.91 (p<0.0001). Three hundred forty patients (81%) had BPd <90 mm Hg after 6 months. Left ventricle mass decreased from 263.24±94.69 to 246.71±89.08 g (p<0.0001), left atrium decreased from 39.78±5.40 to 38.89±4.98 mm (p<0.0001), and E/A ratio increased from 0.91±0.28 to 0.94±0.27 (p<0.0005). Plasma cholesterol level decreased from 5.67±0.87 to 5.44±0.68 mmol/l (p<0.0001) and plasma triglycerides decreased from 1.92±1.07 to 1.78±0.80 mmol/l (p<0.001).

A greater effect on blood pressure reduction was observed in combination ACE-I+diuretics than in combination ACE-I+betablocker or ACE-I+Ca blocker (statistically borderline). A statistically greater effect on left ventricle mass was observed if moexipril was added to a diuretic than to Ca blocker (p=0.02) or betablocker (p=0.04).
Summary: ACE inhibitor moexipril added to combination therapy of hypertension had similar effect on blood pressure reduction and left ventricle mass as in monotherapy trials. The most effective combination is ACE ihibitor+thiazide diuretic. A very small number of adverse events was observed; cough was reported in 2.14% of patients. Decreased heart rate and improvement in lipid parameters were observed in the whole group.

Keywords: Hypertension; Moexipril; Combination therapy; Left ventricular hypertrophy

1. Introduction

Correct detection and appropriate treatment of hypertension is the cornerstone of prevention and treatment of cardiovascular disease [7,25]. Nevertheless, the real situation remains rather frustrating and the rule of halves that

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doi:10.1016/j.ijcard.2004.05.077

was introduced several years ago applies here to promote improvements in hypertension treatment:

- Rule no. 1: only half of hypertensive patients are diagnosed.
- Rule no. 2: only half of the diagnosed hypertensive patients are treated.
- Rule no. 3: only half of the treated hypertensive patients reach normal blood pressure.

It means that 50% of hypertensive people are not aware of their hypertension, 25% are aware of their hypertension yet they are not treated, 12.5% are treated insufficiently, and only 12.5% are treated effectively. This aid was originally postulated for the criteria of hypertension exceeding 160/95 mm Hg but recent research suggests, however, that this applies even today yet for more strict limits of 140/90 mm Hg (for diabetics or patients with chronic kidney disease 130/80 mm Hg) that basically indicates large advancement and success in diagnostics and treatment of hypertension in the past 20 years. [13] The recent U.S. data from patients <75 years have indicated awareness in 70%, treatment in 59%, and control in 34% [7]. The situation is worse in patients over 75 years, where isolated systolic hypertension is the most common type of high blood pressure [3,5,15].

How to improve rule no. 1? The mistake is not in the patient but in physician. About 70% of general population pays a visit to their general practitioner once a year; approximately 90% of all people see their doctor at least once every 5 years. Provided that blood pressure would be measured at every office visit, the detection rate of hypertension could reach 90% within 5 years.

Also, the issue of treatment (rule no. 2) and especially effective treatment (rule no. 3) are in the hands of physician. Majority of patients, when properly educated, are ready to cooperate and comply and the physician's objective should be to select such treatment that would be the least burden for the hypertensive patient. From the view of hypertensive treatment, it means to select products with:

- minimum adverse effects,
- long-term effect (that enables once daily dosing),
- they might have benefits on concomitant diseases beyond the effect on hypertension,
- the least number of tablets per day.

Majority of modern drugs have similar spectrum of adverse effects as they are usually class effects. When selecting a drug from this point of view, we usually adhere to known class contraindications. Long-term effect and once-daily dosing can be found nowadays in several drugs within each main class antihypertensive class [8,25]. When considering concomitant diseases, the most frequent indications can be found for ACE inhibitors that are indicated in all patients with heart failure, coronary artery disease, diabetes mellitus, and history of stroke, etc. [1,4,10,11,18].

The last criterion—the least number of tablets per day—is currently achieved by new combination products that contain two or more active antihypertensive drugs. Large clinical trials suggest that only 30–40% of patients will reach effective control of blood pressure in monotherapy and all others require combination therapy [6]. This combination therapy is fully in the hands of physician; however, he needs to discuss with the patient both the strategy and the target, which is normal blood pressure level. The data from HOT trial have suggested that 72% of patients required combination therapy to reach target blood pressure: in patients with target blood pressure <90 mm Hg, it was 63%; in patients with target blood pressure <85 mm Hg, 68% patients; and in target blood pressure >80 mm Hg, 74% of patients [6]. In the largest concluded antihypertensive treatment trial so far (ALLHAT), after 5 years, 56.9%, 65.7%, and 60.3% patients were treated with antihypertensive combination that were originally randomized to monotherapy with chlorthalidone, amlodipine, and lisinopril, respectively [16,17].

Our study has attempted to answer the question how moexipril 7.5–15.0 mg is effective in already treated hypertensive patients whose blood pressure has not normalized yet. Moexipril was not to replace current medication but was added in a combination with the current medication.

2. Materials and methods

2.1. Trial design

Eligibility to the trial was met by patients who had been treated for hypertension longer than 3 months with monotherapy or antihypertensive combination that did not include ACE inhibitor or AII-receptor blocker. Baseline systolic blood pressure during this treatment must have been >140 mm Hg and/or diastolic blood pressure must have exceeded 90 mm Hg. The diagnoses required essential hypertension, exclusion criteria included pregnancy, hyperkalemia over 5.8 mmol/l, several renal insufficiency defined as serum creatinine level above 180 μmol/l, etc.

The study was carried out according to the principles of the Declaration of Helsinki and approved by local ethic committee. Informed consent was obtained from all participating patients.

Before enrolment to the trial, blood samples were taken for routine biochemical examination and ECG was recorded by their attending physician. Subsequently, patients were referred for echocardiography examination to a reselected and contracted echocardiography laboratory where they were investigated before entering the trial and 6 months later. ECG and biochemical investigation were repeated also

after 6 months. The physician performing echocardiography investigation was not aware of which combination therapy was used in the patient. Basic clinical and biochemical investigation was also performed in the first and third months.

The design of the trial is open label multicentric without placebo arm, with all patients on active treatment; echocardiography was single blinded.

The primary target of the trial was to evaluate the efficacy and safety of moexipril treatment in combination with other antihypertensive drugs and to evaluate the effect of such combination therapy on the left ventricle mass enlargement as determined by echocardiography.

The secondary target was to evaluate the effect of certain biochemical parameters while on long-term therapy with moexipril in combination with other antihypertensive agents. Another secondary aim of the study was to compare the effect on blood pressure and the left ventricle mass when moexipril was added to various antihypertensive agents.

Statistical analysis was performed with paired and unpaired *t*-test, Mann–Whitney test for numeric parameters, and χ^2 test for non-numeric values on a PC using the Statistics and Excel software.

2.2. Trial participants

The trial was conducted in offices of 40 general practitioners and internists throughout the Czech Republic.

2.3. Patients

The total of 426 patients were included, 6 patients did not follow through—3 due to adverse effects and 3 due to protocol breach—and they were not included to the final analysis. A total of 420 patients were analyzed, 188 males and 232 females, with mean age 61.5±10.71 years, mean weight 81.98±14.86 kg, mean height 169.61 ±8.61 cm, mean weight of men was 88.13±13.06 kg, mean height 176.33±6.77 cm, mean weight of women 77.12±14.38, mean height 164.14±5.61 cm. Positive family history was present in 272 (64.7%) patients, mean duration of hypertension was 93.09±83.95 months. History of myocardial infarction was present in 64 (16%) patients, history of angina pectoris in 119 (28.3%) patients, 109 (25.9%) had diabetes mellitus, 43 (10.2%) had history of coronary artery disease, and 276 (65.7%) knew of their high lipid levels or had history of hyperlipidemia or it was detected at baseline investigation.

Beta blockers were used in the treatment of 243 (58%) patients, out of which 138 had beta blockers in monotherapy and 105 in combination (51 with diuretics and 28 with calcium channel blockers, 15 in triple combination). Diuretics were used by 175 (42%) patients, out of which 51 in combination with beta blocker and 22 in combination with calcium channel blocker (CAA). Calcium channel blockers were used by 160 (38%) patients [dihydropyridine type calcium channel blocker were used by 144 (90%) patients, verapamil type by 15 (9%) and benzothiazepin type by 1 (1%) patients]. The overview of baseline therapy is shown in Table 1.

Besides, 287 (68.3%) patients used other than antihypertensive medication, especially lipid-lowering drugs by 157 (37.3%) patients (statins 108, fibrates 49) and aspirin 149 (35.4%) patients.

3. Results

The primary end point, blood pressure, and echocardiography parameters are shown in Table 2. Secondary end points, biochemistry results, and ECG are shown in Table 3. The effect of primary end point after moexipril addition to diuretic is shown in Table 4. The effect of moexipril addition to beta blockers on primary end point is shown in Table 5. The effect of moexipril addition to calcium channel blocker on the primary end points is shown in Table 6.

Mean age of diuretic-treated patients was 61.34±10.76 years, mean systolic blood pressure reduction in sitting patient following moexipril addition to diuretic was 27.00±13.90 mm Hg, mean diastolic blood pressure reduction in sitting patient was 14.51±8.58 mm Hg, and mean reduction of the left ventricle mass was 20.79±38.38 g.

Mean age of beta blocker-treated patients was 61.03±10.87 years, mean systolic blood pressure reduction in sitting patients following moexipril addition to beta blocker was 24.07±11.83 mm Hg, mean diastolic blood pressure reduction was 14.41±7.48 mm Hg, and mean left ventricle mass reduction was 17.34±28.89 g.

Mean age of CAA-treated patients was 63.42±9.75 years, mean systolic blood pressure reduction in sitting patient following moexipril addition to calcium channel blocker was 26.17±13.63 mm Hg, mean diastolic blood pressure reduction was 14.2±8.76 mm Hg, and mean left ventricle mass reduction was 14.64±31.89 g.

The difference between systolic blood pressure after moexipril addition to diuretic versus beta blocker was 2.93

Table 1
Overview of antihypertensive therapy in MORE trial

Antihypertensive agent	Number of patients	%
β-blockers in monotherapy	138	32.8
Diuretics in monotherapy	92	21.9
Calcium channel blocker in monotherapy	74	17.6
β-blockers+diuretics	51	12.1
β-blockers+calcium channel blocker	28	6.7
Diuretics+calcium channel blocker	22	5.2
β-blockers+diuretics+calcium channel blocker	15	3.6

Table 2
MORE trial primary end points

	Randomization	Month 6	p
Blood pressure parameters			
sBP sitting (mm Hg)	161.43±12.84	135.87±9.98	<0.0001
dBP sitting (mm Hg)	96.72±7.74	82.36±5.83	<0.0001
HR sitting	73.08±9.87	69.80±7.91	<0.0001
sBP standing (mm Hg)	158.77±14.07	134.37±11.54	<0.0001
dBP standing (mm Hg)	95.09±8.66	81.49±7.22	<0.0001
PP sitting	64.81±12.39	53.5±9.22	<0.0001
PP standing	63.62±13.47	52.68±10.53	<0.0001
Workload sitting	11804±1965	9488±1389	<0.0001
Echocardiography			
LA (mm)	39.78±5.40	38.89±4.98	<0.0001
LVDD (mm)	51.23±7.59	51.52±6.71	NS
LVSD (mm)	35.54±6.82	34.86±6.89	0.02
IVSd (mm)	11.19±2.13	10.71±1.98	<0.0001
LVPWd (mm)	10.56±1.87	10.20±1.82	<0.0001
E/A (1)	0.91±0.28	0.94±0.27	<0.0005
LVM (g)	263.24±94.69	246.71±89.08	<0.0001
LVMi (g/m^2)	146.24±52.6	137.06±49.49	<0.0001

sBP—systolic blood pressure; dBP—diastolic blood pressure; PP—pulse blood pressure; HR—heart rate; workload—blood pressure multiplied by heart rate; LA—left atrium; LVDD—left ventricle diastolic dimension; LVSD—left ventricle systolic dimension; IVSd—interventricular septum diastolic dimension; LVPWd—left ventricle posterior wall diastolic dimension; LVM—left ventricle mass; LVMi—left ventricle mass index (per m^2 body surface area).

mm Hg (P=0.02), the difference in the left ventricle mass reduction between those two groups was 3.45 g (NS).

The difference between systolic blood pressure following moexipril addition to diuretic and calcium channel blocker was 0.83 mm Hg (NS), the difference in left ventricle mass reduction between those two groups was 6.15 g (p=0.03).

The difference in systolic blood pressure reduction after moexipril addition to calcium channel blocker and beta blocker was 2.1 mm HG (NS); the difference in left ventricle mass reduction between those two groups was 2.7 g (NS).

Table 3
MORE trial secondary end points

	Randomization	Month 6	p
Laboratory parameters			
Na (mmol/l)	140.54±3.42	140.41±3.46	NS
K (mmol/l)	4.36±0.42	4.44±0.44	0.0013
BUN (mmol/l)	6.19±1.56	6.25±1.50	NS
Creat (μmol/l)	90.7±15.39	91.89±15.43	0.008
Glu (mmol/l)	5.82±1.61	5.7±1.34	NS
Chol (mmol/l)	5.67±0.86	5.44±0.068	<0.0001
TG (mmol/l)	1.92±1.07	1.78±0.80	0.01
ECG			
HR (−1)	71.42±10.0	69.48±8.51	<0.0001
PQ (ms)	162.76±27.96	163.16±28.55	NS
QRS (ms)	83.33±20.48	84.14±21.50	0.04
QT (ms)	381.46±47.89	377.13±44.58	NS
SL (mV)	28.08±10.04	27.98±10.34	NS
Mc Phie (mV)	29.77±9.24	29.47±9.20	0.009

Na—sodium; K—potassium; BUN—blood urea nitrogen; Creat—creatinine; Glu—blood glucose level; Chol—cholesterol; TG—triglycerides; SL—Sokolow Lyon index; Mc Phie—Mc Phie index.

Table 4
Primary end point change after moexipril addition to a diuretic

	Randomization	Month 6	p
Parameter			
sBP sitting (mm Hg)	161.59±12.68	134.59±9.92	<0.0001
dBP sitting (mm Hg)	96.93±7.74	82.35±5.78	<0.0001
HR sitting	73.56±9.25	69.53±7.82	<0.0001
sBP standing (mm Hg)	158.18±13.31	133.23±10.92	<0.0001
dBP standing (mm Hg)	95.11±8.89	80.8±7.48	<0.0001
PP sitting	64.65±12.72	52.15±8.94	<0.0001
PP standing	62.63±12.67	52.00±10.1	<0.0001
Workload sitting	11898±1935	9349±1341	<0.0001
Echocardiography			
LA (mm)	39.81±5.55	39.04±5.39	0.002
LVDD (mm)	51.68±7.36	51.5±0.67	0.03
LVSD (mm)	36.34±7.55	35.51±7.74	0.04
IVSd (mm)	11.38±1.95	10.76±1.85	<0.0001
LVPWd (mm)	10.66±1.63	10.22±1.63	<0.0001
E/A (1)	0.86±0.29	0.90±0.29	<0.001
LVM (g)	267.42±92.43	246.63±83.89	<0.0001
LVMi (g/m^2)	148.56± 51.37	137.02±46.6	<0.0001

sBP—systolic blood pressure; dBP—diastolic blood pressure; PP—pulse blood pressure; HR—heart rate; LA—left atrium; LVDD—left ventricle diastolic dimension; LVSD—left ventricle systolic dimension; IVSd—interventricular septum diastolic dimension; LVPWd—left ventricle posterior wall diastolic dimension; workload—blood pressure multiplied by heart rate; LVM—left ventricle mass; LVMi—left ventricle mass index (per m^2 body surface area).

Table 5
Primary end point change after moexipril addition to a beta blocker

	Randomization	Month 6	p
Parameter			
sBP sitting (mm Hg)	160.17±11.57	136.1±9.13	<0.0001
dBP sitting (mm Hg)	97.00±7.57	82.53±5.80	<0.0001
HR sitting	71.8±10.17	69.17±7.97	<0.0001
sBP standing (mm Hg)	157.63±13.48	134.42±11.2	<0.0001
dBP standing (mm Hg)	95.28±8.64	81.79±7.37	<0.0001
BPPP sitting	63.36±11.31	53.55±8.63	<0.0001
BPPP standing	62.3±13.03	52.63±9.99	<0.0001
Workload sitting	11515.2±2011.9	9421.9±1366.8	<0.0001
Echocardiography			
LA (mm)	39.92±5.36	39.11±5.05	<0.0001
LVDD (mm)	51.05±7.23	51.11±6.22	<0.001
LVSD (mm)	35.19±6.67	34.88±6.95	NS
IVSd (mm)	11.19±2.12	10.73±2.10	<0.0001
LVPWd (mm)	10.62±1.93	10.16±1.94	<0.0001
E/A (1)	0.90±0.30	0.95±0.27	<0.0001
LVM (g)	261.53±94.32	244.19±89.23	<0.0001
LVMi (g/m^2)	145.29±42.4	135.66±49.57	<0.0001

sBP—systolic blood pressure; dBP—diastolic blood pressure; BPPP—pulse blood pressure; HR—heart rate; LA—left atrium; LVDD—left ventricle diastolic dimension; LVSD—left ventricle systolic dimension; IVSd—interventricular septum diastolic dimension; LVPWd—left ventricle posterior wall diastolic dimension; workload—blood pressure multiplied by heart rate; LVM—left ventricle mass; LVMi—left ventricle mass index (per m^2 body surface area).

Table 6
Primary end point change after moexipril addition to a calcium channel blocker

	Randomization	Month 6	*p*
Parameter			
sBP sitting (mm Hg)	163.93±13.73	137.75±10.1	<0.0001
dBP sitting (mm Hg)	97.13±8.2	82.91±5.9	<0.0001
HR sitting	74.62±10.02	70.55±8.17	<0.0001
sBP standing (mm Hg)	162.27±15.88	135.65±12.25	<0.0001
dBP standing (mm Hg)	95.87±8.68	82.02±7.25	<0.0001
BPPP sitting	66.8±12.62	54.81±8.37	<0.0001
BPPP standing	66.54±14.24	53.46±10.65	<0.0001
Workload sitting	12229±2085	9721±1492	<0.0001
Echocardiography			
LA (mm)	40.24±5.03	39.15±4.39	<0.0001
LVDD (mm)	51.24±8.15	52.48±6.95	<NS
LVSD (mm)	35.0±6.19	34.66±6.2	NS
IVSd (mm)	11.55±2.17	10.97±1.92	<0.0001
LVPWd (mm)	10.72±1.85	10.31±1.78	<0.0001
E/A (1)	0.89±0.27	0.91±0.25	NS
LVM (g)	274.79±98.35	260.16±92.76	0.0009
LVMi (g/m^2)	152.66±54.64	144.53±51.53	0.0009

sBP—systolic blood pressure; dBP—diastolic blood pressure; PP—pulse blood pressure; HR—heart rate; LA—left atrium; LVDD—left ventricle diastolic dimension; LVSD—left ventricle systolic dimension; IVSd—interventricular septum diastolic dimension; LVPWd—left ventricle posterior wall diastolic dimension; workload—blood pressure multiplied by heart rate; LVM—left ventricle mass; LVMi—left ventricle mass index (per m^2 body surface area).

The difference in pulse pressure reduction after moexipril addition to diuretic or beta-blocker was 2.7 mm Hg (12.5 resp 9.8 mm Hg, $p<0.01$), the difference in pulse pressure reduction after moexipril addition to calcium channel or beta-blocker was 2.2 mm Hg (12.0 after CAA, $p<0.01$), no difference was seen between the combination of moexipril and diuretic and moexipril+calcium channel blocker.

The difference in the heart rate reduction following moexipril addition to beta blocker was 2.6±7.66 beats per minute, addition to diuretic 4.06±7.82 beats/min, to calcium channel blocker 4.09±8.53 beats/min ($P=0.03$ diuretic vs. beta blocker, $P=0.06$ calcium channel blocker vs. beta blocker, P=NS for diuretic vs. calcium channel blocker). Among adverse effects, 13 (3%) patients reported dry irritating cough and neither a single case of clinically significant hyperkalemia nor a single case of angioedema. All the other reported adverse effects (headache, sleeplessness, weakness) did not exceed 1% incidence rate.

4. Discussion

The fact that combination antihypertensive treatment is the treatment of future has also been manifested in the history of hypertension treatment guidelines (Table 7) [8,23,25]. The table clearly reveals that a quarter century ago the guidelines were based on high doses of diuretics and later on beta blockers. The doses were gradually reduced and the basic drug classes are to be selected as individually tailored which means addressing concomitant diseases. 2003 ESH/ESC recommendations post the following as the most effective combinations:

1. ACE inhibitor+diuretic.
2. ACE inhibitor+calcium channel blocker.
3. Beta blocker+diuretic.
4. Beta blocker+dihydropyridine calcium channel blocker.

JNC VII guidelines recommendation is diuretics+ACE inhibitor or calcium channel blocker or beta blocker.

In the case of triple and multiple combinations, diuretic agent should be always present [8].

Currently, the highest number of combination products includes diuretic, which is the golden standard because of its efficacy and cost effectiveness. Thiazide and similar diuretics in low doses are used preferably because they have demonstrated high efficacy in large mortality studies such as STOP II or ALLHAT [16,17].

In the point of view of concomitant diseases, the most beneficial drug for the combination is ACE inhibitor, which,

Table 7
Development of hypertension treatment guidelines

Guideline	Year	Leading idea
JNC I	1977	High-dosed diuretic
JNC II	1980	High-dosed diuretic
JNC III	1984	Low-dosed diuretic or beta blocker
JNC IV	1988	Low-dosed diuretic or beta blocker (ACE inhibitor and calcium channel blocker as alternatives)
JNC V	1993	Diuretics and beta blockers as first-line drugs; ACE inhibitors and calcium channel blockers as alternatives. Titration of single agent is preferable.
JNC VI	1997	Individually tailored treatment, diuretics, and beta blockers as the first-line drugs; ACE inhibitors and calcium channel blockers as alternatives; antihypertensive combination should be step 2.
World Health Organization	1999	Individually tailored antihypertensive treatment, diuretics, beta blockers, ACE inhibitors, calcium channel blockers, AII receptor antagonists, and alpha-blockers are all equal.
JNC VII	2003	Individually **tailored combination therapy**, diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, and AII antagonists are all equal. If blood pressure is >20/10 mm Hg above goal blood pressure, consideration should be given to initiating therapy with **two agents**, one of which should be a thiazide-type diuretic.
ESH/ESC	2003	To initiate therapy either with low dose of a single agent or with **low dose combination** of two agents and the main benefits are due to lowering (normalization) of blood pressure per se

JNC=Joint National Committee; ESH=European Society of Hypertension; ESC=European Society of Cardiology.

besides hypertension, has a wide spectrum of other indications including all forms of coronary artery disease ranging from asymptomatic to heart failure patients, diabetes mellitus both with and without kidney damage and most likely also all patients needed a secondary prevention of stroke [4,9,14,18,21,24]. Another indication of ACE inhibitor or AII blocker treatment is the left ventricle hypertrophy but also hypertension associated with metabolic syndrome [2,4,8,22].

This is the first randomized study confirming that the combination of diuretic+ACE inhibitor is more effective on blood pressure control and left ventricle hypertrophy regression than a combination of beta blocker+ACE inhibitor or calcium channel blocker+ACE inhibitor. We believe that low dose of thiazide diuretic would by the best strategy for monotherapy and the combination thiazide diuretic+ACE-I the best strategy for combination therapy in most of our hypertensive patients.

Our study confirms that the addition of ACE inhibitor moexipril to combination treatment results in the blood pressure reduction, which has reached statistical significance in all studied groups and subgroups (monotherapy, double combination, and triple combination). When assessing blood pressure reduction, significant difference was observed in all subgroups between baseline (randomization) and treatment month 6 in all cases on a highly significant level ($p<0.001$). However, the difference between individual antihypertensive agents have been observed; addition of moexipril to diuretic was associated with significantly larger blood pressure reduction than addition to beta blocking agent, which confirms the hypothesized additive effect of combination ACE inhibitor+diuretic agent.

Combination of moexipril+beta blocker was also associated with the least reduction of heart rate by 2 beats per minute unlike combination of moexipril+diuretic or moexipril+calcium channel blocker where this reduction was as twice as large.

Changes in the left ventricle mass have also their rationale. Combination of moexipril+diuretic was the most significant, most likely because moexipril is added to a combination where the established antihypertensive agent (diuretic) achieved only minimal regression of left ventricle hypertrophy and there is also very likely activation of renin angiotensin system unlike in other antihypertensives [23]. On the other side, addition of moexipril to dihydropyridine was associated with rather limited reduction of the left ventricle mass most likely because dihydropyridine had directly influenced the left ventricle mass before the trial commencement [7].

Combination of ACE inhibitors with diuretics has its rationale. ACE inhibitors enhance sodium elimination and reduce results of renin angiotensin system activation induced by diuretics and partially compensate hypokalemia induced by loop and thiazide diuretics. The patients treated with large doses of diuretics (heart failure) with secondary hyperreninemia may experience severe hypotension and significant kidney function reduction after ACE inhibitor institution; therefore, before starting such patients on ACE inhibitor, it is feasible to reduce high doses of diuretics, especially loop diuretics [14]. In the case of hypertension, there is no reason to use high doses of diuretics and therefore we have not experienced such phenomena. Combination of ACE inhibitor+diuretic is the basic antihypertensive combination recommended by both ESH/ESC and JNC VII guidelines; it is a very effective combination where both drug groups increase the effect of each other [8,25].

Combination of ACE inhibitor and calcium channel blocker is also very promising in the antihypertensive treatment. Calcium channel blockers are effective vasodilating agents and several older drugs of this class activate the renin angiotensin system. Recent II and III generation dihydropyridines are free of such property and therefore combination with ACE inhibitors does not potentiate each others effect but has additive influence [23]. Combination of ACE inhibitor and calcium channel blocker is especially beneficial in their renal action as they both affect vas afferens as well as vas efferens utilizing different mechanism of action, which in turn results in reduced microalbuminuria. Meta-analyses of the left ventricle hypertrophy clinical trials suggest that both these drug groups have the largest effect on the left ventricle hypertrophy regression. Based on our data, it appears that the effect on left ventricle mass is no more additive and the addition of ACE inhibitor to II and III generation dihydropyridine is not associated with such left ventricle mass reduction as when ACE inhibitor is started in monotherapy or when it is added to an established diuretic treatment.

In clinical practice, combination of ACE inhibitor and beta blocker has suggested that such a long-term treatment delays the left ventricle function impairment, heart failure symptoms, and delays the need of heart transplant [14,19,20]. Multicentric double-blind carvedilol trials, CIBIS II (The Cardiac Insufficiency Bisoprolol Study) and MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Heart Failure), clearly demonstrated the reduction of total mortality, hospitalization rate, risk of sudden death and heart failure progression after beta blocker was added to ACE inhibitor [19,20]. When assessing hypertension, such combination is not so optimistic. Beta blockers reduce renin secretion and thus may influence the capability of ACE inhibitors to reduce both plasma and tissue concentration of angiotensin II [25]. It can be, therefore, hypothesized that such a combination will be less effective as to blood pressure reduction [23]. Our study also suggested that the blood pressure reduction following moexipril addition to established beta blocker was lower than in other combinations. However, this does not change the fact that such a combination is optimal for all patients with coronary

artery disease and heart failure where it extends the life expectancy [14,19,20].

In our study, we have observed the minimum incidence of adverse effects reported. The most frequent clinical adverse effect following the ACE inhibitor administration was dry, irritating cough that was reported in 5–15% of our trial, cough was present in 3% of patients and in 2 patients resulted in the withdrawal from the study. The most frequent laboratory adverse effect was hyperkalemia, which, however, reached clinical significance in less than 1% of patients and potassium level was increased usually only by 0.2–0.4 mmol/l. In our study, we have not detected a single case of clinically significant of hyperkalemia and the serum potassium increase in our study was 0.12 mm/l, which reached statistical but not clinical significance. The most serious adverse effect reported is angioedema, which in large clinical trials such as ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Attack Trial) or OCTAVE (Omapatrilat Cardiovascular Treatment Assessment versus Enalapril) occurs in less than 0.5% of patients and was not cause of death in one single case among 20,000 patients treated with ACE inhibitors in these two trials [16,17]. No case of angioedema was reported in our trial.

5. Conclusion

Moexipril added to a combination antihypertensive therapy demonstrated very good tolerability and efficacy. The blood pressure reduction reached 15–20% of baseline values; the left ventricle mass reduction was 7–10% after 6 months of treatment. The most promising combination when assessing both blood pressure reduction and left ventricle mass regression was combination of moexipril with a diuretic.

6. Uncited reference

[12]

Acknowledgement

We acknowledge all physicians–investigators participating in the trial (list of participating physicians attached). Besides, we would like to acknowledge high school students from Vídeòská Street in Brno-Monika Špinarová and Veronika Kopèíková, who performed statistical analyses under supervision of Computation Technology Center of Masaryk University School of Medicine. We also acknowledge pharmaceutical manufacturer SCHWARZ PHARMA for significant assistance with preparing the trial, printing protocols, selection of investigators, and data collection.

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References

[1] American Diabetes Association. Diabetic nefropathy. Diabetes Care 2002;25(Supp. 1):85–9.
[2] Dahlof B, Devereux RB, Kjeldsen SE, for the LIFE investigators. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoints reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995–1003.
[3] Franklin S, Larson MG, Khan SA, et al. Does the raltion of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation 2001;103:1245–9.
[4] Hansson L, Lindholm LH, Niskanen L, et al. For the CAPPP study group. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611–6.
[5] Hansson L, Lithell H, Skoog I, for the SCOPE investigators. Study on cognition and prognosis in elderly hypertensives (SCOPE). Blood Pressure 1999;8:177–83.

[6] Hansson L, Zanchetti A, Caruthers SG, et al. Effect of intensive blood pressure lowering and low dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet 1998;351:1755–62.
[7] Chambers J. Left ventricular hypertrophy. BMJ 1995;311:s.273–4.
[8] Chobanian AV. JNC 7 Express. NIH Publ 2003;03-5233:1–52.
[9] Kannel WB. Cardioprotection and antihypertensive therapy: the key importance of addressing the associated coronary risk factors (the Framingham experience). Am J Cardiol 1996;77:6B–11B.
[10] Kannel WB, Castelli WP, McNamara PM, Mckee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure: The Framingham Study. NEJM 1972;287:781–7.
[11] Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275: 1557–1562.
[12] Pepine CJ, for the INVEST Group. Outcomes from randomized trial of a calcium antagonists and non calcium antagonist blood pressure treatment strategy in patients with coronary artery disease. The INternational VErapamil–trandolapril STudy (INVEST). ACC Chicago Meeting, 2.4.2003, Late-Breaking Clinical Trials III.
[13] Primetesta P, Brookes M, Poulter NR. Improved hypertension management and control. Results from the Health Survey for England 1998. Hypertension 2001;38:827–32.
[14] Remme JW, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–60.
[15] Staessen JA, Fagard R, Thijs L, et al. For the Syst-Eur Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997;350:757–64.
[16] The ALLHAT Officers and Coordinators. Major outcomes in high-risk hypertensive patients randomised to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Attack Trial (ALLHAT). JAMA 2002;23:2981–97.
[17] The ALLHAT Officers, Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomised to pravastatin vs. usual care; the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998–3007.
[18] The CAPP investigators. CAPPP: effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project randomised trial. Lancet 1999;353:611–6.
[19] The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.
[20] The MERIT HF study group. Effect of metoprolol CR/XL in chronic hear failure: C.R. Metoprolol/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2000–7.
[21] The UKPDS investigators. UKPDS 33: intensive blood–glucose control with sulphonylureas or insulin compared with conventional treatment and risk complications in patients with type 2 diabetes. Lancet 1998;352:837–65.
[22] Vedecchia P, Schillaci G, Borgioni C, et al. Prognostic significance in left ventricular mass in essential hypertension. Circulation 1998; 97:48–54.
[23] Vítovec J, Špinar J. Hypertension and combination drug therapy. Cor Vasa 2000;42(9):461–7.
[24] Yususf S, Gerstein H, Hoogwerf B, Pogue J, Wolffenbuttel BH, Zinman B. The HOPE study. JAMA 2001;286:1882–5.
[25] Zanchetti A, for the guidelines committee: 2003 European Society of Hypertension. European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011–23.