Anti-hypertensive strategies in patients with MEtabolic parameters, DIabetes mellitus and/or NephropAthy (the M E D I N A study)

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Aims. The primary questions asked by the MEDINA (MEtabolic parameters, DIabetes mellitus and NephropAthy) study are: 1) Do angiotensin converting enzyme inhibitors (ACE-I) have any advantages over angiotensin receptor blockers (ARB)? 2) Should the other drug for combination be a diuretic or a calcium-channel blocker (CCB)? 3) How are the risks reduced by the co administration of a statin?
Methods. A total of 439 hypertensive patients with metabolic syndrome and/or diabetes mellitus were randomized to 2 groups: group 1 - ramipril (ACE-I) or perindopril and group 2 - losartan (ARB). Hydrochlorothiazide (diuretic) or amlodipine (CCB) were added to both groups. As a third step, a statin was added.
Results. Blood pressure decreased 24.1/13.3 mmHg in the ACE inhibitor group and 25.9/13.5 in the losartan group. The difference was insignificant. Adding either hydrochlorothiazide or amlodipin was equally effective. There were no significant differences on metabolic parameters in the trial arms. Cholesterol level decreased by 0.95 mmol/L in the ACE-I group and 1.02 mmol/L in the ARB group (ns).
Conclusion. MEDINA has so far confirmed the equivalence of ACE-I and ARB in hypertension treatment. Adding either diuretic or CCB was equally effective. Our data support the current recommendations on adding a statin to reduce cardiovascular risk.

Key words: hypertension, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, diuretic, calcium-channel blocker, combinations

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INTRODUCTION

Cardiovascular pharmacotherapy is experiencing an unprecedent boom. Despite immense progress in the treatment of acute myocardial infarction/ heart failure, prevention is increasingly being emphasised with consistent treatment of diseases considered main risk factors for ischemic heart disease, namely hypertension and diabetes mellitus. These conditions often have a common cause, insulin resistance or the METABOLIC SYNDROME.

The metabolic syndrome (MS) is a term for a number of risk factors/ diseases which frequently appear together and lead to premature health complications. It is also known as syndrome X, Reaven's syndrome, insulin resistance syndrome or the deadly quartet. Insulin resistance is regarded as the pathophysiological basis of the metabolic syndrome.

According to the 2005 definition of the International Diabetes Federation, metabolic syndrome applies to the presence of abdominal obesity (waistline $\geq$ 94 cm in men and $\geq$ 80 cm in women) and two of the following: hypertension, diabetes mellitus, triglycerides $\geq$ 1.7 mmol/L on therapy, HDL cholesterol < 0.9 mmol/L in men and <1.0 mmol/L in women).

It is estimated that approximately 25% of the US population aged 18+ suffers from the metabolic syndrome, while hypertension and diabetes mellitus affect approximately 40% and 8% of the population, respectively[1]. The treatment of metabolic syndrome is thus a great challenge in the primary prevention of ischemic heart disease (IHD).

Cardiovascular pharmacotherapy is experiencing an unprecedented boom with new drug groups appearing and "older" ones obtaining new indications. The drug groups that have experienced huge growth in recent years include the angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB) (ref.[2]). No direct comparison between ACE-I and ARB in diabetic or hypertensive patients has yet been made in a major trial (many similar subjects were involved in the ONTARGET trial). A comparison was made after myocardial infarction (VALIANT and OPTIMAAL trials) and heart failure (ELITE II and Val Heft trials), where both drug groups were equally effective. For this reason, ACE inhibitors or ARBs, preferably in combination with calcium-channel blocker, are currently recommended for the secondary prevention of IHD and/or in cases of diabetes mellitus type 1 and 2. In addition, clinical trials in hypertensive pa-

tients (ASCOT LLA) and in diabetic patients (CARDS) have demonstrated that the treatment of hypertension should be accompanied by at least a small dose of statins (atorvastatin 10 mg) (ref.[3]).

MEDINA

MEDINA (MEtabolic parameters, DIabetes mellitus and Nephroprotective Action) aims to find an optimal treatment strategy for the metabolic syndrome, or diabetes mellitus and hypertension. The primary issues covered by the trial include:

1. Does ACE-I therapy have any advantages over ARB therapy?
2. Should the other drug for combination be a diuretic (D) or a calcium-channel blocker (CCB)?
3. How are patient risks for the patient reduced by the concurrent administration of statin?

The trial was approved by the Ethics Committee of the University Hospital Brno and each patient signed a written prior consent.

METHODS

It is a randomized, open label, single blind trial with an independent statistical evaluation (PROBE design). The randomisation was done by the Institute of Biostatistics and Analyses of the Masaryk University in Brno (IBA MU). Data were collected electronically by the same institute. Each patient is identified by a unique number. The statistical evaluation was performed at IBA MU.

Hypertensive patients with metabolic syndrome and/or patients with diabetes mellitus were enrolled in the trial. If patients were taking 1-2 antihypertensive drugs, this had to be stopped at least one week before the trial (a combined diuretic is regarded as one hypertensive drug).

Patients over 40 years old had to fulfill one of the following criteria (more than a week after the antihypertensive drugs had been discontinued).

- Diabetes mellitus type 2 (defined as - treated by peroral antidiabetic drugs (PAD) and/or insulin) and a systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg
- Hypertension and metabolic syndrome criteria fulfilled
- Abdominal obesity and two criteria of the metabolic syndrome diagnosis (except for blood pressure) and systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg.

The main exclusion criteria included myocardial infarction, a cerebrovascular event, angioplasty or aortocoronary by-pass in the past three months, known secondary hypertension, clinically manifested heart failure, diabetes mellitus type 1, an accompanying disease with a bad prognosis (death probability > 30% within 1 year), pregnant women and women of reproductive age without sufficient contraceptives, and a known tolerance to ACE-I, ARB or CCB. If the patient died, suffered myocardial infarction or stroke during the study, they were excluded from the final evaluation.

Blood pressure is measured in a sitting position according to ESH (European Society of Hypertension) and ESC (European Society of Cardiology) guidelines for office blood pressure measurement – that is three times in a sitting position.

If data from the LIFE or ASCOT trials are taken as the basis, the occurrence of both fatal and non-fatal IHD and fatal and non-fatal stroke can be expected at a rate of approx. 1% per year; the expected combined target of IHD and stroke is approximately 1.5% per year. In order to achieve statistical significance in these targets, it will be necessary to create a cohort of 20,000 subjects followed-up for 3–5 years.

Therefore, the selected primary objective is achievement of target values for blood pressure and total cholesterol, and estimated value of cardiovascular event risk in the next 10 years using SCORE risk charts based on age, sex, systolic blood pressure, cholesterol and smoking. The correction in patients with diabetes mellitus (quadruple for women, double for men) was not made. The objective was both absolute risk reduction and the number of persons whose risk will not exceed 5%.

Antihypertensive therapy

Patients are randomized to two groups: treatment with a medium dose of ARB – 50 mg of losartan or a medium dose of ACE-I - 5 mg of ramipril or 4 mg of perindopril (erbumine salt) in a ratio of 1:1. If blood pressure was not < 130/85 mmHg during any follow-up visit, titration was then performed (follow-up visits in months 1, 3, 6, 9, 12):

Step 1: All patients in both groups are further randomized for the addition of hydrochlorothiazide 25 mg or amlodipine 5 mg to the basic treatment.

Step 2: Losartan or ramipril or perindopril were increased to 100 mg, 10 mg or 8 mg, respectively.

Step 3: If the patient was already on a double-combination and had losartan increased to 100 mg or ramipril to 10 mg or perindopril to 8 mg, such drug would be added to the patient's medication that was not part of titration 2, i.e. all these patients took a combination of 100 mg of losartan or 10 mg of ramipril or 8 mg of perindopril + 25 mg of hydrochlorothiazide + 5 mg of amlodipine.

Step 4: If the patient was already on a triple combination, amlodipine was increased to 10 mg and all these patients took a combination of 100 mg of losartan or 10 mg of ramipril or 8 mg of perindopril + 25 mg of hydrochlorothiazide + 10 mg of amlodipine.

If the patient did not have a blood pressure ≤140/90 mmHg even after the step 4 titration, the patient then fulfilled the criteria for resistant hypertension and was recommended to a specialist.

Lipid-lowering therapy

Only those patients who had not yet been treated with statin could be included in this arm; if patients were al-

ready treated with a statin, they continued such therapy and were not included in this lipid-lowering therapy substudy. All patients were instructed on diet. Inclusion in the lipid-lowering therapy arm was not an obligatory part of the trial.

Patients examined during the follow-up visit in month 3, on an odd day continued the diet. Patients examined during the follow-up visit in month 3 on an even day received additional doses of 10 mg atorvastatin.

If during the trial a patient who was on a diet clearly needed statin or if a patient receiving 10 mg of atorvastatin needed a higher dose, such change could then be implemented by the doctor and the patient would only be evaluated in the anti-hypertensive arm.

RESULTS

A total of 535 patients were enrolled in the trial, of which 439 patients completed it, 96 patients prematurely withdrew for their own reasons. During the trial, one patient died, two suffered myocardial infarction and three suffered cerebrovascular events. There were no cases of a worsening of the kidney or liver test results that would be a reason to terminate the therapy. Eight patients in the ACE-I group and one patient in the losartan group terminated the therapy due to dry cough, while in two patients the addition of dihydropyridine resulted in swelling in the ankle area, which were grounds for termination. These patients are not considered in the final evaluation.

A total of 439 patients were evaluated and completed the trial, of whom 217 were treated with an ACE-I and 222 with an ARB. Forty-nine (22.6%) patients completed the trial on ACE-I monotherapy, 117 (53.9%) patients on a double combination (59 a diuretic, 58 a CCB) and 51 (23.5%) patients on a triple combination. Forty-seven (21.2%) patients completed the trial on ARB monotherapy, 129 (58.1%) patients on a double combination (70 a diuretic, 59 a CCB), 46 (20.7%) patients on a triple combination – NS ACE-I versus ARB. Hydrochlorothiazid (HCHT) was added to the RAAS blocker in a total of 129 patients, while amlodipin channel blocker was added in 117 patients (Fig. 1). A total of 248 patients were on a statin from the start, while it was later added to the therapy in 113 patients. Statin therapy was not initiated in 78 patients.

A total of 439 patients with an average systolic pressure of 156.3 mmHg and an average diastolic pressure of 92.6 mmHg were enrolled in the trial. Men numbered 214 (48.8%), women 225 (51.2%). The SCORE calculation in 88 patients over 70 years old was performed in the highest quadrant, i.e. as if the patients were 70. The basic characteristics of the subjects are shown in Table 1:

It is evident from the table that there is no difference between the two groups.

Table 3 shows changes in blood pressure, pulse rate and SCORE classification according to the type of therapy initiation in patients who remained on monotherapy.

Table 4 shows changes in blood pressure, pulse rate and SCORE classification according to the type of therapy initiation in patients who completed the trial on combination therapy (double or triple combination).

It is clear from the table that there is no difference between the two groups.

Table 5 and Fig. 2 show changes in blood pressure, pulse rate and SCORE classification according to the type

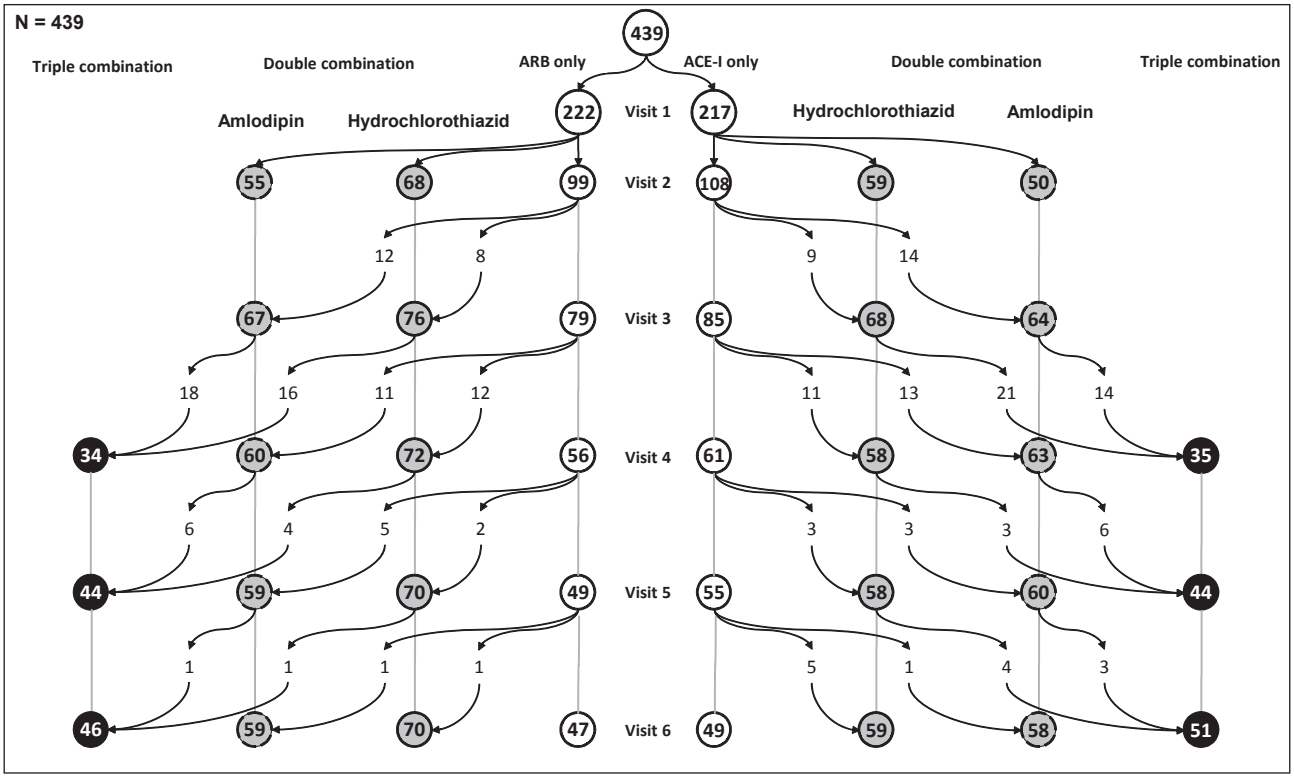

Fig. 1. Therapy titration.

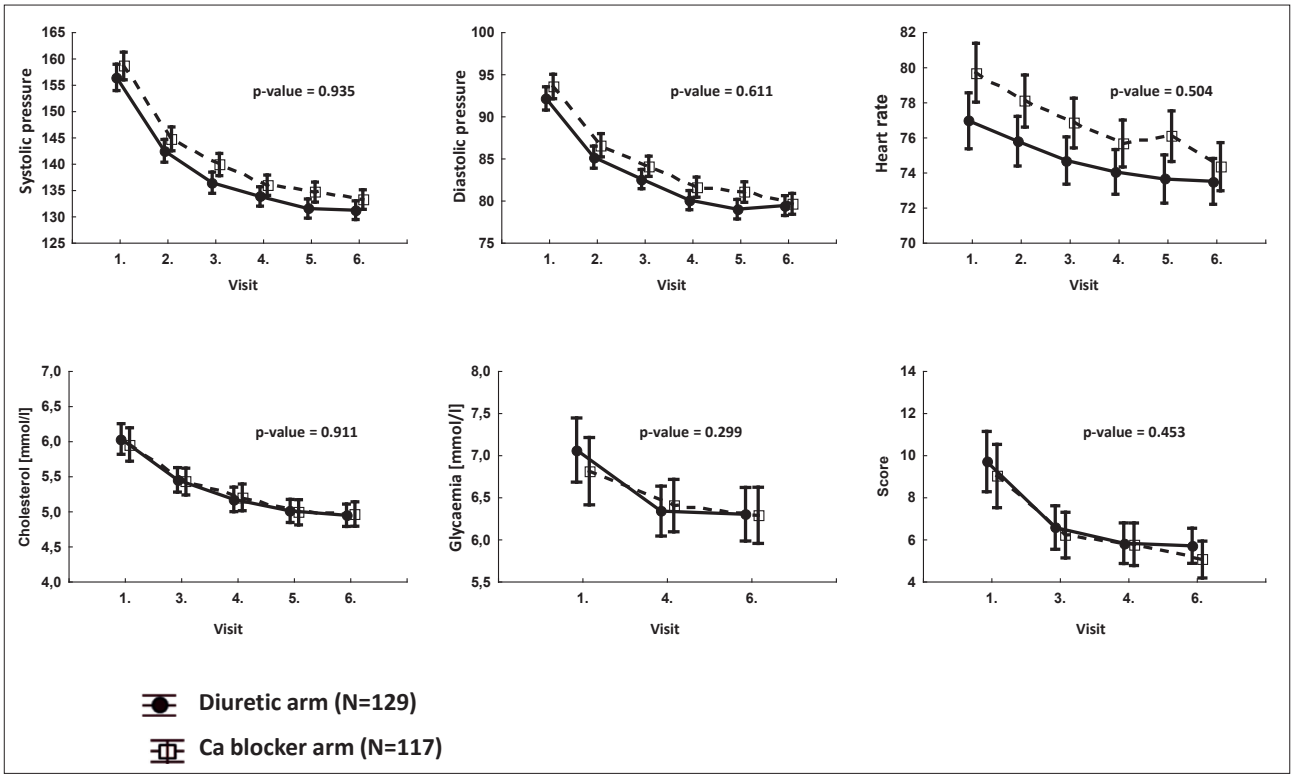

Fig. 2. Comparison of hydrochlorothiazide and amlodipine in combination therapy.

Table 1. Baseline characteristics of the subjects.

Parameter	Total (N=439)	ACE-I (N=217)	ARB (N=222)	*P*	Diuretic (N=129)	CCB (N=117)	*P*
Age (years)	60.7 (10.3)	60.6 (9.9)	60.9 (10.8)	0.745	61.6 (10.6)	60.1 (9.7)	0.227
N (%) men	214 (48.8)	105 (48.4)	109 (49.1)	0.881	70 (54.3)	54 (46.2)	0.204
Weight men (kg)	95.3 (16.5)	97.6 (16.9)	92.9 (15.9)	0.187	97.6 (15.9)	99.3 (20.9)	0.729
Height men (cm)	177.2 (5.6)	177.6 (5.6)	176.8 (5.6)	0.783	177.5 (5.5)	176.5 (6.9)	0.579
Weight women (kg)	81.8 (12.8)	83.2 (13.0)	80.3 (12.7)	0.297	81.7 (13.4)	79.5 (6.9)	0.353
Height women (cm)	165.2 (6.5)	165.7 (7.0)	164.6 (5.9)	0.414	163.7 (5.7)	165.0 (6.8)	0.773
DM n (%)	263 (59.9)	132 (60.8)	131 (59.0)	0.821	85 (65.9)	69 (59.0)	0.399
Smoking	140 (31.9)	69 (31.8)	71 (32.0)	0.967	38 (29.5)	34 (29.1)	0.945
SBP (mmHg)	156.3 (14.3)	155.6 (13.8)	156.9 (14.7)	0.364	156.5 (14.1)	158.7 (14.7)	0.193
DBP (mmHg)	92.6 (8.1)	92.5 (8.0)	92.6 (8.2)	0.922	92.2 (7.5)	93.6 (8.4)	0.163
Heart rate	78.1 (8.9)	77.9 (9.1)	78.4 (8.8)	0.150	77.0 (9.5)	79.7 (8.8)	**0.016**
Chol (mmol/L)	5.85 (1.29)	5.79 (1.27)	5.92 (1.30)	0.386	5.92 (1.25)	5.83 (1.09)	0.562
LDL (mmol/L)	3.37 (1.01)	3.33 (1.04)	3.41 (0.98)	0.528	3.34 (0.90)	3.36 (0.94)	0.723
HDL (mmol/L)	1.25 (0.41)	1.23 (0.39)	1.27 (0.43)	0.256	1.25 (0.37)	1.19 (0.42)	0.156
Gly (mmol/L)	6.77 (1.97)	6.76 (1.65)	6.78 (2.24)	0.276	7.07 (2.34)	6.82 (2.02)	0.398
Waist men (cm)	107.9 (11.3)	107.8 (11.5)	108.0 (11.2)	0.912	109.3 (11.8)	106.8 (11.4)	0.234
Waist women (cm)	97.5 (10.8)	98.5 (11.0)	96.4 (10.6)	0.151	98.1 (10.5)	97.1 (8.8)	0.566
SCORE	6.49 (7.97)	6.35 (8.47)	6.63 (7.47)	0.345	7.05 (8.25)	6.41 (8.24)	0.276

DM = diabetes mellitus, SBP = systolic blood pressure, DBP = diastolic blood pressure, Chol = total cholesterol, LDL = low density lipoproteins cholesterol, HDL = high density lipoproteins cholesterol, Gly = glycemia

of drug added to double combination in patients who completed the trial on double combination.

The table shows that adding either hydrochlorothiazide or amlodipine was equally effective.

Cholesterol decreased from 5.79 + 1.27 to 4.84+ 0.90 mmol/L in the ACE-I group and from 5.92 + 1.30 to 4.90 + 0.91 mmo/L in the ARB group (ns). There was a significant drop in plasma glucose level in both groups. Creatinine and urea remained unchanged in both groups. There was no difference between ACE-I and ARB.

There were also no differences between CCB and diuretics on metabolic parameters and kidney function

Table 2. Changes in blood pressure, pulse rate and SCORE classification according to the type of therapy initiation.

Parameter	ACE-I (n=217)	ARB (n=222)	*P*
SBP baseline (mmHg)	155.6 (13.8)	156.9 (14.7)	0.364
SBP month 1 (mmHg)	142.5 (12.3)	142.7 (12.1)	0.781
SBP month 3 (mmHg)	138.4 (10.7)	136.9 (11.1)	0.079
SBP month 6 (mmHg)	135.1 (9.9)	134.5 (11.0)	0.194
SBP month 12 (mmHg)	131.5 (9.9)	131.0 (9.2)	0.706
***P* baseline vs 12**	**< 0.001**	**< 0.001**	
DBP baseline (mmHg)	92.5 (8.0)	92.6 (8.2)	0.922
DBP month 1 (mmHg)	84.8 (7.3)	85.5 (7.5)	0.362
DBP month 3 (mmHg)	83.6 (6.7)	82.5 (7.1)	0.083
DBP month 6 (mmHg)	81.1 (6.4)	81.1 (7.3)	0.935
DBP month 12 (mmHg)	79.2 (6.8)	79.1 (6.5)	0.977
***P* baseline vs 12**	**< 0.001**	**< 0.001**	
Heart rate baseline	77.9 (9.1)	78.4 (8.8)	0.150
Heart rate month 1	76.1 (7.6)	76.4 (8.0)	0.842
Heart rate month 3	75.5 (7.6)	75.3 (7.0)	0.912
Heart rate month 6	74.7 (7.0)	75.0 (7.2)	0.831
Heart rate month 12	73.1 (6.9)	74.1 (7.6)	0.445
***P* baseline vs 12**	**< 0.001**	**< 0.001**	
SCORE baseline	6.35 (8.47)	6.63 (7.47)	0.345
SCORE month 3	4.55 (6.26)	4.52 (5.15)	0.662
SCORE month 6	4.03 (5.74)	4.28 (4.86)	0.556
SCORE month 12	3.66 (4.57)	4.06 (4.45)	0.416
***P* baseline vs 12**	**< 0.001**	**< 0.001**	

Table 3. Changes in blood pressure, pulse rate and SCORE classification according to the type of therapy initiation in patients who completed the trial on monotherapy.

Parameter	ACE-I (n=49)	ARB (n=47)	*P*
SBP baseline (mmHg)	149.6 (12.3)	154.5 (15.8)	0.088
SBP month 12 (mmHg)	129.4 (9.2)	129.6 (7.6)	0.953
***P* baseline vs 12**	**< 0.001**	**< 0.001**	
DBP baseline (mmHg)	92.5 (7.4)	92.9 (7.3)	0.896
DBP month 12 (mmHg)	78.3 (5.8)	79.4 (6.4)	0.443
***P* baseline vs 12**	**< 0.001**	**< 0.001**	
Heart rate baseline	79.7 (7.7)	78.3 (7.6)	0.335
Heart rate month 12	73.4 (7.2)	73.2 (7.3)	0.493
***P* baseline vs 12**	**< 0.001**	**< 0.001**	
SCORE baseline	5.15 (10.42)	5.84 (5.71)	0.183
SCORE month 12	3.32 (4.64)	3.82 (3.98)	0.452
***P* baseline vs 12**	**< 0.001**	**< 0.001**	

according to the type of therapy added to the double combination.

In five patients, diabetes mellitus was diagnosed during the trial, all of them being on combination therapy: two patients on the ARB + diuretic combination and one patient on the ARB + CCB, ACE-I + diuretic and ACE-I + CCB combinations each (ns).

Statin was added from month 3 in 113 patients, added to a diuretic in 33 patients and to amlodipine in 27 patients.

Table 6 shows the effect of adding statin to the therapy.

Table 7 shows the overall therapy evaluation.

It is evident from the table that better systolic blood pressure and SCORE system values were achieved in

Table 4. Changes in blood pressure, pulse rate and SCORE classification according to the type of therapy initiation in patients who completed the trial on combination therapy.

Parameter	**ACE-I (n=168)**	**ARB (n=175)**	*P*
SBP baseline (mmHg)	157.6 (10.8)	156.9 (15.8)	0.281
SBP month 12 (mmHg)	130.3 (8.5)	130.9 (8.4)	0.587
***P* baseline vs 12**	**< 0.001**	**< 0.001**	
DBP baseline (mmHg)	92.5 (8.1)	91.0 (10.1)	0.219
DBP month 12 (mmHg)	78.2 (6.7)	78.6 (6.6)	0.843
***P* baseline vs 12**	**< 0.001**	**< 0.001**	
Heart rate baseline	76.3 (8.5)	77.6 (9.9)	0.222
Heart rate month 12	72.5 (6.3)	73.6 (7.3)	0.470
***P* baseline vs 12**	**0.033**	**0.009**	
SCORE baseline	7.24 (7.07)	6.64 (6.42)	0.592
SCORE month 12	3.73 (4.39)	3.95 (3.25)	0.804
***P* baseline vs 12**	**< 0.001**	**< 0.001**	

Table 5. Changes in blood pressure, pulse rate and SCORE classification according to the type of double combination.

Parameter	**Diuretic (n=129)**	**CCB (n=117)**	*P*
SBP baseline (mmHg)	156.5 (14.1)	158.7 (14.7)	0.193
SBP month 12 (mmHg)	131.3 (10.0)	133.3 (10.5)	0.122
p baseline vs 12	**< 0.001**	**< 0.001**	
DBP baseline (mmHg)	92.2 (7.5)	93.6 (8.4)	0.163
DBP month 12 (mmHg)	79.5 (6.5)	79.7 (7.1)	0.715
***P* baseline vs 12**	**< 0.001**	**< 0.001**	
Heart rate baseline	77.0 (9.5)	79.7 (8.8)	**0.016**
Heart rate month 12	73.5 (6.6)	74.4 (8.5)	0.494
***P* baseline vs 12**	**< 0.001**	**< 0.001**	
SCORE baseline	7.05 (8.25)	6.41 (8.26)	0.276
SCORE month 12	4.21 (5.11)	3.76 (4.43)	0.343
***P* baseline vs 12**	**< 0.001**	**< 0.001**	

women. There is no difference between the RAAS blockade type and the added therapy type.

The incidence of nephropathy in the whole cohort was minimal. Urea > 10 mmol/L was recorded in eight patients upon the initial examination and in only three patients after a year; creatinine > 150 umol/L was observed in one patient upon the initial examination and in three patients after a year; both parameters were higher (Urea > 8 mmol/L and creatinine > 150 umol/L) in two patients upon the initial examination and in zero patients after a year. The calculated glomerular filtration ((140-age) x (weight in kg) x (1.23 for men and 1.04 for women): serum creatinine in umol/L)) of less than 50 ml/min was observed in only 37 (8.4%) patients at the start of the trial and in 35 (8.0%) patients at the end of the trial (ns).

DISCUSSION

Hypertension therapy can be initiated with monotherapy or with a combination of two drugs at low doses. Hypertension monotherapy is usually successful in a maximum of 30% of patients. In other patients, blood pressure can be normalized by means of a combination of two or

Table 6. The effect of adding statin in month 3.

Parameter	Total (N=113)	Diuretic (N=33)	CCB (N=27)	*P*
Cholesterol baseline (mmol/L)	*6.53 (1.09)*	*6.41 (1.08)*	*6.21 (0.81)*	*0.419*
Cholesterol month 3 (mmol/L)	*5.76 (0.94)*	*5.51 (0.91)*	*5.61 (0.95)*	*0.653*
Cholesterol month 12 (mmol/L)	4.97 (0.83)	4.97 (0.85)	4.92 (0.88)	0.819
***P* month 3 vs month 12**	**< 0.001**	**0.002**	**0.006**	
Glycemia baseline (mmol/L)	6.41 (1.35)	6.58 (1.33)	6.25 (1.31)	0.193
Glycemia month 3 (mmol/L)	5.94 (1.11)	6.01 (1.33)	5.88 (0.85)	0.894
Glycemia month 12 (mmol/L)	5.69 (0.83)	5.84 (0.81)	5.71 (0.72)	0.479
***P* month 3 vs month 12**				
SCORE baseline	7.12 (8.23)	8.22 (6.83)	5.92 (8.01)	0.072
SCORE month 3	4.28 (6.67)	4.38 (7.39)	4.08 (4.91)	0.545
SCORE month 12	3.40 (4.61)	3.63 (5.38)	3.01 (4.00)	0.287
***P* month 3 vs month 12**	**< 0.001**	**0.012**	**< 0.001**	

Table 7. Target values achieved.

Parameter	Blood pressure < 140/90 mmHg	SBP < 140 mmHg	DBP < 90 mmHg	Chol < 5 mmol/L	SCORE < 5
Total	334 (76.1%)	351 (80.0%)	400 (91.1%)	234 (53.3%)	269 (61.3%)
Men	154 (72.0%)	162 (75.7%)	196 (91.6%)	111 (51.9%)	99 (46.3%)
Women	180 (80.0%)	189 (84.0%)	204 (90.7%)	123 (54.7%)	170 (75.6%)
P	0.057[+]	**0.032**	0.741	0.567	**<0.001**
≥ 70 years old	68 (77.3%)	73 (83.0%)	77 (87.5%)	55 (62.5%)	31 (35.2%)
< 70 years old	266 (75.8%)	278 (79.2%)	323 (92.0%)	179 (51.0%)	238 (67.8%)
P	0.889[+]	0.551	0.208	0.057	**<0.001**[+]
ACE-I	163 (75.1%)	170 (78.3%)	198 (91.2%)	113 (52.1%)	140 (64.5%)
ARB	171 (77.0%)	181 (81.5%)	202 (91.0%)	121 (54.5%)	129 (58.1%)
P	0.656	0.407	1.000	0.633	0.172
ACE-I mono	41 (83.7%)	42 (85.7%)	48 (98.0%)	27 (55.1%)	35 (71.4%)
ARB mono	37 (78.7%)	40 (85.1%)	43 (91.5%)	29 (61.7%)	28 (59.6%)
P	0.606	1.000	0.199	0.541	0.284
Diuretic	99 (76.7%)	104 (80.6%)	117 (90.7%)	65 (50.4%)	76 (58.9%)
CCB	80 (68.4%)	84 (71.8%)	104 (88.9%)	54 (46.2%)	72 (61.5%)
P	0.154	0.132	0.677	0.525	0.697

more antihypertensive drugs[4,5]. The combination therapy with two antihypertensive drugs at lower doses or with a fixed combination is preferred upon the start of pharmacological treatment if the initial blood pressure values are 160 and/or 100 mmHg or more, or if the blood pressure target values are around 130/80 mmHg. The reasons for recommending the combination therapy as the initial pharmacotherapy are as follows: a) combination treatment is much more effective than monotherapy[6]; b) in high risk patients, it may be crucial how fast the patient's blood pressure is normalized; c) the patient's adherence to the therapy depends, among other things, on the confidence in the capacity to quickly achieve target values. Within MEDINA, monotherapy with an ACE inhibitor or statin was sufficiently effective in only 1/5 of patients (22.6% and 21.2%, respectively) even the full dose of AC-I or ARB was not achieved because step No 2 was adding CCB or diuretics to a medium dose of ACE-I or ARB. More than half the patients were sufficiently controlled by a double combination (53.9% or 58.1%, respectively) and another 1/5 of patients (23.5% or 20.7, respectively) needed a triple combination.

In the pharmacotherapy of hypertension, the following groups of antihypertensive drugs are primarily used for both monotherapy and combination therapy: ACE-I, ARB, CCB with long-term effect, diuretics and beta-blockers. These classes of antihypertensive drugs have shown sufficient success in the reduction of cardiovascular morbidity and mortality, in particular cerebrovascular events. Other drugs are suitable only when successful control of hypertension cannot be achieved using basic antihypertensive drugs. The main contribution of pharmacotherapy of hypertension consists in the reduction of blood pressure; however, when selecting an antihypertensive drug for a specific patient, we also consider other characteristics of preparations, such as their impact on the metabolic and hemodynamic parameters and renal function.

ACE-I have, together with ARB, become universal antihypertensive drugs. Besides their antihypertensive effect, they also have cardio-, vaso- and renoprotective effects and

have a favourable impact on sugar metabolism. They improve the prognosis in high-risk patients with IHD, stroke or peripheral atherosclerosis, and in diabetic patients. Both ACE-I and ARB also reduce the risk of new-onset diabetes. Their major contraindication is hypertension in pregnancy; as regards ACE-I, the adverse effects of treatment also involve dry irritating cough.

ACE-I and ARB have been compared with other classes of antihypertensive drugs in many trials: some of them show the same efficacy as other antihypertensive drugs (e.g. HOT or ALLHAT trials), while others demonstrate their superiority. In 2002, the large clinical trial LIFE (9,193 patients with hypertrophy of the left ventricle) was completed and published, which proved that the strategy of hypertension treatment initiated with losartan was more effective in the prevention of cardiovascular events, in particular stroke (P=0.021), as well as in the prevention of new-onset diabetes mellitus than the strategy of treatment initiated with atenolol[7]. The SCOPE trial compared candesartan with another antihypertensive therapy in 4,937 hypertensive patients over 70 years of age. The primary objective, which consisted in reducing major cardiovascular events (death, myocardial infarction, stroke), was achieved in 10.9%, thus not reaching statistical significance (P=0.19) (ref.[8]). The decrease in cerebrovascular events (P=0.04) was statistically significant while the reduction in new-onset diabetes mellitus was on the border of statistical significance. The MOSES trial compared eprosartan with nitrendipine in 1,405 patients in the secondary prevention of cerebrovascular events; with an equal blood pressure drop, eprosartan more importantly reduced the number of both cardiovascular events (P=0.06) and cerebrovascular events (P=0.03) (ref.[9]). Within the VALUE trial, the ARB valsartan was more effective in the prevention of new-onset diabetes mellitus than the calcium-channel antagonist amlodipine.

No direct comparison between ACE-I and ARB in hypertensive patients within a mortality trial has yet been performed. Partial information is provided by the data resulting from the secondary prevention ONTARGET trial in patients with ischemic heart disease[10]. ONTARGET, performed in 25,557 patients, confirmed the equal effectiveness of the ARB telmisartan and the ACE-I ramipril in the secondary prevention of ischemic heart disease and also clearly pointed out the risk of deterioration of renal functions in case of treatment with a combination of the two preparations[5].

We compared losartan and ramipril in the CORD clinical program[11]. Within CORD IA, we proved in 4,016 patients that moving from ACE-I to losartan is safe, while in CORD IB, performed in 3,813 patients, we proved the equal effects of ramipril and losartan with a more frequent incidence of cough after ramipril.

Within MEDINA, the initiation of treatment with an ACE-I (ramipril or perindopril) and with ARB (losartan) was equally effective. In both the arms, monotherapy was sufficient in approx. 1/5 of patients; blood pressure drop during all follow-up visits was comparable; after 12 months it was 24.1/13.3 after ACE-I and 25.9/13.5 after ARB (ns between groups). We also observed pulse rate reduction in both the arms: 4.8 beats/min after ACE-I and 4.3 beats/min after losartan. A similar small heart rate drop(< 10%) was observed in the CORD and MEDINA trials and we have described it earlier and it also corresponds, for instance, to the LIFE trial, where the pulse rate dropped by 1.9 beats/min. after losartan.

The most preferred combination is the concurrent administration of calcium-channel antagonist and ACE inhibitors[12,4]. Such attitude is based on the ASCOT trial and more importantly on the ACCOMPLISH trial[13], within which patients with hypertension and a high cardiovascular risk were treated with an ACE-I and then randomized for supplementary treatment with the dihydropyridine calcium channel antagonist amlodipine or a thiazide diuretic. It turned out that patients with the combination of an ACE-I and CCB had a 20% lower risk of cardiovascular events. As regards the combination of ARB with CCB, we have no data from a prospective study but a similar effect is presumed. The combination of an ACE-I / ARB with a diuretic is highly effective and can be used, for instance, for hypertension in older or diabetic patients; however, based on the ADVANCE and HYVET trials we choose indapamide (or chlorthalidone) rather than hydrochlorothiazide[14-16]. CCB and diuretics are drug groups with similar characteristics and therefore, their additive antihypertensive effect was not presumed, but this combination has been successfully used in several large trials, most recently in COPE (ref.[17]). Messerli emphasises that in 2008, 47.8 million prescriptions for hydrochlorothiazide alone and 87.1 million for hydrochlorothiazide in combination were given in the United States[16,18]. However, there is no evidence that hydrochlorothiazide at the recommended dose of 12.5-25.0 mg reduces the incidence of myocardial infarction, cerebrovascular events or death. In combination with ACE-I, hydrochlorothiazide was less effective than CCB (ref.[19]).

Similar data for the combination of a CCB + an ACE-I result from the STAR trial, which implied that the combination of ACE-I + CCB (in this case verapamil) might have better metabolic effects than the combination of ARB + diuretic[20].

Within MEDINA, the addition of amlodipine and hydrochlorothiazide to one of the RAAS blockers was equally effective. Blood pressure drop after one year was 5.2/3.1 after a diuretic and 6.6/4.4 mmHg after amlodipine (blood pressure in month 3 when monotherapy was replaced by combination therapy was used as the initial pressure for comparison). The pulse rate dropped by 1.2 after hydrochlorothiazide and, surprisingly, by 2.4 after amlodipine (ns between groups). We have no explanation for this insignificant reduction; it might also be a distortion due to increasing the ACE-I and ARB doses in 1/5 of patients, which was step 3 in month 6 of the trial.

Consequently, our trial did not confirm the inferiority of hydrochlorothiazide, which corresponds to the presumption that in the short term a drop in blood pressure per se is substantial, while the selection of an antihypertensive drug is crucial in the long-term[18].

The effect of adding statin in 113 patients starting from month 3 is difficult to evaluate. Cholesterol dropped from 5.76 mmol/L to 4.97 mmol/L, the drop being even in all the groups.

The values of SCORE risk charts were determined as the primary objective[5]. The overall drop was from 6.35 to 3.66 after ACE-I and from 6.63 to 4.06 after ARB (ns between groups, $P<0.001$ over time). Patients who completed the trial on monotherapy were at less risk from the very start and the drop went from 5.15 to 3.32 after ACE-I and from 5.84 to 3.82 after ARB (ns between groups, $P<0.001$ over time), while in the combination therapy group the drop went from 7.24 to 3.73 after ACE-I and from 6.64 to 3.95 after ARB (ns between groups, $P<0.001$ over time). The major risk reduction was observed after treatment had been initiated, i.e. in the first three months, of almost 2%, while risk rate reduction between months 3 and 12 was less than 1%. A total of 61.3% of patients demonstrated the risk SCORE < 5 upon completing the trial. It should be noted that in a similar population it is never possible to achieve SCORE < 5 in 100% of the population as in persons over 65 years old only women non-smokers with a systolic blood pressure of 120 mmHg or less and with cholesterol ≤ 5 mmol/L have SCORE less than 5 while all the others have 6 or more.

CONCLUSION

MEDINA confirms the equal effectiveness of ACE-I (perindopril and ramipril) and ARB (losartan) if correctly dosed for blood pressure drop, but also for similar SCORE risk reduction, with metabolic neutrality for both lipid parameters and glucose metabolism. However, monotherapy is sufficient in only 1/5 of patients. Combination therapy is required in 4/5 of patients. The diuretic hydrochlorothiazide and the CCB amlodipine added to the therapy for RAAS blockade were equally effective with respect to both blood pressure drop and SCORE charts and also with respect to metabolic parameters. After one year of therapy, we observe no adverse effects of hydrochlorothiazide in terms of cholesterol increase or new-onset diabetes mellitus.

Limitations of the trial

The trial was randomized and open-label. The main limitation of the trial is the cohort size and the length of follow-up, which do not allow us to compare mortality and morbidity. Nevertheless, we believe that the trial confirms RAAS blockade (ACE-I or ARB) as the first choice therapy in non-complicated hypertension, while we recommend including dihydropyridine, which has a long-lasting effect, and/or a diuretic, in our case hydrochlorothiazide at a maximum dose of 25 mg, as the first choice drug for combination therapy.

CONFLICT OF INTEREST STATEMENT

Author's conflict of interest disclosure: *None declared.*

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