# CORD: COmparsion of Recommended Doses of ACE inhibitors and angiotensin II receptor blockers

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**Summary:** *Objectives:* The CORD trials tested ramipril and losartan in patients with hypertension. *Patients and methods:* CORD IA involving switching from an angiotensin-converting enzyme inhibitor (ACEI) to the angiotensin II receptor blocker (ARB) losartan. 4,016 patients with blood pressure (BP) < 160/100 mm Hg who had been treated with an ACEI for > 3 months were enrolled. The mean age was 62.6 ± 11.6 years and 53.1% were women. The patients discontinued ACEI and switched to losartan 50 mg once daily. BP, heart rate, biochemistry, blood counts and ECGs were measured at day 1 and months 1, 3, 6 and 12. If the BP was ≥ 140/90 mm Hg after 1 month or more, the dose of losartan was increased to 100 mg. After 1 month the BP decreased from 147.4 ± 14.8/87.7 ± 9.3 mm Hg to 139.7 ± ± 11.8/83.0 ± 9.3 mm Hg ($p < 0.001$) and after 1 year to 133.7 ± 11.3/79.1 ± 7.06 mm Hg ($p < 0.001$). The rate of adverse events did not significantly increase and no changes in plasma sodium, potassium, urea or creatinine were observed. CORD IB compared ramipril and losartan. 3 813 patients with BP ≥ 140/90 mm Hg who were not being treated with an ACEI or ARB were enrolled. The mean age was 60.5 ± 12,2 years and 50.5% were women. The patients were randomised to ramipril 5 mg (n = 1 926) or losartan 50 mg (n = 1 887). The dose was doubled if BP after 1 month was ≥ 140/90 mm Hg. If the BP after 3 months still was ≥ 140/90 mm Hg, another antihypertensive drug was added, typically a thiazide diuretic. *Results:* After 1 year the BP decreased in the ramipril group from 155.9 ± 13.1/93.0 ± 8.9 mm Hg to 134.1 ± 11.2/81.5 ± 6.8 mm Hg ($p < 0.001$) and in the losartan group from 156.5 ± 13.1/93.4 ± 8.8 to 134.55 ± 11.3/80.16 ± 6.6 mm Hg ($p < 0.001$). No significant differences were found between the groups. A slight increase in plasma potassium (0.2 mmol in both groups) and urea (0.3 mmol in both groups) was observed, but no change in plasma creatinine. There was a small, insignificant decrease in plasma uric acid (in the ramipril group from 325.5 to 320.7 μmol/l and in the losartan group from 321.6 to 318.3 μmol/l) and a slight decrease in plasma glucose and triglycerides (0.2 mmol/l in both measures in both groups). No severe adverse events were observed, but dry cough was 8 times more frequently reported in the ramipril group. *Conclusion:* CORD IA confirmed that switching from an ACEI to losartan is safe and effective. Titrating the dose upwards or adding diuretics leads to good BP control in the majority of patients (2/3). CORD IB showed no differences between ramipril and losartan in lowering BP and both drugs showed a trend to improve metabolic parameters such as glycaemia, triglyceridaemia and uric acid equally. Dry cough was more frequent after ACEI.

**Key words:** hypertension – isolated systolic hypertension – ramipril – losartan – metabolic parameters – cough

Drugs acting via renin-angiotensin-aldosterone (RAA) blockade are the preferred treatment for hypertension when it is combined with other conditions [1] and are indicated in patients with hypertension and diabetes mellitus, metabolic syndrome, ischaemic heart disease, heart failure or paroxysmal atrial fibrillation, as well as in young people with uncomplicated hypertension. Several clinical trials have demonstrated beneficial effects not only in controlling blood pressure (BP), but also in reducing the onset of diabetes. They compared ACEI or ARBs with beta blockers and/or diuretics [2–4] and calcium channel blockers [5,6]. Randomised controlled trials involving approximately 150,000 patients have convincingly demonstrated that angiotensin-converting enzyme inhibitors (ACEI) reduce mortality and rates of myocardial infarction, stroke and heart failure in patients with heart failure, left ventricular dysfunction, and previous vascular disease alone or high risk diabetes [7–12]. Direct comparison of ACEI and angiotensin II receptor blockers (ARB) has been performed in patients with chronic heart failure, post-myocardial infarction and stable coronary artery disease [13–18] and suggests they are equally efficacious. We found a similar effect of captopril 25 mg three times daily and losartan 50 mg once daily on BP lowering and left ventricle remodelling in patients after myocardial infarction [19,20].

The CORD (**CO**mparison of **R**ecommended **D**oses) is a multicenter, prospective, open label, blinded endpoint trial involving hypertensive pa-

**CORD: *CO*mparsion of *R*ecommended *D*oses of ACE inhibitors and angiotensin II receptor blockers.**
**Porovnání doporučených dávek ACE inhibitorů a antagonistů receptoru angiotensinu II.**

**Souhrn:** *Cíle:* Studie CORD testovaly použití přípravků ramipril a losartan u pacientů s hypertenzí. *Pacienti a metodologie:* CORD IA byla zaměřena na přechod z léčby inhibitorem angiotenzin konvertujícího enzymu (ACEI) na léčbu antagonistou receptoru angiotensinu II (ARB) – losartanem. Do studie bylo zařazeno 4 016 pacientů s krevním tlakem (TK) < 160/100 mm Hg léčených ACEI po dobu > 3 měsíce. Průměrný věk byl 62,6 let a 53,1 % pacientů byly ženy. Pacienti ukončili léčbu ACEI a začali užívat losartan 50 mg jednou denně. TK, tepová frekvence, biochemie, krevní obraz a EKG byly měřeny v den 1 a dále měsíc 1, 3, 6 a 12. Pokud byl po 1 a více měsících léčby TK ≥ 140/90 mm Hg, byla dávka losartanu zvýšena na 100 mg. Po měsíci léčby se TK snížil ze 147,4 ± 14,8/87,7 ± 9,3 mm Hg na 139,7 ± 11,8/83,0 ± 9,3 mm Hg (p < 0,001) a po 1 roce léčby na 133,7 ± 11,3/79,1 ± 7,06 mm Hg (p < 0,001). V průběhu léčby nedošlo k nárůstu výskytu nežádoucích účinků a nebyly zaznamenány žádné změny v plazmatických hladinách sodíku, hořčíku, urey ani kreatininu. Studie CORD IB srovnávala ramipril a losartan. Do studie bylo zařazeno 3 813 pacientů s TK ≥ 140/90 mm Hg, kteří nebyli léčeni ani ACEI, ani ARB. Průměrný věk byl 60,5 ± 12,2 let a 50,5 % pacientů byly ženy. Pacienti byly randomizováni do skupiny užívající ramipril 5 mg (n = 1 926) nebo losartan 50 mg (n = 1 887). Pokud byl TK po 1 měsíci ≥ 140/90 mm Hg, byla dávka zdvojnásobena. Pokud byl TK po 3 měsících stále ≥ 140/90 mm Hg, bylo přidáno další antihypertenzivum, obvykle thiazidové diuretikum. *Výsledky:* Ve skupině užívající ramipril došlo po 1 roce léčby ke snížení TK ze 155,9 ± 13,1/93,0 ± 8,9 mm Hg na 134,1 ± 11,2/81,5 ± 6,8 mm Hg (p < 0,001) a ve skupině léčené losartanem ze 156,5 ± 13,1/93,4 ± 8,8 na 134,55 ± 11,3/80,16 ± 6,6 mm Hg (p < 0,001). Mezi skupinami nebyly zjištěny žádné významné rozdíly. Bylo zjištěno mírné zvýšení plazmatických hladin draslíku (0,2 mmol v obou skupinách) a urey (0,3 mmol v obou skupinách), nicméně žádné změny plazmatických hladin kreatininu. Bylo zjištěno mírné, statisticky nevýznamné snížení plazmatických hladin kyseliny močové (z 325,5 na 320,7 μmol/l ve skupině s ramiprilem a z 321,6 na 318,3 μmol/l ve skupině s losartanem) a mírné snížení plazmatických hladin glukózy a triglyceridů (0,2 mmol/l u obou parametrů v obou skupinách). Nebyly zjištěny žádné závažné nežádoucí příhody, avšak suchý kašel byl 8krát častější ve skupině léčené ramiprilem. *Závěr:* Studie CORD IA potvrdila, že změna z ACEI na losartan je bezpečná a účinná. Titrace dávky směrem nahoru nebo přidání diuretika přináší dobrou kontrolu TK u většiny pacientů (2/3). Studie CORD IB prokázala, že mezi přípravky ramipril a losartan není rozdíl v účinnosti s ohledem na snižování TK; u obou přípravků byl navíc zjištěn stejně silný trend směrem ke zlepšení metabolických parametrů, jako jsou glykemie, triglyceridemie a hladiny kyseliny močové. Suchý kašel byl častější po ACEI.

**Klíčová slova:** hypertenze – izolovaná systolická hypertenze – ramipril – losartan – metabolické parametry – kašel

tients (treatment was allocated according to birthdate) and testing two hypotheses:

1. Switching from an ACEI to losartan in patients treated with an ACEI for hypertension for > 3 months is safe and is not accompanied by new adverse events or increases in blood pressure (CORD IA).
2. Adding ramipril or losartan in comparable doses to the treatment of poorly controlled hypertension will lead to similar blood pressure decreases and hypertension control and similar occurrence of adverse events (CORD IB).

## Methods

### Study design

Patients were eligible for CORD IA if they had been treated for hypertension with an ACEI for > 3 months and had a BP < 160/100 mm Hg. Patients with any documented cardiovascular event during last three months were excluded. Treatment with additional antihypertensive agents, other than ARB, was allowed.

After written informed consent was obtained, patients discontinued their ACEI on day 1 and started losartan 50 mg daily on day 2. BP, heart rate, biochemistry, blood counts and ECGs were measured at day 1 and months 1, 3, 6 and 12. The dose of losartan could be lowered to 25 mg at the treating physician's discretion. If after 1 month or more of treatment with losartan BP was ≥ 140/90 mm Hg the dose of losartan was increased to 100 mg. If the BP was ≥ 140/90 mm Hg after at least 3 months of treatment with 100 mg losartan another hypertensive drug was recommended (typically a thiazide diuretic, if this was not already a part of treatment) (Fig. 1).

Patients were eligible for CORD IB if they had BP ≥ 140/90 mm Hg, had been stable for at least 3 months and were not being treated with an ACEI or ARB. Any other antihypertensive treatment was allowed. The exclusion criteria were a history of ACEI intolerance, serum creatinine > 250 μmol/l or preg-

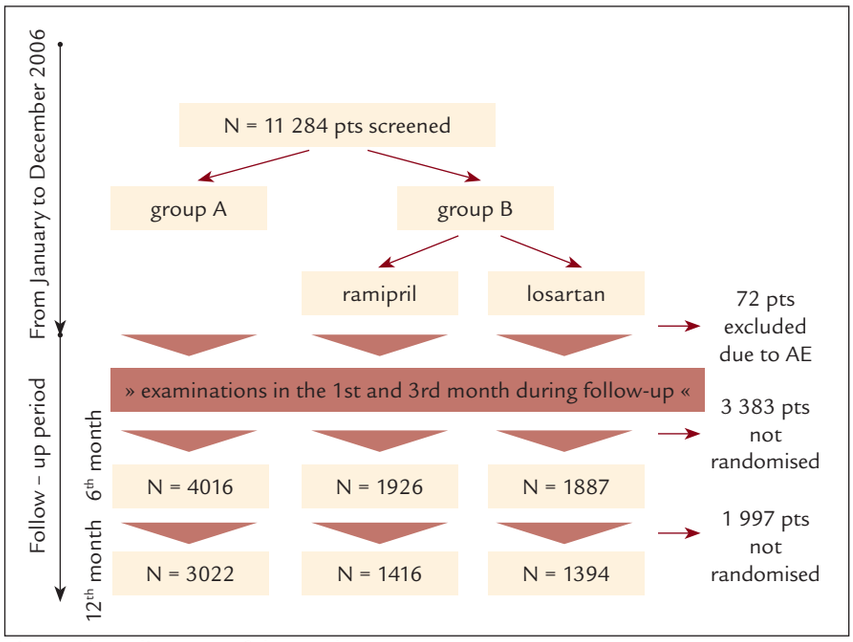


Fig. 1. Flow diagram of the study.

Tab. 1. Baseline characteristics of patients with 6 months of follow-up and who were included in the analysis.

| Characteristics | Group A (N = 4 016) | Group B (N = 3 813) | B – Ramipril (N = 1 926) | B – Losartan (N = 1 887) |
|---|---|---|---|---|
| General characteristic (mean ± SD) | | | | |
| age (years) | 62.6 ± 11.6 | 60.5 ± 12.2 | 60.4 ± 12.5 | 60.6 ± 11.8 |
| female sex (%) | 53.1 | 50.5 | 49.0 | 52.1 |
| weight (kg) | 84.1 ± 14.5 | 84.6 ± 14.9 | 84.5 ± 15.4 | 84.6 ± 14.5 |
| height (cm) | 170.0 ± 8.6 | 170.7 ± 8.8 | 170.9 ± 8.8 | 170.6 ± 8.9 |
| Patient history (%) | | | | |
| positive family history | 67.0 | 66.7 | 67.8 | 65.5 |
| current smoker | 20.3 | 23.3 | 23.0 | 23.5 |
| ex-smoker | 21.4 | 19.9 | 21.3 | 18.5 |
| diabetes mellitus | 33.0 | 29.3 | 28.6 | 30.1 |
| history of IHD | 30.3 | 25.4 | 26.7 | 24.1 |
| previous MI | 13.2 | 11.7 | 13.0 | 10.4 |
| dilated cardiomyopathy | 1.6 | 1.4 | 1.6 | 1.2 |
| heart failure | 7.1 | 5.7 | 6.0 | 5.3 |
| known dyslipidaemia | 60.5 | 55.0 | 55.6 | 54.4 |
| known cough | 34.5 | 6.8 | 5.3 | 8.4 |
| Concomitant medication at baseline (%) | | | | |
| beta blocker | 43.0 | 41.6 | 39.9 | 43.3 |
| Ca blocker type DHP | 28.3 | 28.4 | 29.7 | 27.0 |
| Ca blocker type non-DHP | 5.3 | 5.8 | 5.0 | 6.7 |
| diuretics | 47.8 | 42.8 | 41.6 | 44.0 |
| alpha blocker | 4.4 | 4.0 | 4.1 | 3.9 |
| aspirin | 35.6 | 30.9 | 31.8 | 29.9 |
| clopidogrel | 0.7 | 1.1 | 1.4 | 0.7 |
| warfarin | 4.1 | 3.4 | 3.2 | 3.5 |
| statin | 43.6 | 38.2 | 39.6 | 36.8 |
| nitrate | 15.3 | 12.0 | 11.5 | 12.5 |
| oral antidiabetic medication | 15.3 | 12.0 | 20.0 | 20.8 |
| other medication | 46.2 | 42.7 | 43.2 | 42.2 |

IHD – ischaemic heart disease, MI – myocardial infarction, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, DHP – dihydropyridine

nancy. Patients were randomised according to their day of birth either to treatment with ramipril (born on an odd day) or losartan (born on an even day) (Fig. 1). The recommended starting dose was 5 mg ramipril or 50 mg losartan, but could be 2.5 mg ramipril and 25 mg losartan, at the physician's discretion. The dose was increased if after at least 1 month the BP was not < 140/90 mm Hg; an additional antihypertensive agent was recommended if the patients has been on 10mg ramipril or 100 mg losartan for more than 3 months and the BP was not < 140/90 mm Hg (Fig. 1).

The main primary outcome was BP decrease and normalisation of BP (< 140/90 mm Hg); the main secondary outcome was the incidence of adverse events, clinical as well as laboratory (defined as the percentage of patients with abnormal laboratory values, including renal parameters, potassium and metabolic parameters).

## Patients

The CORD trials were performed throughout the Czech Republic. 585 doctors were involved. Screening began in January 2006 and randomisation continued until December 2006. The aim was to randomise > 5 000 patients into the losartan arm. Altogether, 11,284 patients were screened and 7,829 were randomised. Data from 72 patients with serious adverse events and permanent study discontinuation were available only at the study beginning. These patients were included in the adverse events evaluation. As non-randomised patients were included also patients with insufficient data on baseline, so that they could not be included into statistical analysis. Complete data at 6 months was available for 4,016 CORD IA patients and 3,813 Cord IB patients (1,926 in the ramipril and 1,887 in the losartan group). Complete data at 12 months was available for 3,022 CORD IA patients and 2,810 Cord IB patients (1,416 in the ramipril group and 1,394 in the losartan group).

## Statistical analysis

Descriptive statistics including mean and standard deviation as well as frequency tables were used to describe patient characteristics. Decreases in

Tab. 2. Change in systolic and diastolic blood pressure and heart rate in the sitting position during follow-up.

| | Time | Group A mean ± SD | Group B mean ± SD | B – Ramipril mean ± SD | B – Losartan mean ± SD | p-value ramipril vs. losartan |
|---|---|---|---|---|---|---|
| SBP (mm Hg) | 0 | 147.4 ± 14.8 | 156.2 ± 13.1 | 155.9 ± 13.1 | 156.5 ± 13.1 | |
| | 6 | 134.2 ± 10.5 | 134.9 ± 10.5 | 134.9 ± 10.5 | 134.8 ± 10.5 | 0.176 |
| | 12 | 133.6 ± 10.3 | 134.3 ± 11.2 | 134.1 ± 11.2 | 134.5 ± 11.3 | 0.631 |
| DBP (mm Hg) | 0 | 87.7 ± 9.3 | 93.2 ± 8.8 | 93.0 ± 8.9 | 93.4 ± 8.8 | |
| | 6 | 79.9 ± 6.4 | 80.5 ± 6.5 | 80.3 ± 6.5 | 80.6 ± 6.5 | 0.883 |
| | 12 | 79.0 ± 6.5 | 79.7 ± 6.8 | 79.3 ± 6.9 | 80.1 ± 6.6 | 0.359 |
| HR (–1) | 0 | 73.6 ± 9.6 | 74.9 ± 9.6 | 74.7 ± 9.3 | 75.1 ± 10.0 | |
| | 6 | 71.6 ± 7.5 | 71.9 ± 7.0 | 71.8 ± 7.0 | 72.1 ± 7.0 | 0.971 |
| | 12 | 71.0 ± 7.8 | 71.2 ± 7.4 | 71.3 ± 7.4 | 71.2 ± 7.5 | 0.114 |

Tab. 3. Change in systolic and diastolic blood pressure and heart rate in the standing position during follow-up.

| | Time | Group A mean ± SD | Group B mean ± SD | B – Ramipril mean ± SD | B – Losartan mean ± SD | p-value ramipril vs. losartan |
|---|---|---|---|---|---|---|
| SBP (mm Hg) | 0 | 146.6 ± 15.5 | 155.5 ± 13.4 | 155.3 ± 13.3 | 155.7 ± 13.5 | |
| | 6 | 134.1 ± 11.6 | 134.9 ± 11.5 | 134.8 ± 11.5 | 135.1 ± 11.5 | 0.818 |
| | 12 | 133.3 ± 11.3 | 134.1 ± 11.7 | 134.0 ± 12.1 | 134.2 ± 11.3 | 0.994 |
| DBP (mm Hg) | 0 | 87.2 ± 9.5 | 92.5 ± 8.9 | 92.5 ± 9.0 | 92.5 ± 8.8 | |
| | 6 | 79.9 ± 7.1 | 80.4 ± 7.2 | 80.3 ± 7.2 | 80.6 ± 7.2 | 0.528 |
| | 12 | 79.1 ± 7.0 | 79.7 ± 7.3 | 79.4 ± 7.4 | 80.0 ± 7.2 | 0.209 |
| HR (–1) | 0 | 76.0 ± 8.7 | 77.3 ± 9.6 | 77.3 ± 9.8 | 77.3 ± 9.3 | |
| | 6 | 73.9 ± 7.4 | 74.4 ± 7.4 | 74.3 ± 7.5 | 74.5 ± 7.2 | 0.427 |
| | 12 | 73.7 ± 7.4 | 74.1 ± 7.7 | 74.3 ± 7.9 | 74.0 ± 7.5 | 0.564 |

Tab. 4. Changes in hypertension grade from month 0 to month 6.

| | Group A | Group B | Ramipril | Losartan |
|---|---|---|---|---|
| from ISH to normotension (%) | 15.9 | 13.4 | 14.2 | 12.6 |
| from HT to normotension (%) | 31.7 | 46.1 | 45.6 | 46.6 |
| from HT to ISH (%) | 14.4 | 21.8 | 21.2 | 22.3 |
| improvement ≥ 1 grade but not reaching normotension | 4.0 | 7.0 | 7.2 | 6.9 |
| unchanged (%) | 34.0 | 11.7 | 12.8 | 11.6 |

Tab. 5. Changes in hypertension grade from month 0 to month 12.

| | Group A | Group B | Ramipril | Losartan |
|---|---|---|---|---|
| from ISH to normotension (%) | 8.6 | 7.4 | 7.6 | 7.8 |
| from HT to normotension (%) | 39.8 | 53.8 | 54.7 | 53.0 |
| from HT to ISH (%) | 6.0 | 7.7 | 7.6 | 7.2 |
| improvement > 1 grade but not reaching normotension | 9.4 | 15.8 | 15.3 | 16.2 |
| unchanged (%) | 36.2 | 15.3 | 14.8 | 15.8 |

the primary outcomes were assessed for the different patient groups using paired t-tests. Differences between the ramipril and losartan groups in the magnitude of any decreases were evaluated with two sample t-tests. Assessment of difference in the proportions of patients whose BP was normalized between comparable groups was performed using Fisher's exact test for contingency tables.

### Ethics approval

The trial was approved by a multicentric ethics committee and the patients signed an informed consent form before entering the study. The study was monitored by an independent monitoring company, the Institute for Biostatistics and Analysis of the Masaryk University Brno. The safety committee was represented by the members of the Academic Board of the Medical Faculty, Masaryk University, Brno, Czech Republic. The study was not sponsored by any pharmaceutical company; data collection was done by Institute of Biostatistical Analysis, Medical Faculty, Masaryk University. The drugs were prescribed on prescription, recommended was to prescribe drugs from pharmaceutical company Zentiva, a.s.

## Results

Baseline characteristics of the patients with complete 6 month data are shown in tab. 1. There were no differences in concomitant antihypertensive treatment, 47.8% in CORD IA and 42.8% in CORD IB were treated with diuretics, 43.0%, resp. 41.6% with beta blocker and 33.6% vs 34.1% with calcium chanel blockers (ramipril vs losartan ns).

BP decreases are shown in tab. 2 (sitting position) and tab. 3 (standing position). The BP decreases at months 6 and 12 were highly statistically significant when compared to baseline. There were no statistical differences in BP between ramipril and losartan in CORD IB. The BP decrease was significantly higher in CORD 1B than in CORD IA ($p < 0.001$).

Changes in the grade of hypertension are shown in tab. 4, 5. 64.2% patients in CORD IA and 59.5% in CORD IB were normotensive at month six. 64.5% patients in CORD IA and 61.2% in CORD IB were normotensive at month twelve. 59.1% patients on losartan and 59.9% patients on ramipril were normotensive at month six (ns). 60.5% patients on losartan were normotensive and 62.2% patients on ramipril were normotensive at month twelve (ns). Changes in laboratory parameters are shown in tab. 6, 7.

Serious adverse events are shown in tab. 8. All adverse events occurred at a frequency of < 1%, except cough in ramipril group. 72 patients discontinued the study because of adverse events, 25 in CORD IA and 47 in CORD IB (14 on losartan and 34 on ramipril). In 21 (1%) patients on ramipril, the reason for discontinuation was cough.

The treatment dose was classified as low (2.5 mg ramipril or 25 mg losartan), medium (5.0–7.5 mg ramipril or 50–75 mg losartan), high (10 mg ramipril or 100 mg losartan) or high+ (if another antihypertensive drug was added during the study). For baseline evaluation, equipotent doses of various ACEI in CORD IA patients were classified (tab. 9).

**Tab. 6. Laboratory changes between baseline and month 12 (all not significant).**

| Parameter | Group A | | Group B | |
|---|---|---|---|---|
| | Baseline | Month 12 | Baseline | Month 12 |
| cholesterol (mmol/l) | 5.44.4 ± 0.4 | 5.2 ± 0.8 | 5.5 ± 1.0 | 5.2 ± 0.8 |
| glycaemia (mmol/l) | 5.9 ± 1.6 | 5.7 ± 1.4 | 5.9 ± 1.7 | 5.7 ± 1.4 |
| triglycerides (mmol/l) | 1.9 ± 0.9 | 1.8 ± 0.8 | 1.9 ± 0.9 | 1.8 ± 0.7 |
| uric acid (μmol/l) | 322.8 ± 82.9 | 319.3 ± 74.8 | 323.1 ± 84.6 | 319.5 ± 78.2 |
| sodium (mmol/l) | 139.9 ± 3.7 | 139.6 ± 3.8 | 140.2 ± 3.7 | 139.7 ± 3.8 |
| potassium (mmol/l) | 4.4 ± 0.5 | 4.4 ± 0.4 | 4.4 ± 0.4 | 4.4 ± 0.4 |
| creatinine (μmol/l) | 91.5 ± 20.7 | 91.6 ± 19.5 | 90.3 ± 19.3 | 90.7 ± 19.7 |
| urea (mmol/l) | 6.3 ± 2.1 | 6.4 ± 2.2 | 6.3 ± 2.0 | 6.3 ± 1.9 |
| erythrocytes ($10^6$/l) | 4.5 ± 0.5 | 4.5 ± 0.5 | 4.6 ± 0.6 | 4.5 ± 0.5 |
| haemoglobin (g/dl) | 141.1 ± 12.6 | 140.4 ± 11.6 | 142.3 ± 12.6 | 141.7 ± 11.5 |
| hematocrit (%) | 42.0 ± 5.0 | 42.0 ± 4.0 | 42.0 ± 5.0 | 42.0 ± 5.0 |

**Tab. 7. Laboratory changes between baseline and month 12 (all not significant).**

| Parameter | Group B – Ramipril | | Group B – Losartan | |
|---|---|---|---|---|
| | Baseline | Month 12 | Baseline | Month 12 |
| cholesterol (mmol/l) | 5.4 ± 1.0 | 5.2 ± 0.8 | 5.5 ± 1.0 | 5.3 ± 0.9 |
| glycaemia (mmol/l) | 5.9 ± 1.8 | 5.7 ± 1.3 | 5.8 ± 1.6 | 5.7 ± 1.5 |
| triglycerides (mmol/l) | 1.9 ± 0.9 | 1.8 ± 0.7 | 1.9 ± 0.9 | 1.8 ± 0.7 |
| uric acid (μmol/l) | 324.8 ± 81.4 | 320.0 ± 76.5 | 321.4 ± 87.7 | 318.9 ± 79.9 |
| sodium (mmol/l) | 140.4 ± 3.7 | 169.7 ± 3.9 | 140.1 ± 3.7 | 139.7 ± 3.8 |
| potassium (mmol/l) | 4.4 ± 0.5 | 4.4 ± 0.4 | 4.4 ± 0.4 | 4.4 ± 0.4 |
| creatinine (μmol/l) | 89.5 ± 18.5 | 90.2 ± 18.4 | 91.1 ± 20.1 | 91.2 ± 20.2 |
| urea (mmol/l) | 6.3 ± 1.9 | 6.4 ± 1.9 | 6.3 ± 2.0 | 6.3 ± 2.0 |
| erythrocytes ($10^6$/l) | 4.6 ± 0.6 | 4.5 ± 0.5 | 4.6 ± 0.5 | 4.6 ± 0.5 |
| haemoglobin (g/dl) | 142.6 ± 12.5 | 141.9 ± 11.5 | 142.0 ± 12.6 | 141.5 ± 11.5 |
| hematocrit (%) | 42.0 ± 4.0 | 42.0 ± 4.0 | 42.0 ± 5.0 | 42.0 ± 5.0 |

**Tab. 8. Serious adverse events (number of patients).**

| | Death | Myocardial infarction | Stroke | New diabetes mellitus | Cough |
|---|---|---|---|---|---|
| group A | 6 | 7 | 14 | 9 | 3 |
| group B | 9 | 7 | 17 | 11 | 37 |
| B – ramipril | 4 | 4 | 8 | 6 | 33 (2%) |
| B – losartan | 5 | 3 | 9 | 5 | 4 |

## Discussion

ACEI have been convincingly shown to reduce rates of death, myocardial infarction, stroke, heart failure and revascularization among patients with previous cardiovascular disease and in patients with diabetes mellitus who were at high risk of complications [12,21,22]. Both ACEI and ARB reduce the risk of stroke and new onset diabetes mellitus in hypertensive patients [2–4,23,24]. Therefore, to provide clinically relevant information, trials evaluating ARB in hypertensive patients must include a proven dose of an ACEI as a comparator [18,19]. We tested the hypothesis of the non-inferiority of losartan in two different situations. CORD IA involved switching from a regular dose of an ACEI to losartan and increasing the dose if necessary. We confirmed our hypothesis and found that switching was not accompanied by new adverse events, renal deterioration or hypotension.

BP control improved during CORD IA, probably because of dose titration. At baseline, nearly 1/2 the patients were on a lose dose of an ACEI (e. g., ramipril 2.5 mg, perindopril 2.0 mg or

Tab. 9. Doses of ramipril (or other ACEI at baseline) and losartan (%).

| | Ramipril or other ACEI at baseline | | | | Losartan | | | |
|---|---|---|---|---|---|---|---|---|
| | Low | Medium | High | High + | Low | Medium | High | High + |
| baseline – group A | 43.0 | 53.7 | 6.3 | – | – | – | – | – |
| month 12 – group A | – | – | – | – | 0.1 | 38.0 | 48.3 | 13.6 |
| month 12 – group B | 1.6 | 33.3 | 37.4 | 27.7 | 2.0 | 36.6 | 40.3 | 21.1 |

trandolapril 0.5 mg) and only 6.3% of all patients were on a high dose, but by the end of the study more than 2/3 (65.1%) were on a high dose of losartan (100 mg). The observed BP decrease of 13.3/8.7 mm Hg can be explained not only by a dose effect, but also by an observation effect, as patients in the placebo arms of clinical trials are known to have small BP reductions, probably because of better adherence to any other antihypertensive medications and possibly because of lifestyle modifications. For example, Dahlof recently presented a meta analysis of trials comparing the novel renin inhibitor aliskiren with placebo in more than 3,500 patients and found that BP decreased by 6.2/5.9 mm Hg in the placebo arm and that this decrease was higher in patients over 65 years, which was 1/3 of our study population [25].

CORD IB tested the antihypertensive efficacy, safety and tolerability of losartan and ramipril in patients with mild to moderate hypertension, either previously untreated or treated with antihypertensive drugs from classes other than blockers of the renin angiotensin system (ACEI, ARB, aldosterone blockers or direct renin inhibitors). Treatment commenced with a low or middle-range dose with upwards titration if normotension was not reached. The antihypertensive efficacy was similar and was about 15% of the original BP value. This is close to the BP decrease in the LIFE and ASCOT trials, where the decrease was slightly higher at 16–17%, probably because more combination therapy was used. We found no difference between losartan and ramipril, confirming the findings of the ONTARGET or VALIANT studies [2–4,17,18].

At the end of CORD 1B about two-thirds of the patients were normotensive (62.2% ramipril, 60.2% losartan); about 10% were hypertensive with systolic and diastolic readings above 140/90 mm Hg (10.1% ramipril, 11.9% losartan); and about a quarter had isolated systolic hypertension (27.2% ramipril, 27.3% losartan). The number of patients with isolated systolic hypertension actually increased in the ramipril arm from 22.6% to 27.2% and in the losartan arm from 18.6% to 27.3%. This represents a change from grade I or II hypertension to isolated hypertension. Mancia has described how difficult it is to reach systolic values under 140 mm Hg (130 mm Hg in diabetics), even if the diastolic value is under 90 mm Hg (80 mm Hg in diabetics) [26]. In many large clinical trials, such as HOT, UKPDS, INSIGHT, VALUE and STOP 2, most patients achieved the endpoint of a diastolic under 90 mm Hg but failed to reach a systolic under 140 mm Hg, leaving them with isolated systolic hypertension. For example, in the LIFE trial, 89% of patients in both arms reached a diastolic BP under 90 mm Hg, but only 46% achieved a systolic below 140 mm Hg. In our trial, 21.2% in the ramipril group and 22.3% in the losartan group who had hypertension developed isolated systolic hypertension. Even in these patients, the decrease in systolic BP was over 10%, which is a measure of some success. No patients with significant decreases in diastolic BP had an accompanying increase in systolic BP, which would have been a marker of poor prognosis [27,28]. In addition, the pulse pressure decreased by 8.2 mm Hg (from 62.8 to 54.6 mm Hg) after 12 months in the ramipril arm and by 9.0 mm Hg (from 63.2 to 54.2 mm Hg) in the losartan arm, which is a marker of improved prognosis [29]. Nevertheless, the aim of the future studies of the treatment hypertension should be improved control of systolic BP [1,30].

Hypertension is a part of metabolic syndrome in all its definitions [1]. An optimal antihypertensive drug should have good BP control, positive metabolic effects and a low number of adverse events. The LIFE, ASCOT and VALUE trials described a decreased incidence of diabetes mellitus in patients treated with ACEI or ARB compared to beta blockers or calcium channel blockers. We observed an improvement in all measured metabolic parameters – glycaemia, cholesterol, triglycerides and uric acid – which confirms the improvement in metabolic sensitivity after RAA blockade note in other studies. There was no increase in renal insufficiency or clinically significant increase in potassium, which confirms the data from the ONTARGET trial, where monotherapy was accompanied by a less than 1.0% reduction in renal function.

A meta analysis of BP-lowering treatment described similar BP-dependent effects of ACEI and ARB on the risk of stroke, coronary heart disease and heart failure and a BP-independent effect on the risk of major coronary disease event for ACEI but not for ARB [31]. We cannot confirm the BP-independent effect on myocardial infarction, and this is in agreement with the ONTARGET results, where the myocardial infarction rates were 4.8% for ramipril and 5.2% for telmisartan. In our trial, the incidence of myocardial infarction, stroke or death was low because of our relatively low risk population and the short duration of trial.

Cough was the most frequent adverse event in patients treated with ACEI but not with ARB in several trials [7,8,11,13,16,17]. Similarly, in our study the incidence of cough was 8 times higher in patients treated with ramipril than in patients treated with losartan. Patients were not specifically asked about cough, so the incidence of 2% represents self-reported cough affecting quality of life. 21 patients (1%) in the ramipril arm and no patients in the losartan arm discontinued treatment because of cough. ARB and ACEI are thought to be the antihypertensive agents with the highest compliance [32]. Our study suggests this is true: the drop-out rate because of adverse events was small and the reported tolerability very good.

We observed a small heart rate decrease of 2–3 beats per minute, which is consistent with previous findings, such as the LIFE trial where the heart rate decrease in the losartan arm was 1.9 beats per minute.

## Summary

The CORD trial is the largest trial comparing the antihypertensive effects of ACEI and ARB and confirms that these treatments are safe, effective and well tolerated. CORD IA confirms that switching from ACEI to losartan is not accompanied by worsening BP control or new adverse events and that titrating the losartan dose leads to a further BP fall and improvement in hypertension control. CORD IB confirms the non-inferiority of ACEI and ARB, with both drugs having a similar effect on BP and hypertension control. Finally, CORD confirms that reaching normal diastolic BP is much easier than controlling systolic BP and that treatment shifts patients with combined systolic/diastolic hypertension to milder, isolated systolic hypertension accompanied by a pulse pressure decrease, which can be taken as a positive sign of BP control.

We observed a trend for positive effect of ramipril and losartan on metabolic parameters; a lack of adverse effect on renal function; and a higher incidence of cough with ramipril.

In conclusion both ramipril and losartan are effective drugs of first choice for many hypertensive patients, especially those with metabolic syndrome, diabetes mellitus, microalbuminuria, left ventricle hypertrophy or ischaemic heart disease. In patients with dry cough after ramipril treatment, losartan could be chosen. For other patients economic parameters will probably be the most important influences when choosing between ramipril and losartan.

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