Comparison Of Recommended Doses

Outcomes of the non-interventional clinical trial CORD – pilot data analysis

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CORD

VVZ MŠMT 0021 622 402
Prevention of cardiovascular diseases

CORD A
Journal of hypertension 2008; 56, Suppl 1, PS32/WED/57: 464

CORD B
Journal of hypertension 2008; 56, Suppl 1, PS33/THU/43: 475

CORD
Late breaking clinical trials

CORD: *CO*mparison of *R*ecommended *D*oses of ace inhibitors and angiotensin II receptor blockers

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International Journal of Cardiology 2009; 144 (2): 293-4; **IF 2,9**

Сравнение рекомендованных доз блокаторов рецепторов ангиотензина и ингибиторов ангиотензин-превращающего фермента (исследование CORD)

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Comparing recommended doses of angiotensin receptor blockers and ACE inhibitors (CORD Study)

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Цель. В исследовании CORD оценивались эффективность и переносимость лозартана и рамиприла у пациентов с артериальной гипертонией (АГ).

Материал и методы. В исследовании участвовали две группы: В группе А больных переводили с лечения ингибиторами ангиотензин-превращающего фермента (ИАПФ) на лозартан; участвовали 4016 больных с АД < 160/100 мм рт.ст., принимавших различные ИАПФ в течение > 3 мес.; средний возраст пациентов — 62,6±11,6 лет; 53,1% этой выборки составляли женщины. АД, частота сердечных сокращений, биохимические показатели, общий анализ крови и ЭКГ контролировались в первый день и затем через 1, 3, 6

Hypotheses of ACE-I – AIIA noninferiority

- **Chronic heart failure**
  - The ELITE, ELITE II and Val Heft trials have shown similar effect on mortality and morbidity.
- **Post MI**
  - The OPTIMAAL and VALIANT trials have shown similar effect on mortality and morbidity.
- **Stable IHD**
  - The ON TARGET trial has shown similar effect on morbidity and mortality.
- **Renal Functions**
  - The COOPERATE trial has shown similar effect on renal functions.

Mentioned are only trials comparing ACE-I and AIIA

Hypotheses of ACE-I – AIIA superiority

- **LIFE**
  - Losartan is superior to atenolol in stroke, mortality and onset of new diabetes mellitus.
- **ASCOT**
  - Perindopril is superior to atenolol in stroke, mortality and onset of new diabetes mellitus.
- **VALUE**
  - Valsartan is not superior to amlodipin with the exception of onset of new diabetes mellitus.
- **ALLHAT, STOP I + II**
  - Lisinopril (enalapril) in not superior to other antihypertensive drugs with the exception of onset of new diabetes mellitus .

Mentioned are trials comparing ACE-I and AIIA with other antihypertensive drugs

Hypotheses of the clinical trial CORD

- **Hypothesis 1.**
  - AIIA losartan in dosage 25-100 mg has the same effect on blood pressure as ACE-I in an a▮▮▮te dose.
- **Hypothesis 2.**
  - The change in medication ▮▮▮CE-I to losartan in comparable doses isn't associated with an in▮▮▮ f adverse events.
- **Hypothesis 3.**
  - The treatment with the ad▮▮▮ ose of losartan or ACE-I results in a similar decrease of the bl▮▮▮ sure.
- **Hypothesis 4.**
  - The treatment with the ad▮▮▮ ose of losartan or ACE-I is associated with less frequ▮▮▮ onstration of adverse events (cough).

Categorization of patients in clinical trial CORD

C O R D

- **Group A**
  - Substitution of AIIA losartan for ACE-I treatment in patients with well or marginally controlled hypertension (BP < 160/100 mmHg).
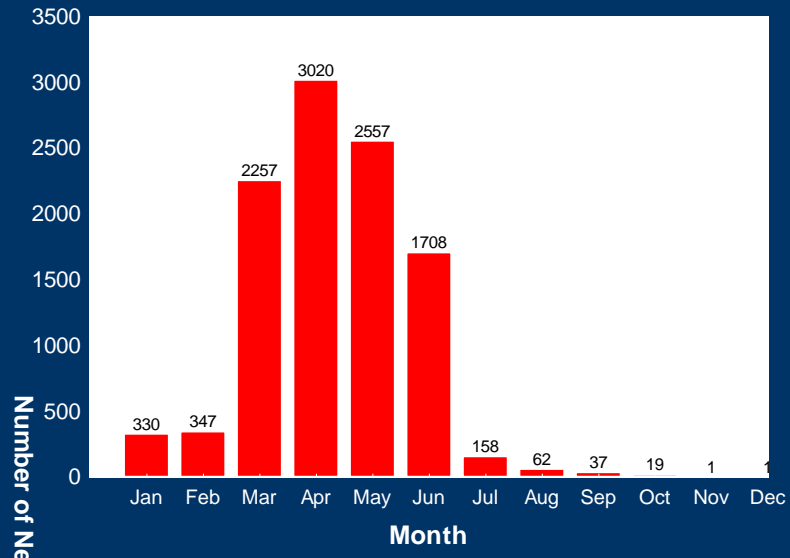 - Patients treated with ACE-I for > 3months.

- **Group B**
  - Addition of AIIA to ACE-I treatment in the case of insufficiently controlled hypertension (BP $\geq$ 140/90 mmHg).
  - Patients treated or untreated with antihypertensive drugs but no ACE-I or AIIA allowed.
  - Patients born on the even day randomised to AIIA losartan 50 mg.
  - Patients born on the odd day randomised to ACE-I ramipril 5 mg.
  - Increasing dosing in case of not reaching normotension.
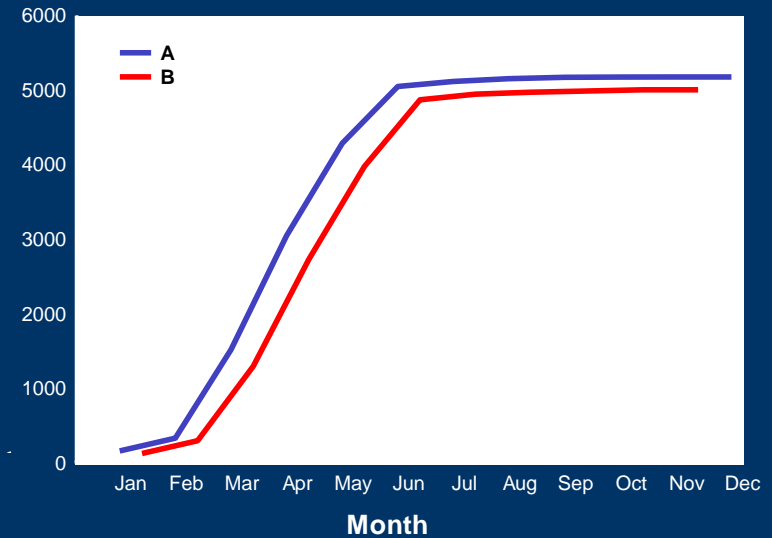
Numbers of screened patients

Czech Republic

- 585 centres

- 11 284 screened

New Patients Enrolled Each Month

Jan: 330
Feb: 347
Mar: 2257
Apr: 3020
May: 2557
Jun: 1708
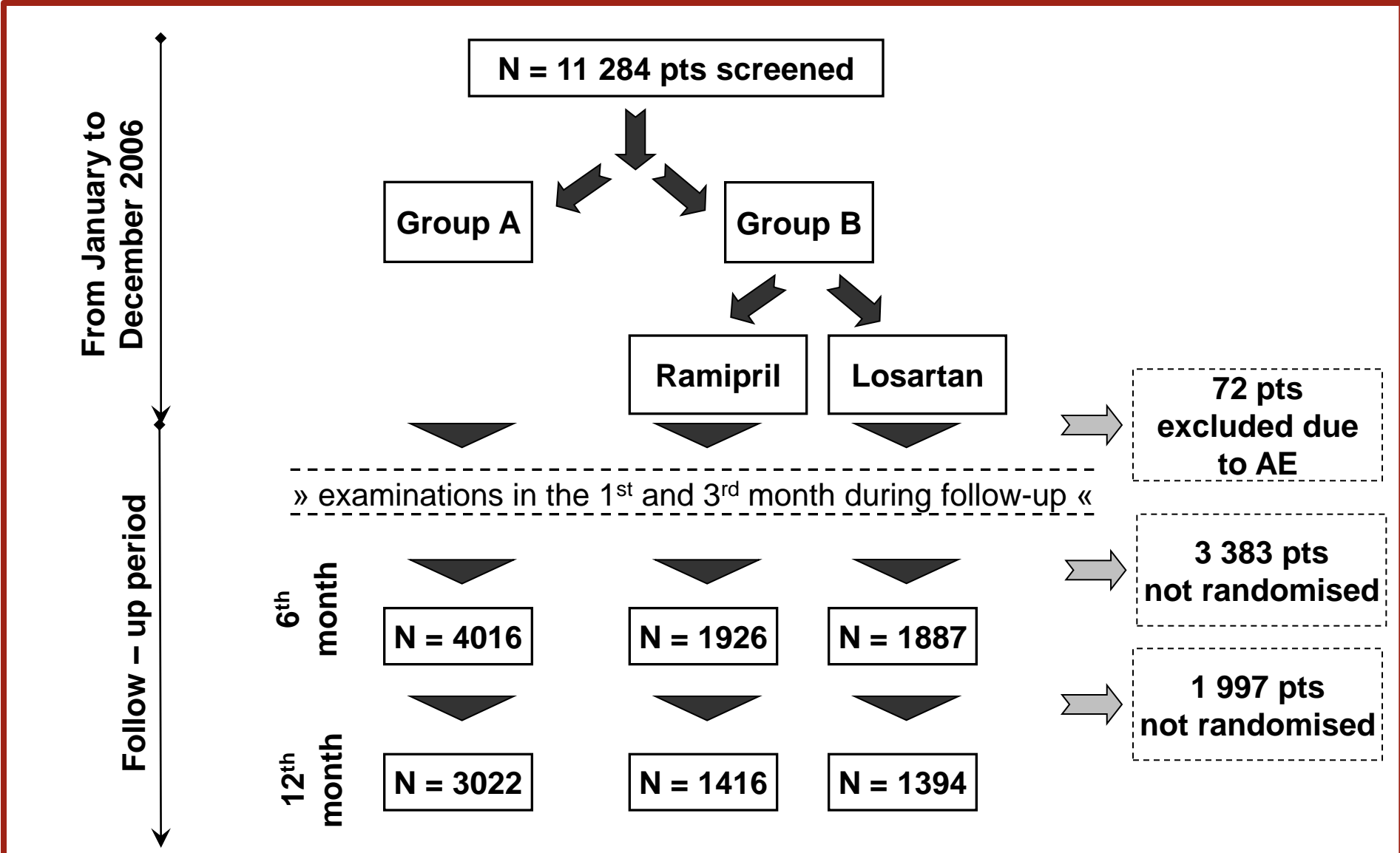Jul: 158
Aug: 62
Sep: 37
Oct: 19
Nov: 1
Dec: 1

Cumulative Enrolment by Treatment

A
B

Screening started in January 2006 and continued till December 2006. 11 284 patients in 585 centres were screened, 7 829 patients were randomised and included into the trial.

C O R D

Flow diagram of the study

Risk factors in patients history (n = 7 829)

C O R D

% of positive answers	Group A	Group B	B – Ramipril	B – Losartan
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 ischemic heart disease	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 dyslipidemy	60.5	55.0	55.6	54.4

Co - medication (n = 7 829)

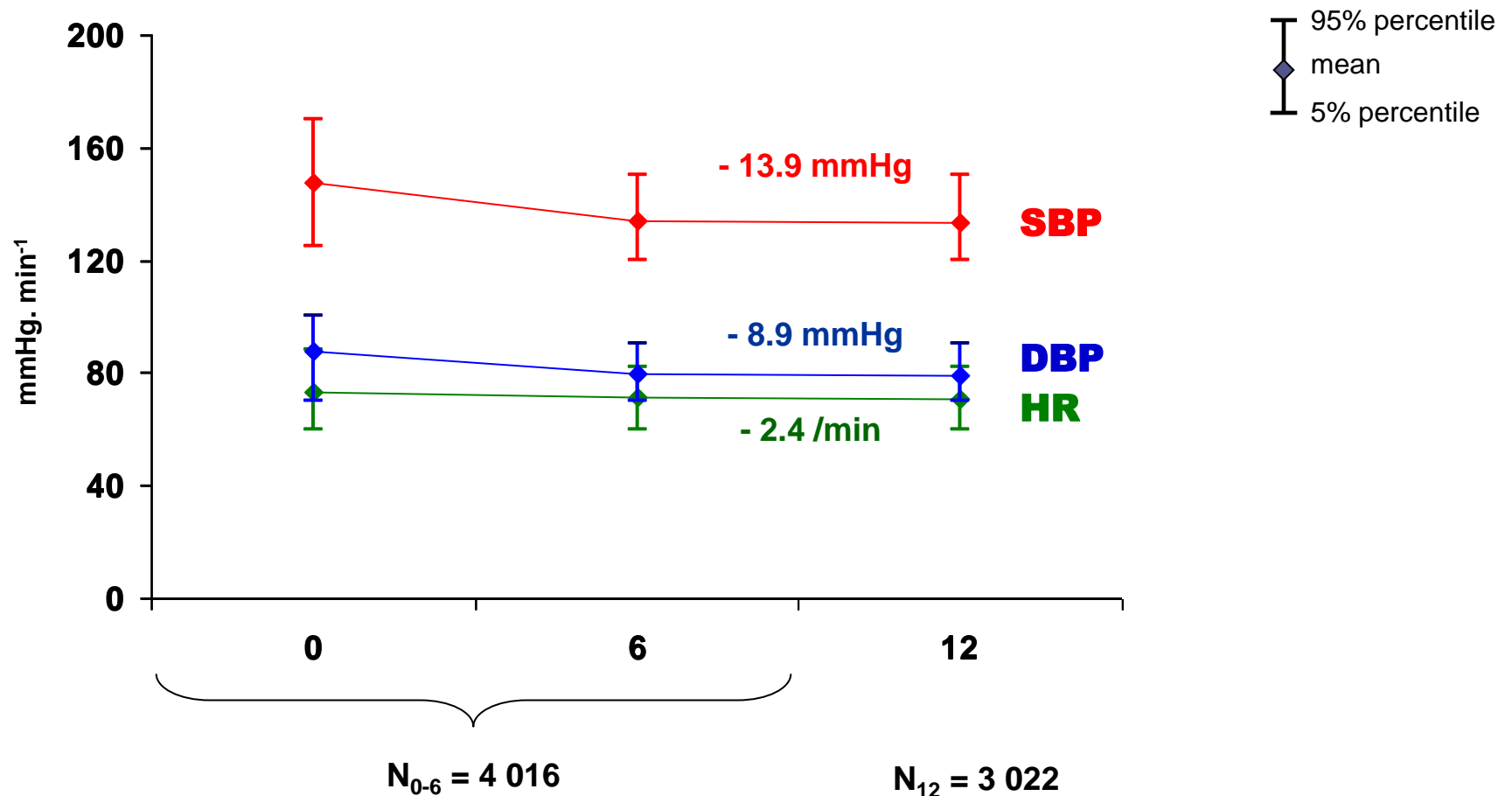| % of positive records	Group A	Group B	B - Ramipril	B - Losartan
Betablockers	43.0	41.6	39.9	43.3
Ca blocker type DHP	28.3	28.4	29.7	27.0
Ca blocker type non DHP	5.3	5.8	5.0	6.7
Diuretics	47.8	42.8	41.6	44.0
Alpha blockers	4.4	4.0	4.1	3.9
ASA	35.6	30.9	31.8	29.9
Clopidogrel	0.7	1.1	1.4	0.7
Warfarin	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
Peroral antidiabetics	23.6	20.4	20.0	20.8
Other medicine	46.2	42.7	43.2	42.2

CORD

Chapter 1

Analysis of change in target parameters in time 0 and 6 months

- Systolic blood pressure
- Diastolic blood pressure
- Heart rate

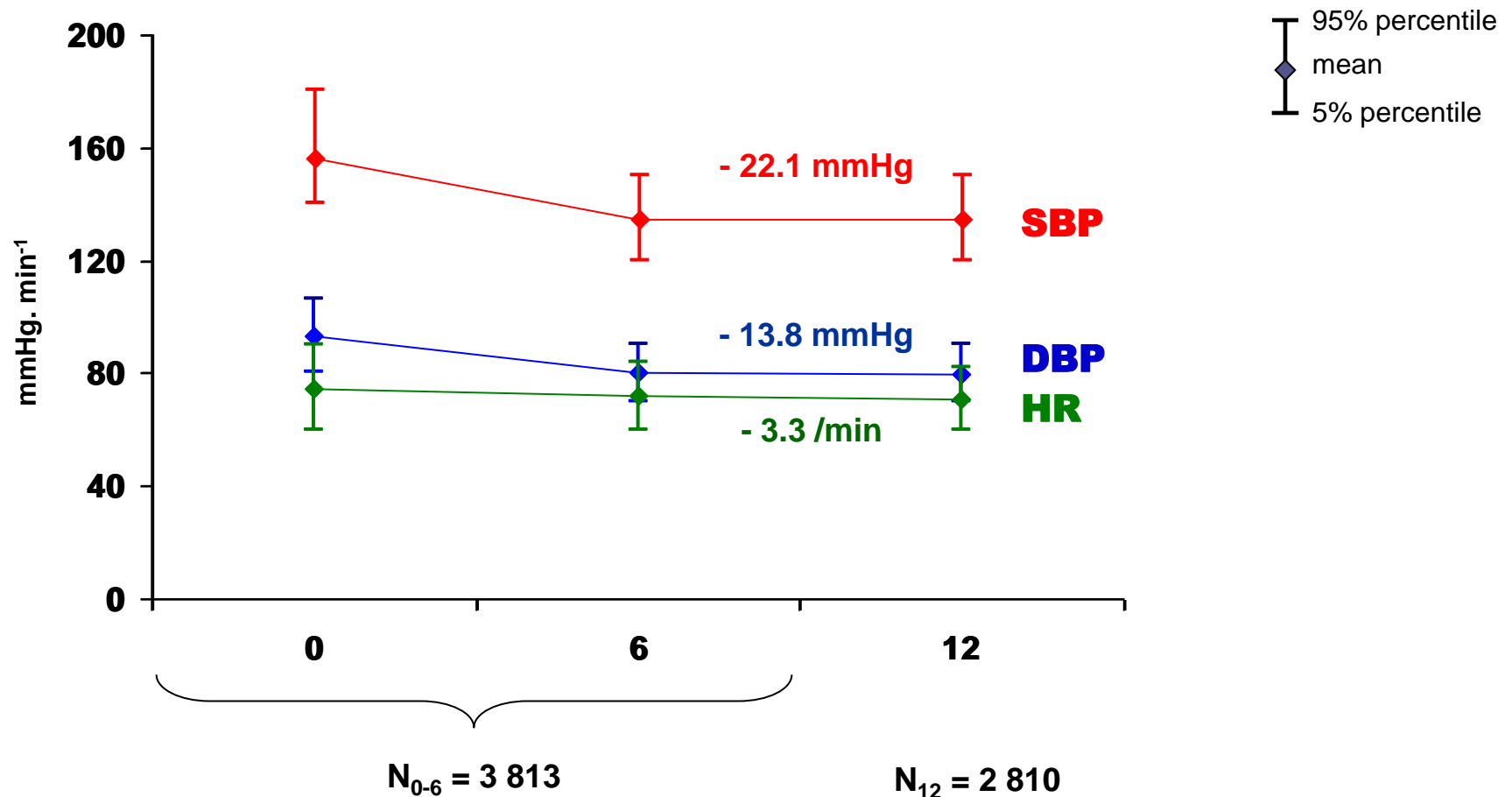C O R D
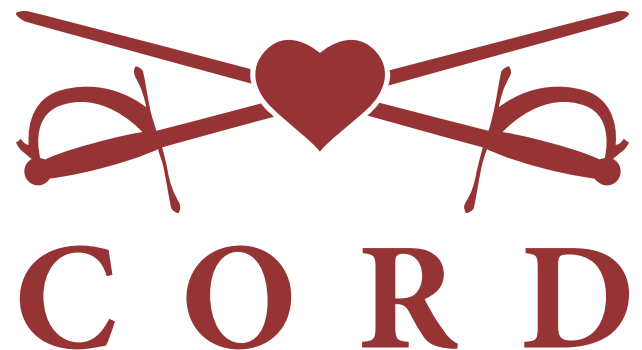
Clinical parameters in time – group A

Parameters measured in sitting position

Legend:
- 95% percentile
- mean
- 5% percentile

SBP: - 13.9 mmHg
DBP: - 8.9 mmHg
HR: - 2.4 /min

$N_{0-6} = 4\ 016$ $N_{12} = 3\ 022$

Clinical parameters in time – group B

C O R D

Parameters measured in sitting position

- 22.1 mmHg — SBP

- 13.8 mmHg — DBP

- 3.3 /min — HR

$N_{0-6} = 3\ 813$

$N_{12} = 2\ 810$

Clinical parameters in time – group B Ramipril

Parameters measured in sitting position

Legend:
- 95% percentile
- mean
- 5% percentile

SBP: - 22.2 mmHg
DBP: - 14.0 mmHg
HR: - 3.0 /min

y-axis: mmHg. min^{-1} (200, 160, 120, 80, 40, 0)

x-axis: 0, 6, 12

$N_{0-6} = 1\ 926$

$N_{12} = 1\ 416$
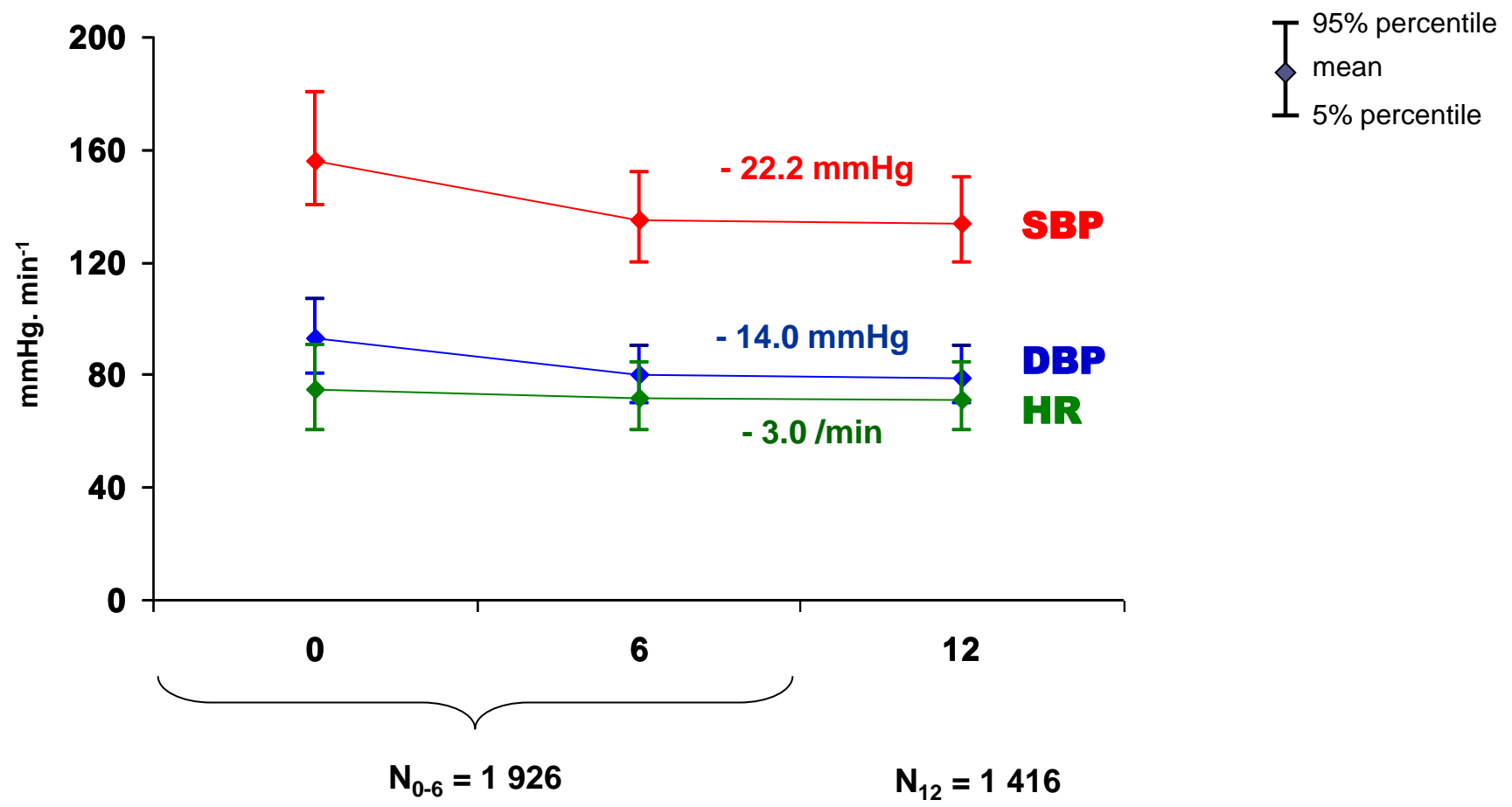
Clinical parameters in time – group B Losartan

Parameters measured in sitting position

N_{0-6} = 1 887

N_{12} = 1 394
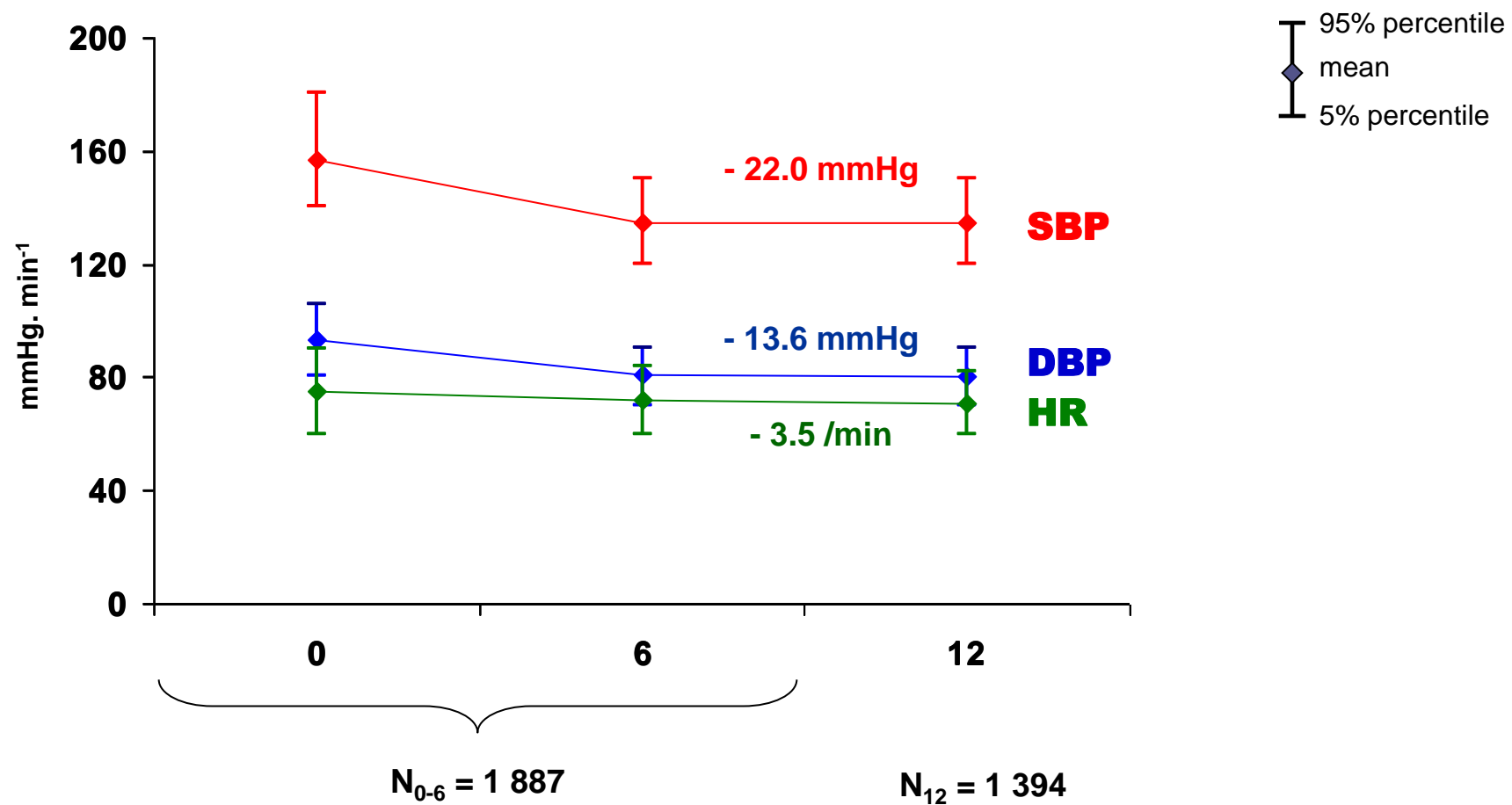
Summary of parameter change over time (0 and 12 months)

CORD

Parameters measured in sitting position

Difference in parameter means in time 0 and 12 months

Parameter	Group	Value
Systolic BP (mmHg)	Group A	-13.9
	Group B	-22.1
	B - Ramipril	-22.2
	B - Losartan	-22.0
Diastolic BP (mmHg)	Group A	-8.9
	Group B	-13.8
	B - Ramipril	-14.0
	B - Losartan	-13.6
Heart rate (min^{-1})	Group A	-2.4
	Group B	-3.3
	B - Ramipril	-3.0
	B - Losartan	-3.5
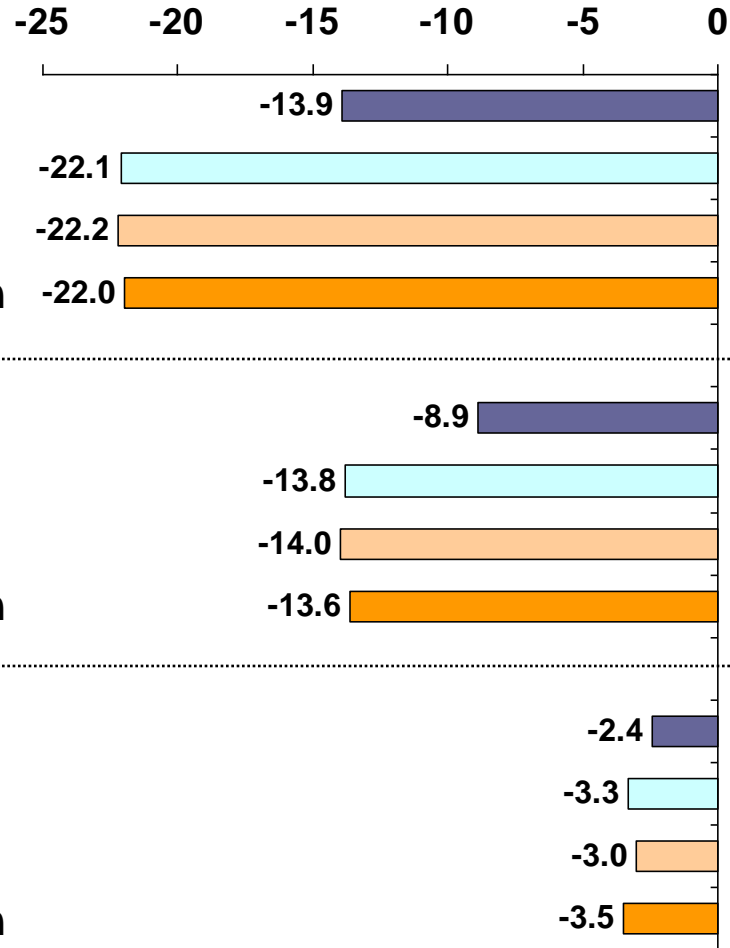
Chapter 2
Analysis of secondary parameter in time

- Biochemistry
- Renal functions
- Haematology

C O R D

Biochemical parameters in time 0 and 12 months

		Group A		Group B	
		Time 0	**12 months**	**Time 0**	**12 months**
Cholesterol (mmol/l)	Mean ± SD	5.4 ± 1.0	5.2 ± 0.8	5.5 ± 1.0	5.2 ± 0.8
	Median (Min-Max)	5.3 (2.3-11.1)	5.1 (2.2-10.0)	5.4 (2.0-11.9)	5.2 (2.3-9.4)
Glycemia (mmol/l)	Mean ± SD	5.9 ± 1.6	5.7 ± 1.4	5.9 ± 1.7	5.7 ± 1.4
	Median (Min-Max)	5.5 (3.0-18.0)	5.4 (3.2-15.8)	5.4 (2.5-21.1)	5.4 (3.1-21.4)
Triglycerides (mmol/l)	Mean ± SD	1.9 ± 0.9	1.8 ± 0.8	1.9 ± 0.9	1.8 ± 0.7
	Median (Min-Max)	1.8 (0.5-7.5)	1.8 (0.5-8.0)	1.8 (0.5-7.9)	1.7 (0.5-6.7)
Uric acid (mmol/l)	Mean ± SD	322.8 ± 82.9	319.3 ± 74.8	323.1 ± 84.6	319.5 ± 78.2
	Median (Min-Max)	320.0(100.0-653.0)	318.0(108.0-741.0)	317.0 (114.0-745.0)	315.0 (108.0-696.0)

Biochemical parameters in time 0 and 12 months

		Group B - Ramipril		Group B - Losartan	
		Time 0	12 months	Time 0	12 months
Cholesterol (mmol/l)	Mean ± SD	5.4 ± 1.0	5.2 ± 0.8	5.5 ± 1.0	5.3 ± 0.9
	Median (Min-Max)	5.3 (2.0-11.9)	5.1 (2.7-9.4)	5.4 (2.0-11.3)	5.2 (2.3-9.0)
Glycemia (mmol/l)	Mean ± SD	5.9 ± 1.8	5.7 ± 1.3	5.8 ± 1.6	5.7 ± 1.5
	Median (Min-Max)	5.4 (2.5-21.1)	5.4 (3.2-14.5)	5.4 (2.9-14.8)	5.4 (3.1-21.4)
Triglycerides (mmol/l)	Mean ± SD	1.9 ± 0.9	1.8 ± 0.7	1.9 ± 0.9	1.8 ± 0.7
	Median (Min-Max)	1.8 (0.5-7.7)	1.8 (0.5-6.0)	1.8 (0.5-7.9)	1.7 (0.5-6.7)
Uric acid (mmol/l)	Mean ± SD	324.8 ± 81.4	320.0 ± 76.5	321.4 ±87.7	318.9 ± 79.9
	Median (Min-Max)	318.0 (114.0-718.0)	313.0 (108.0-650.0)	315.0 (117.0-745.0)	315.0 (120.0-696.0)

Ionts, renal functions in time 0 and 12 months

		Group A		Group B	
		Time 0	12 months	Time 0	12 months
Natrium (mmol/l)	Mean ± SD	139.9 ± 3.7	139.6 ± 3.8	140.2 ± 3.7	139.7 ± 3.8
	Median (Min-Max)	140.0 (120.0-156.0)	140.0 (120.0-160.0)	140.0 (120.0-160.0)	140.0 (120.0-160.0)
Potassium (mmol/l)	Mean ± SD	4.4 ± 0.5	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4
	Median (Min-Max)	4.3 (2.6-6.8)	4.3 (3.0-7.0)	4.3 (2.9-6.7)	4.3 (2.8-6.8)
Creatinine (umol/l)	Mean ± SD	91.5 ± 20.7	91.6 ± 19.5	90.3 ± 19.3	90.7 ± 19.3
	Median (Min-Max)	89.0 (50.0-244.0)	90.0 (50.0-249.0)	88.0 (50.0-247.0)	88.3 (50.0-240.0)
Urea (mmol/l)	Mean ± SD	6.3 ± 2.1	6.4 ± 2.2	6.3 ± 2.0	6.3 ± 1.9
	Median (Min-Max)	6.1 (3.0-23.1)	6.1 (3.0-24.7)	6.0 (3.0-24.0)	6.1 (3.0-23.8)

Ionts, renal functions in time 0 and 12 months

CORD

		Group B - Ramipril		Group B - Losartan	
		Time 0	**12 months**	**Time 0**	**12 months**
Natrium (mmol/l)	Mean ± SD	140.4 ± 3.7	139.7 ± 3.9	140.1 ± 3.7	139.7 ± 3.8
	Median (Min-Max)	140.0 (120.0-158.0)	140.0 (120.0-160.0)	140.0 (120.0-160.0)	140.0 (120.0-151.0)
Potassium (mmol/l)	Mean ± SD	4.4 ± 0.5	4.4 ± 0.4	4.3 ± 0.4	4.4 ± 0.4
	Median (Min-Max)	4.3 (3.0-6.7)	4.3 (2.8-6.4)	4.3 (2.9-6.0)	4.3 (3.2-6.8)
Creatinine (umol/l)	Mean ± SD	89.5 ± 18.5	90.2 ± 18.4	91.1 ± 20.1	91.2 ± 20.2
	Median (Min-Max)	88.0 (50.0-235.4)	88.0 (50.0-215.0)	89.0 (51.8-247.0)	89.0 (50.0-240.0)
Urea (mmol/l)	Mean ± SD	6.3 ± 1.9	6.4 ± 1.9	6.3 ± 2.0	6.3 ± 2.0
	Median (Min-Max)	6.0 (3.0-19.3)	6.1 (3.0-23.8)	6.0 (3.0-24.0)	6.1 (3.1-23.4)

Haematology in time 0 and 12 months

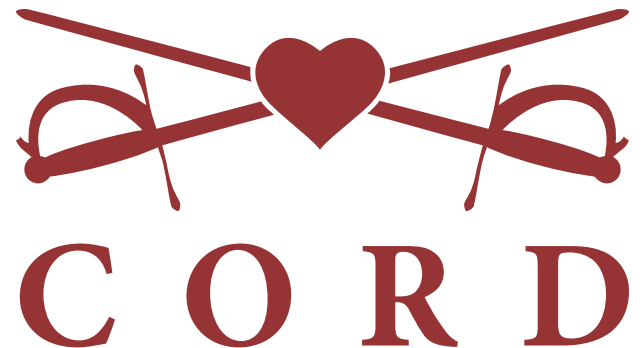|		Group A		Group B	
		Time 0	12 months	Time 0	12 months
Erythrocytes (10^6/l)	Mean ± SD	4.5 ± 0.5	4.5 ± 0.5	4.6 ± 0.6	4.5 ± 0.5
	Median (Min-Max)	4.5 (1.0-6.3)	4.5 (1.0-7.0)	4.6 (1.1-6.5)	4.5 (1.2-6.8)
Hemoglobin (g/dl)	Mean ± SD	141.1 ± 12.6	140.4 ± 11.6	142.3 ± 12.6	141.7 ± 11.5
	Median (Min-Max)	141.0 (69.0-180.0)	140.0 (83.0-180.0)	142.0 (88.0-180.0)	141.0 (94.0-180.0)
Hematokrit (%)	Mean ± SD	0.42 ± 005	0.42 ± 0.04	0.42 ± 0.05	0.42 ± 0.05
	Median (Min-Max)	0.42 (0.18-0.58)	0.42 (0.19-0.58)	0.42 (0.19-0.68)	0.42 (0.20-0.70)

Haematology in time 0 and 12 months

		Group B - Ramipril		Group B - Losartan	
		Time 0	**12 months**	**Time 0**	**12 months**
Erythrocytes (10^6/l)	Mean ± SD	4.6 ± 0.6	4.5 ± 0.5	4.6 ± 0.5	4.5 ± 0.5
	Median (Min-Max)	4.6 (1.2-6.5)	4.5 (1.2-6.6)	4.6 (1.1-6.5)	4.5 (1.8-6.8)
Hemoglobin (g/dl)	Mean ± SD	14264 ± 12.5	141.9 ± 11.5	142.0 ± 12.6	141.5 ± 11.5
	Median (Min-Max)	142.0 (90.0-180.0)	142.0 (95.0-178.0)	141.0 (88.0-180.0)	141.0 (94.0-180.0)
Hematokrit (%)	Mean ± SD	0.42 ± 0.04	0.42 ± 0.04	0.42 ± 0.05	0.42 ± 0.05
	Median (Min-Max)	0.42 (0.20-0.68)	0.42 (0.20-0.66)	0.42 (0.19-0.66)	0.42 (0.20-0.70)

Chapter 3
Analysis of serious adverse events

- Death
- Myocardial infarction
- Stroke
- New diabetes mellitus
- Cough

C O R D

Serious adverse events

	Death	Myocardial infarction	Stroke	New DM	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

All AE < 1%.

25 patients in group A and 47 patients in group B discontinuated due to AE.
21 (1%) patients discontinuated ramipril due to cough in group B, no patient discontinuated losartan due to cough.
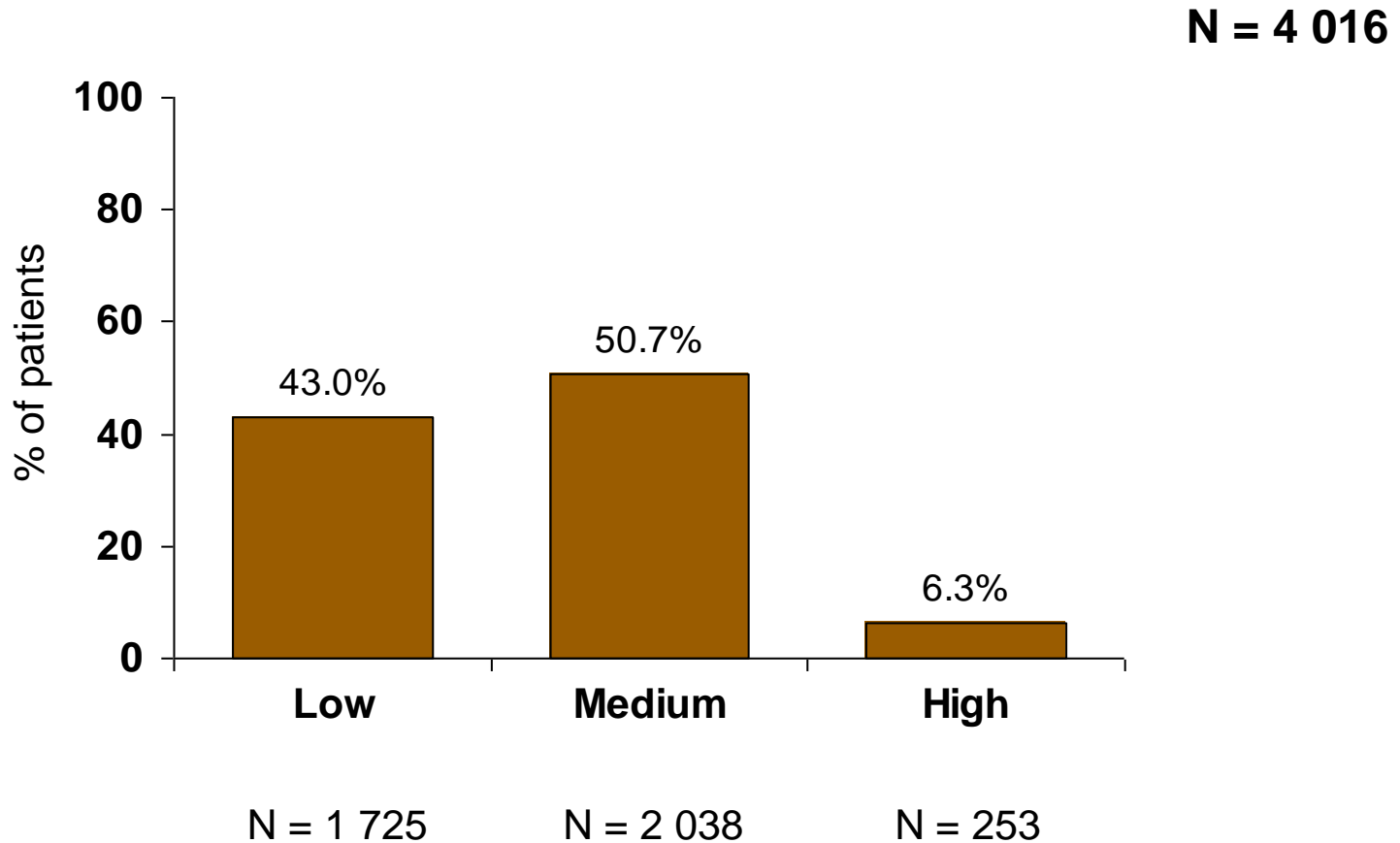These patients are not included into the final analysis and are mentioned as not randomised at baseline.

Chapter 4
Analysis of dose

- Initial dose of ACE-I – group A
- 6 month dose of losartan – group A

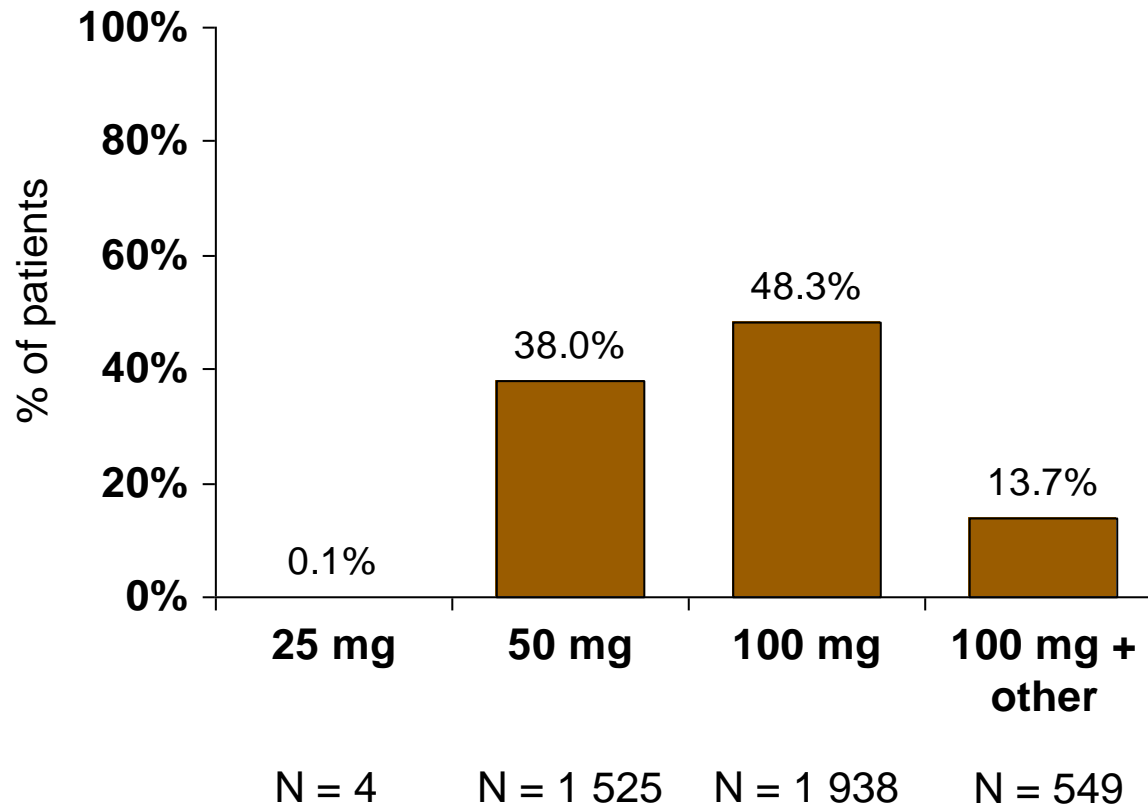- 6 month dose of losartan – group B
- 6 month dose of ramipril – group B
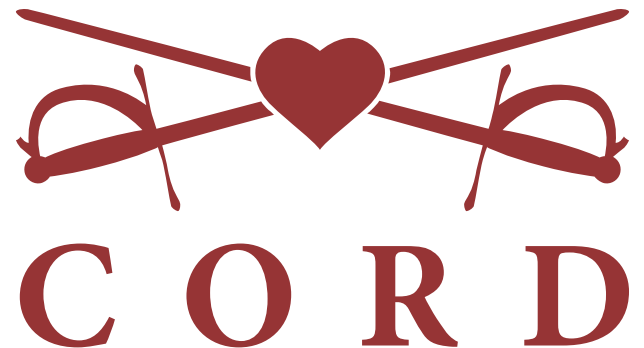
Dose of ACE-I - group A – at month 0

N = 4 016

% of patients

- Low: 43.0%
- Medium: 50.7%
- High: 6.3%

N = 1 725 N = 2 038 N = 253

Dose of Losartan – group A – at month 6

N = 4 016

	25 mg	50 mg	100 mg	100 mg + other
%	0.1%	38.0%	48.3%	13.7%
N	N = 4	N = 1 525	N = 1 938	N = 549

Dose of Ramipril – group B Ramipril – at month 6

N = 1 926

Chart showing % of patients by dose:
- 2.5 mg: 1.6% (N = 30)
- 5.0 mg: 33.3% (N = 641)
- 10.0 mg: 37.4% (N = 721)
- 10.0 mg + other: 27.7% (N = 534)
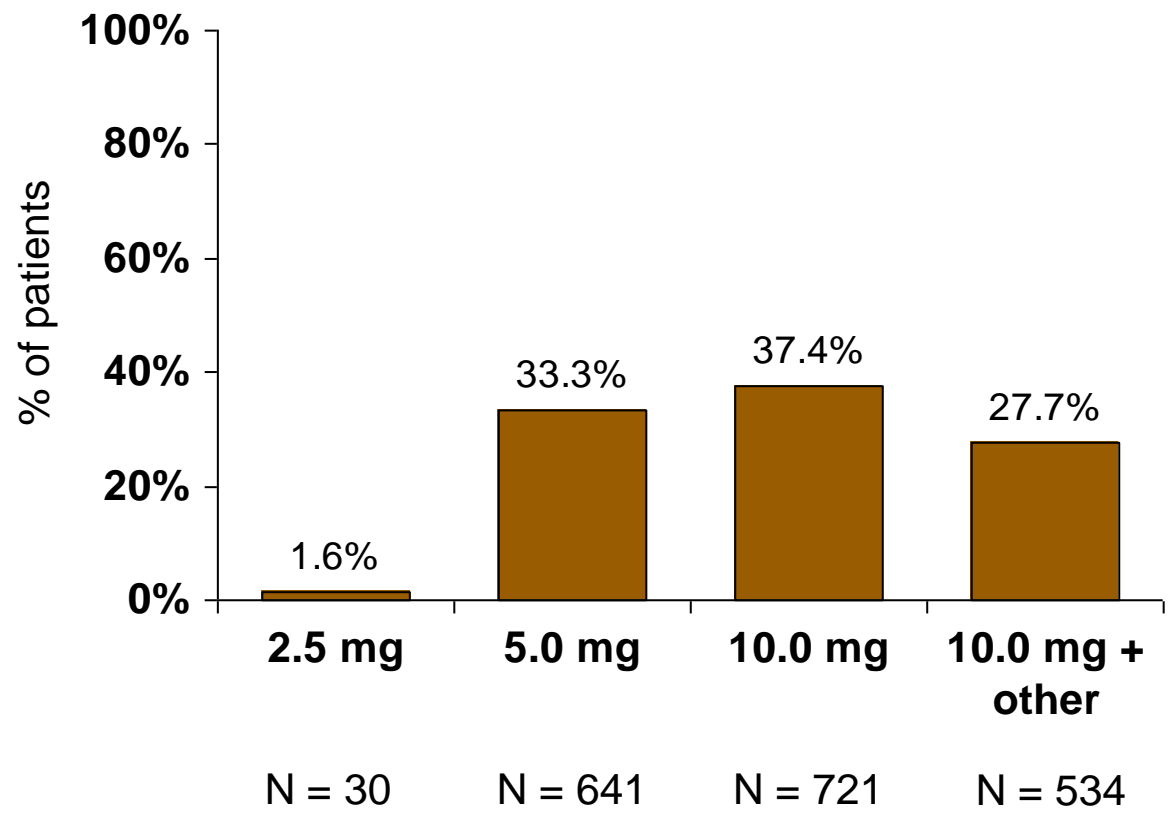
Dose of Losartan – group B Losartan – at month 6

N = 1 887

% of patients

Dose	%
25 mg	2.0%
50 mg	36.6%
100 mg	40.3%
100 mg + other	21.1%

N = 38   N = 690   N = 760   N = 399
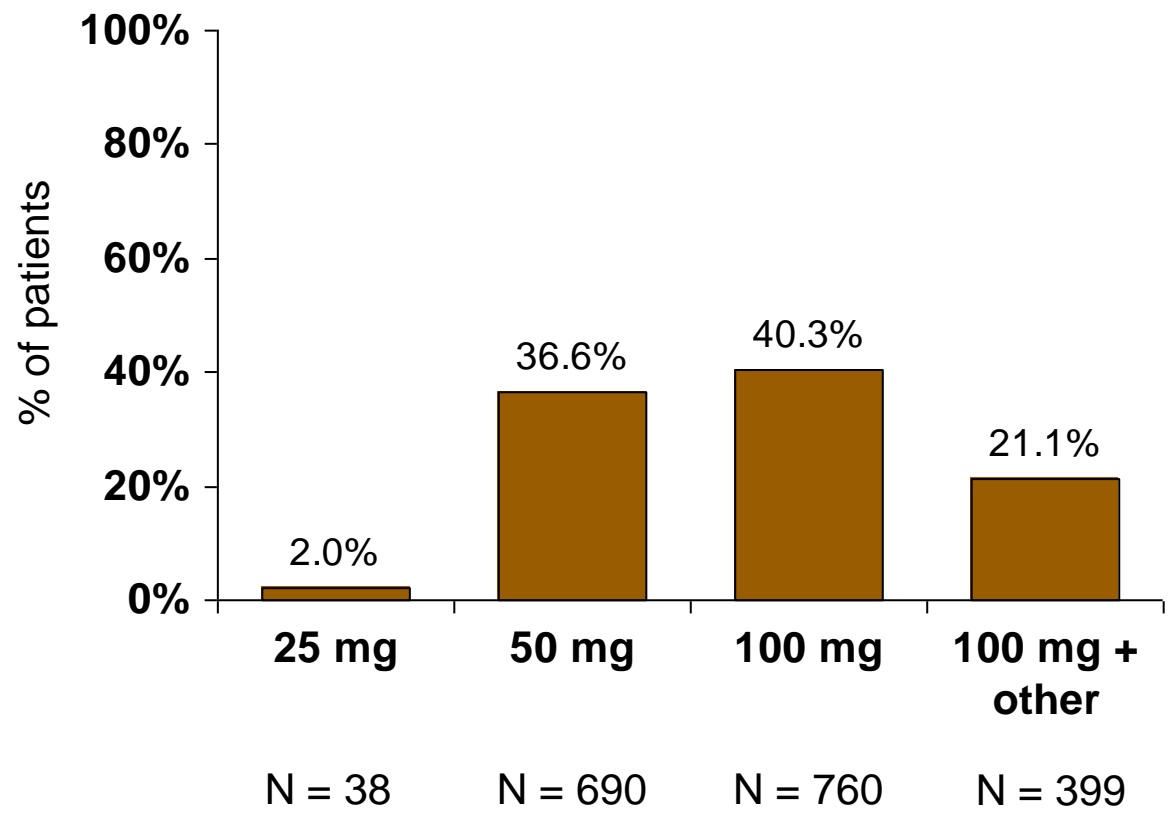
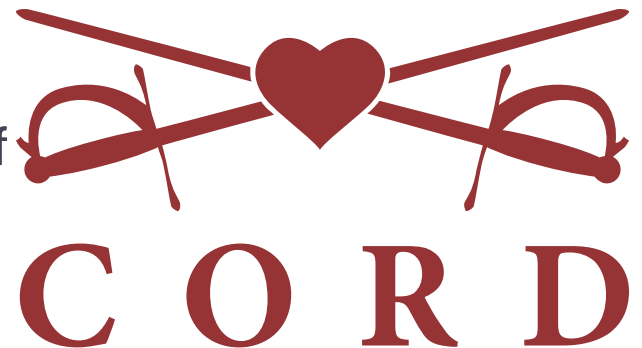# Chapter 5
Summary – group A

- Switching from an ACE-I to losartan is safe and effective

- Effectiveness : dose effect
                        placebo (trial) effect

- Safety : no increase in AE or BP

Chapter 6
Summary – group B

- Ramipril and losartan have comparable effect on BP
- 5mg ramipril is equivalent to 50mg losartan
- 10mg ramipril is equivalent to 100mg losartan

- Adverse effects are similar, with the exception of cough, which is 8x higher after ramipril
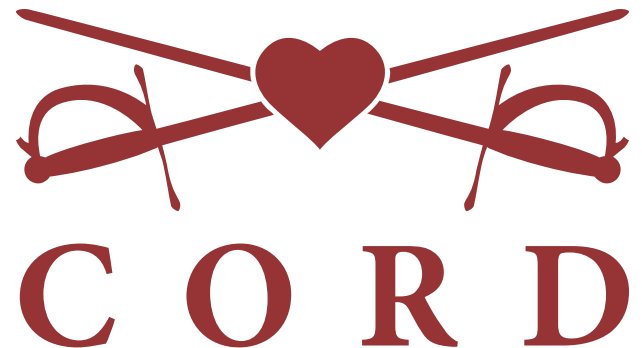
C O R D

Chapter 6
Summary – secondary endpoints

- Both ramipril and losartan have favorable metabolic effect.

- We observed no deterioration of renal functions or pottasium increase.

- We observed NO decrease in blood count.
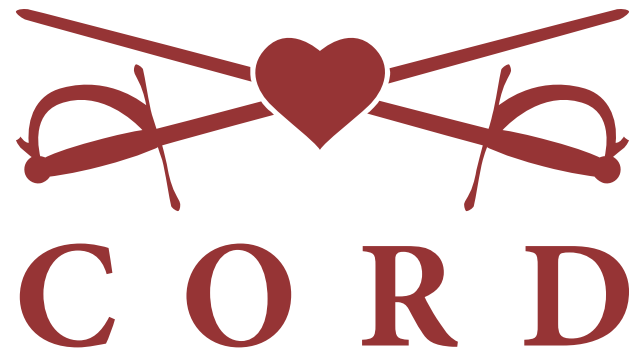
C O R D

Summary – message from the CORD study

- Can you imagine, that the ARB would be first on the market – before ACE-I ?

C O R D

Summary – message from the CORD study

Do you beleive, that FDA or any other institution would allow ACE-I, if they are as effective as ARB, but with 8 times higher adverse events (dry cough)?

B. Pitt after the presentation of ELITE II study.

Summary – message from the CORD study

- What is the drug of first choice in the treatment of hypertension ACE-I or ARB ?

CORD

Summary – message from the CORD study

- In the case of dry cough after ACE-I we must prescribe ARB. If there is NO cough and we know, that both groups are similarly effective, than the price will play the main role. And the prices differe in various countries. So if in your country the ARB are cheaper – choose ARB, if the ACE-I are cheaper – choose ACE-I.

G. Mancia after the first presentation of ESC guidelines 2007.

CORD