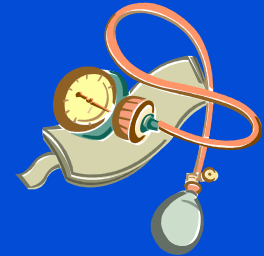


CARDIOVASCULAR APPLICATIONS OF COENZYME Q10

Treatment of hypertension
and
Holistic Preparation for Cardiac Surgery

*F.L. Rosenfeldt, S. Pepe, J.Y.Leong, A. Hadj, D.S.Esmore,
S.J.Haas, H.Krum, K. Ng*

HYPERTENSION



- Hypertension is one of the most common forms of cardiovascular disease especially in the elderly
- Many of current drugs used to treat hypertension are expensive and have undesirable side effects such as postural hypotension, depression, bronchospasm, cough etc

COENZYME Q₁₀ AND HYPERTENSION

- Use of CoQ₁₀ in the treatment of hypertension has been reported in many published studies since 1997
- This treatment has not gained substantial clinical usage.

Why?

INEFFECTIVE ?

SIDE EFFECTS ?

AIMS

- To review all published clinical trials of the use of CoQ₁₀ in the treatment of hypertension
- Assess the overall efficacy and consistency of the therapeutic effect
- Assess the incidence of side effects

METHODS

- Searched electronic databases
1996 to present:
 - Medline
 - Embase
 - Pubmed
- Collected **all** published clinical trials of
coenzyme Q₁₀ in the treatment of
hypertension

METHODS

- Performed a meta-analysis by pooling results of individual studies
- Assigned relative weight to each study on the basis of the size of the treatment group and the magnitude of the effect observed.
- Presented results as effect size with 95% confidence limits

TWELVE STUDIES IN 387 PATIENTS OF COENZYME Q₁₀ THERAPY FOR HYPERTENSION

- Open label studies: 8
- Randomised controlled clinical trials: 3
- Crossover study: 1

ANALYSED SEPARATELY

EIGHT OPEN LABEL STUDIES

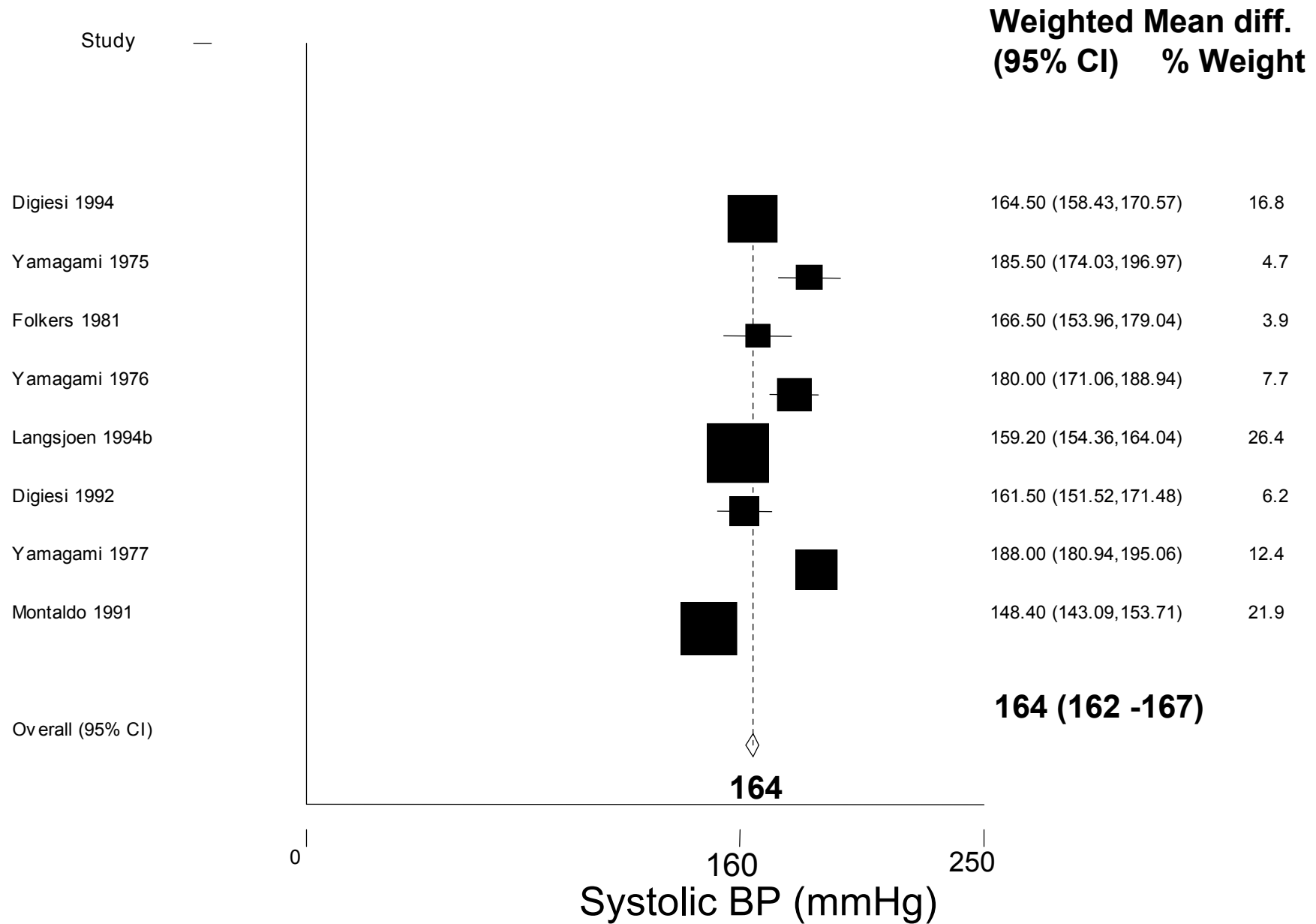
- No control group
- 214 patients

EIGHT OPEN LABEL STUDIES OF COENZYME Q₁₀ IN THE TREATMENT OF HYPERTENSION

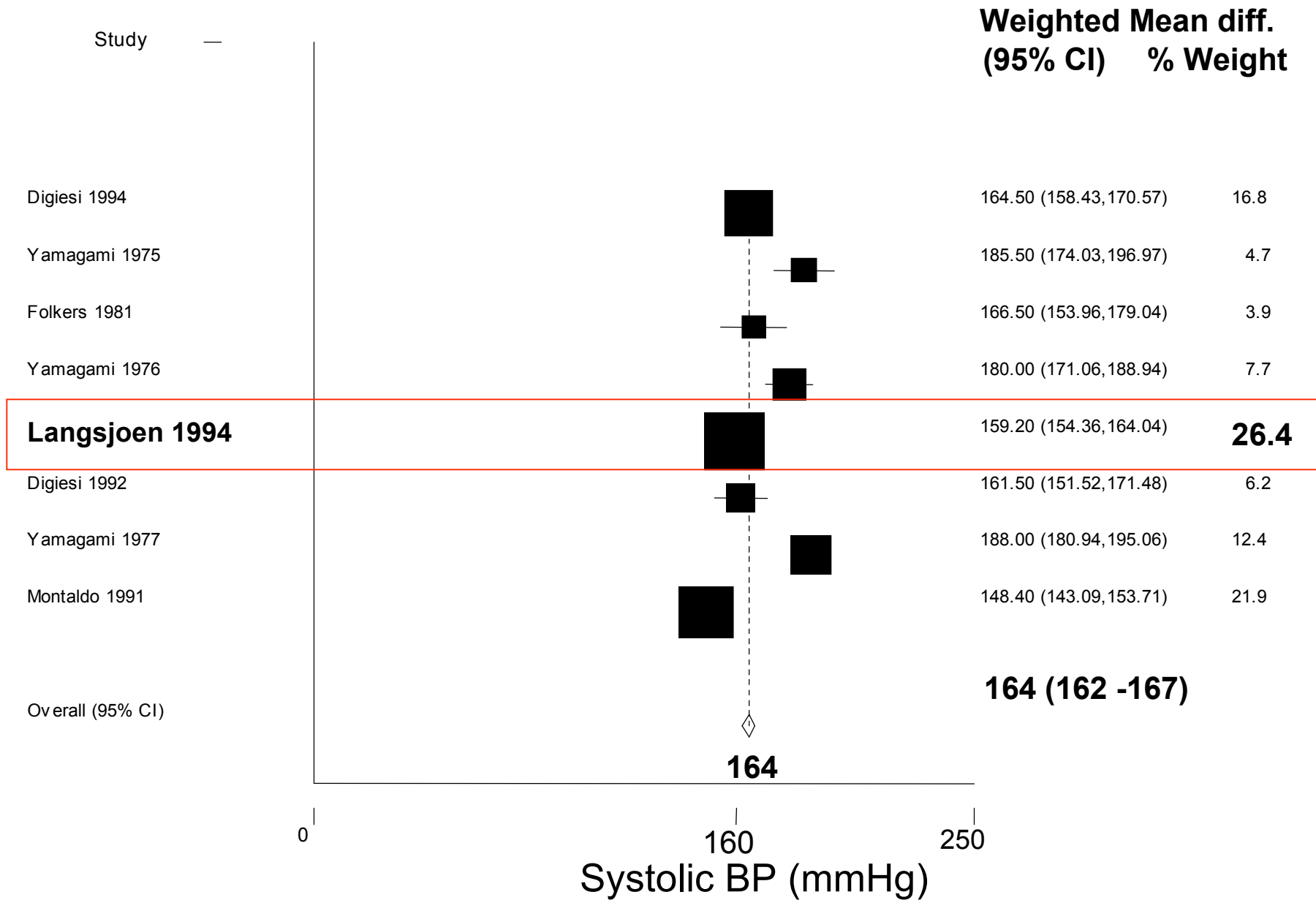
Open label studies	N	CoQ10 dose mg/day	Period weeks	Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure mmHg		
				Baseline	Final	SBP Diff.	Baseline	Final	DBP Diff.
Yamagami 1975	4	30- 45	4- 16	186 ± 3.6	167 ±6.8	-20	103 ±4.0	93 ±2.5	-10
Yamagami 1976	5	30 -75	1- 20	180 ±5.9	156 ±8.0	-25	103 ±4.5	92 ±5.0	-11
Yamagami 1977	29	170 -140	8-12	188 ±3.6	176 ±4.5	-12	104 ±2.7	98 ±2.9	-6
Folkers 1981	16	60	8	167 ± 6.4	145 ±5.2	-21	98 ±14.2	82 ±5.0	-16
Montaldo 1991	15	100	12	146 ±4.3	138 ±3.3	-8	97.3 ±5.0	90.1 ±1.7	-7
Digiesi 1992	10	100	10	162 ±5.1	142 ±5.3	-19	99 ±1.7	83 ±15.4	-15
Digiesi 1994	26	100	10	165 ±3.1	147 ±4.1	-18	98 ±1.7	86 ±1.3	-12
Langsjoen 1994	109	225	24	159 ±25.8	147 ±21.1	-12*	94 ±12.5	85 ±10.2	-9*

* >50% of subjects ceased taking at least one of their antihypertensive medications

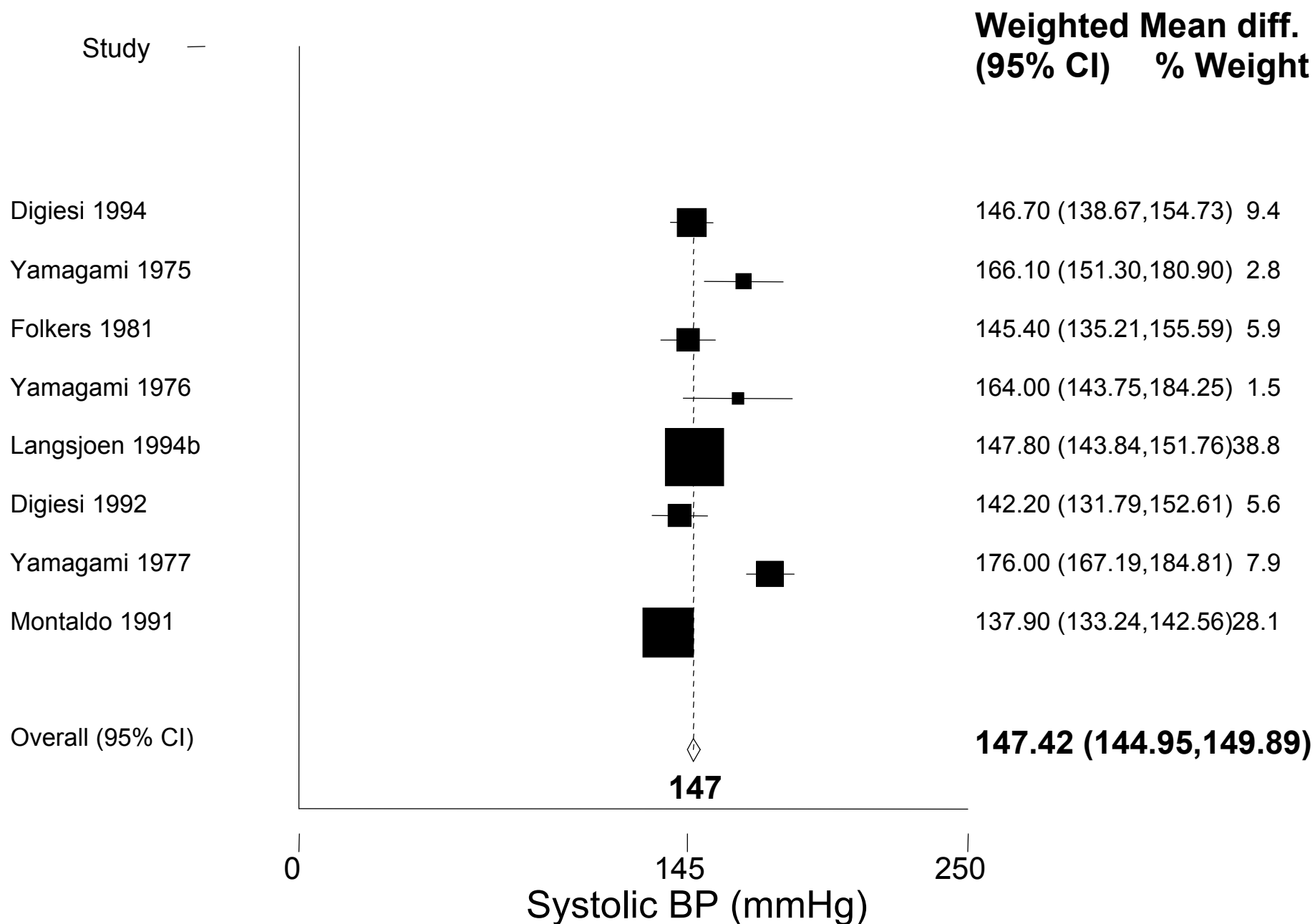
SYSTOLIC BP BEFORE STUDY



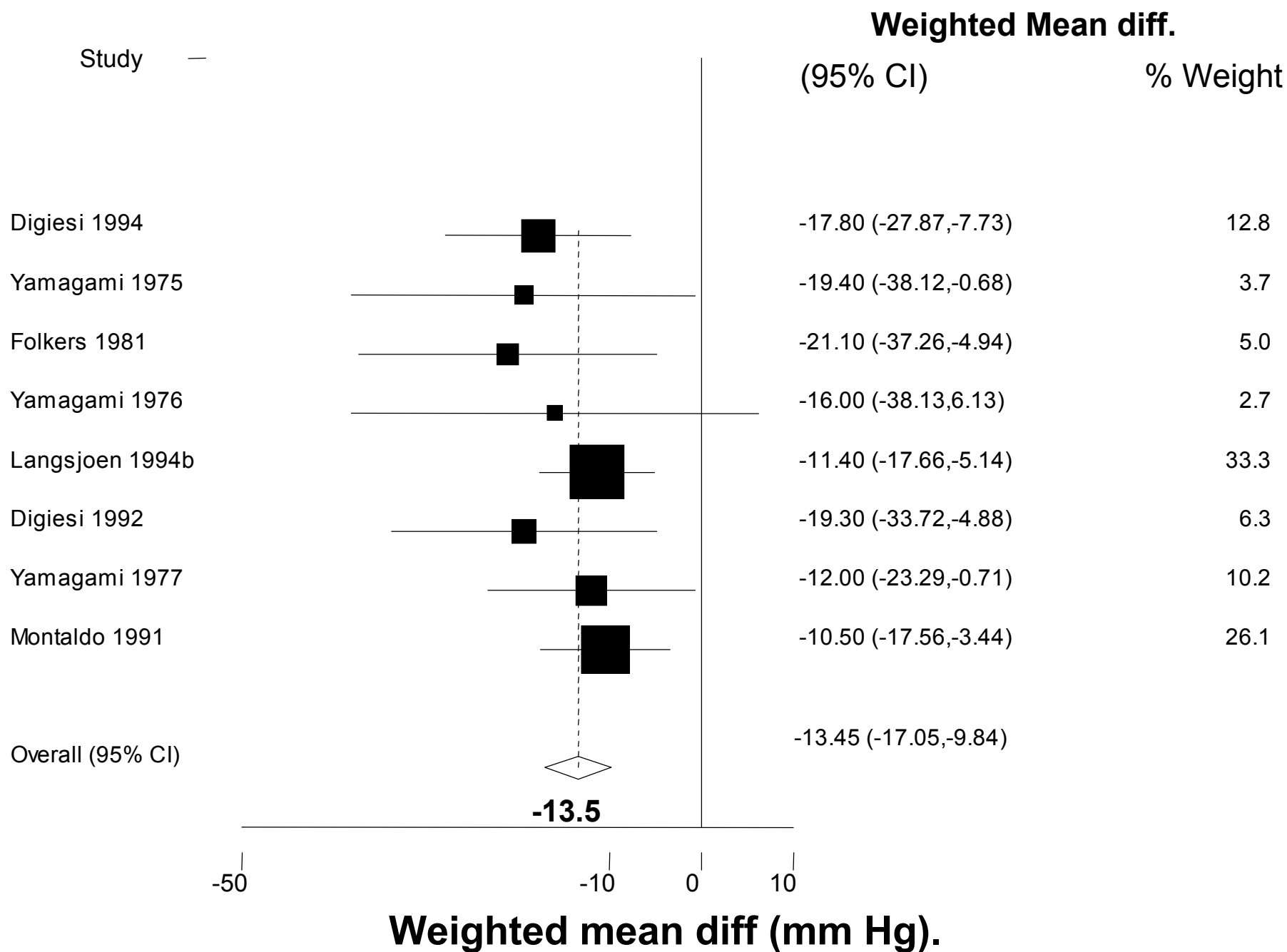
SYSTOLIC BP BEFORE STUDY



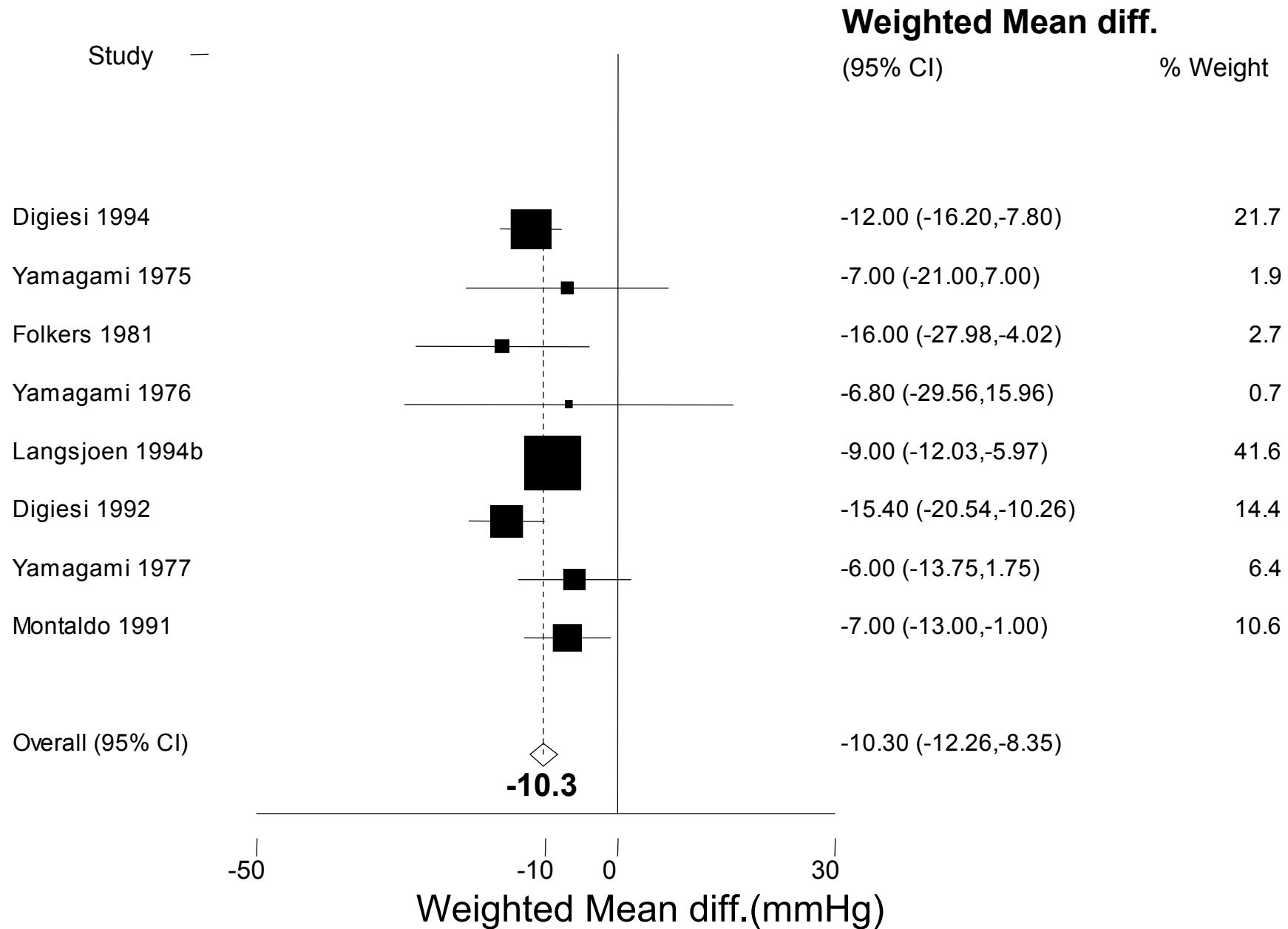
SYSTOLIC BP AFTER STUDY



SYSTOLIC BP WEIGHTED MEAN DIFFERENCE - BEFORE TO AFTER



DIASTOLIC BP - WEIGHTED MEAN DIFFERENCE BEFORE TO AFTER



THREE RANDOMISED TRIALS

- With a control group
- 155 patients

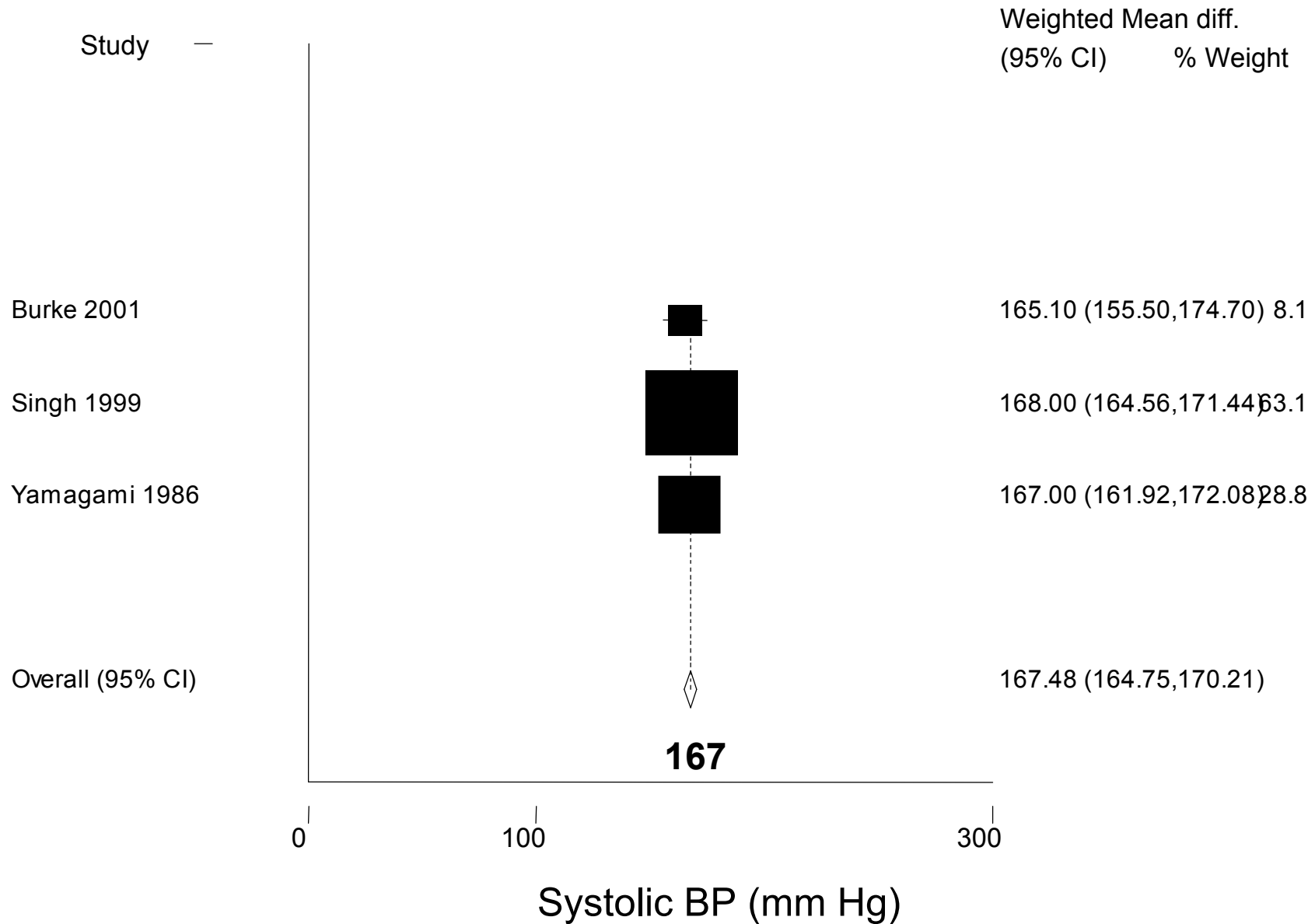
RANDOMISED CONTROLLED TRIALS

Treated Group

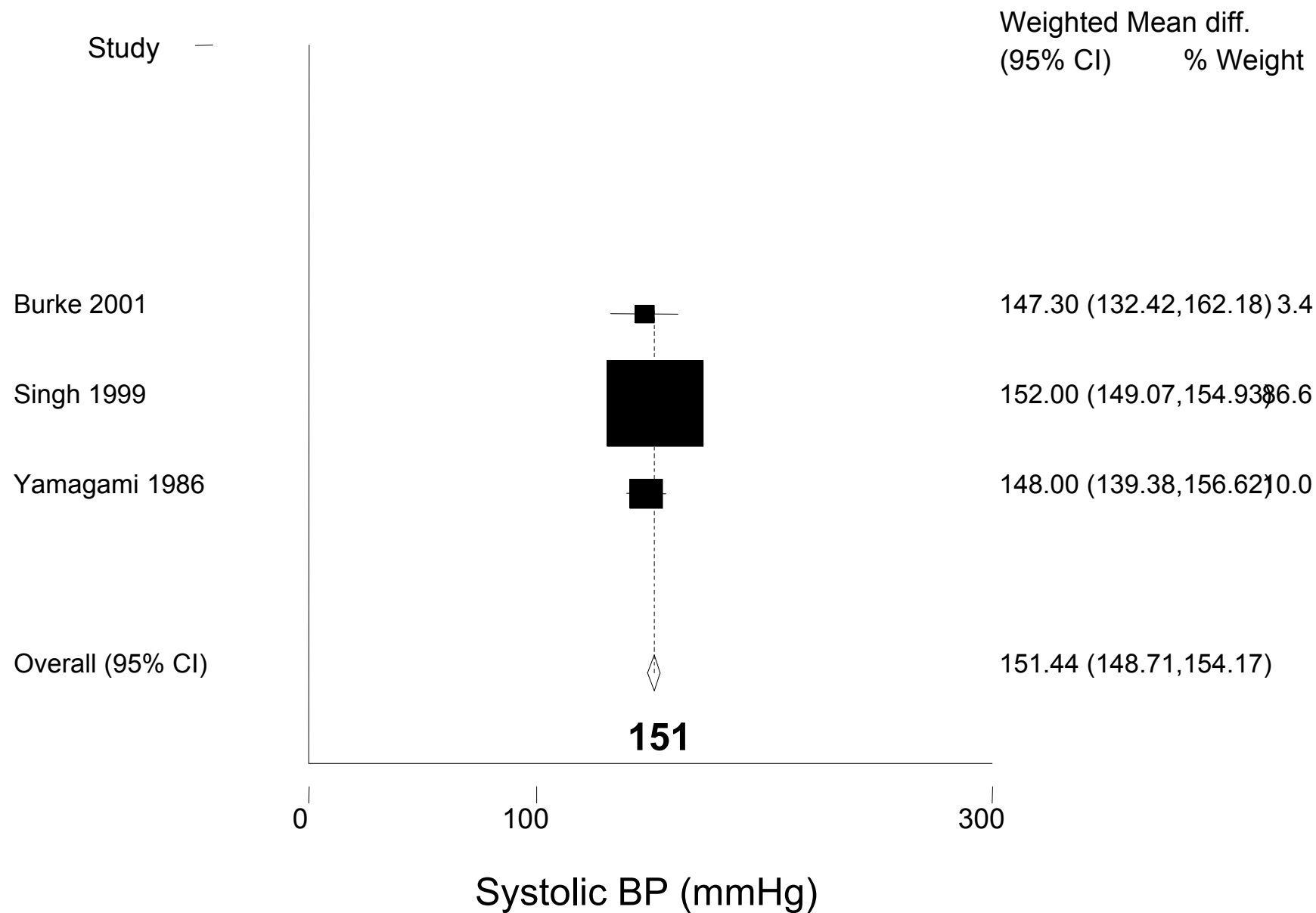
Randomised controlled trials	N	Patient characteristics	CoQ10 dose (mg/day)	Period (weeks)	Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure (mmHg)		
					Baseline	Final	Diff. SBP	Baseline	Final	Diff. DBP
Yamagami 1986	10/20	Essential hypertension	100	12	167 ±2.6	148 ±4.4	-19	97 ±1.8	91 ±3.7	- 6
Singh 1999	32/64	Hypertension and CAD	120	8	168 ±1.8	152 ±1.5	-16 *	106 ±0.9	97 ±0.8	- 9 *
Burke 2001	39/71	Isolated systolic primary hypertension	120	12	165 ±4.9	147 ±7.6	-18	81 ±1.6	78 ±2.9	- 3

* Reduced consumption of 3 other antihypertensive medications

Systolic BP in treated group before therapy



Systolic BP in treated group after therapy



Systolic bp before to after - weighted mean difference treated group

Weighted Mean diff.

(95% CI)

% Weight

Study

Burke 2001

17.80 (0.09,35.51)

5.1

Singh 1999

16.00 (11.48,20.52)

78.8

Yamagami 1986

19.00 (9.00,29.00)

16.1

Overall (95% CI)

16.57 (12.56,20.58)

-16

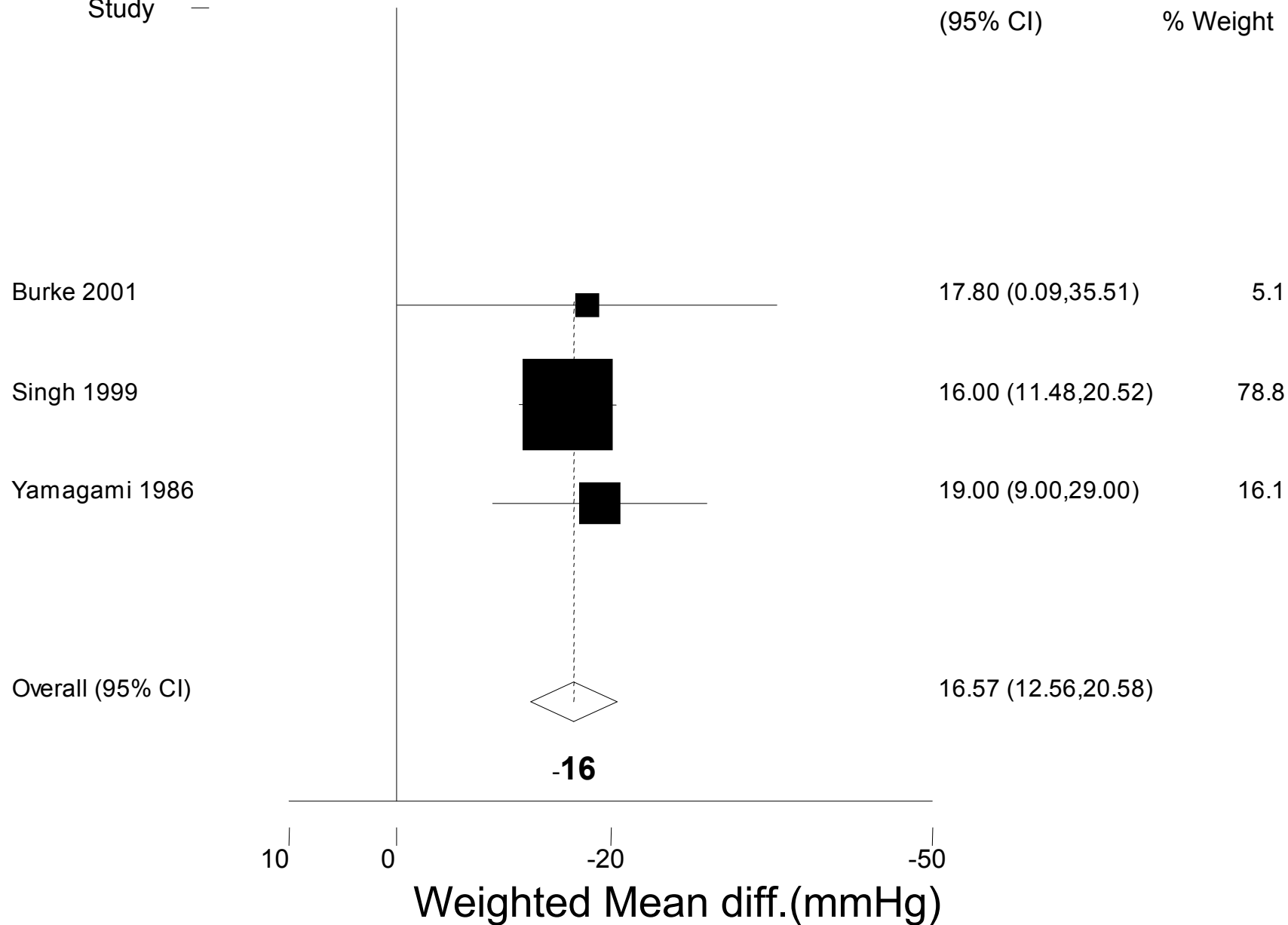
10

0

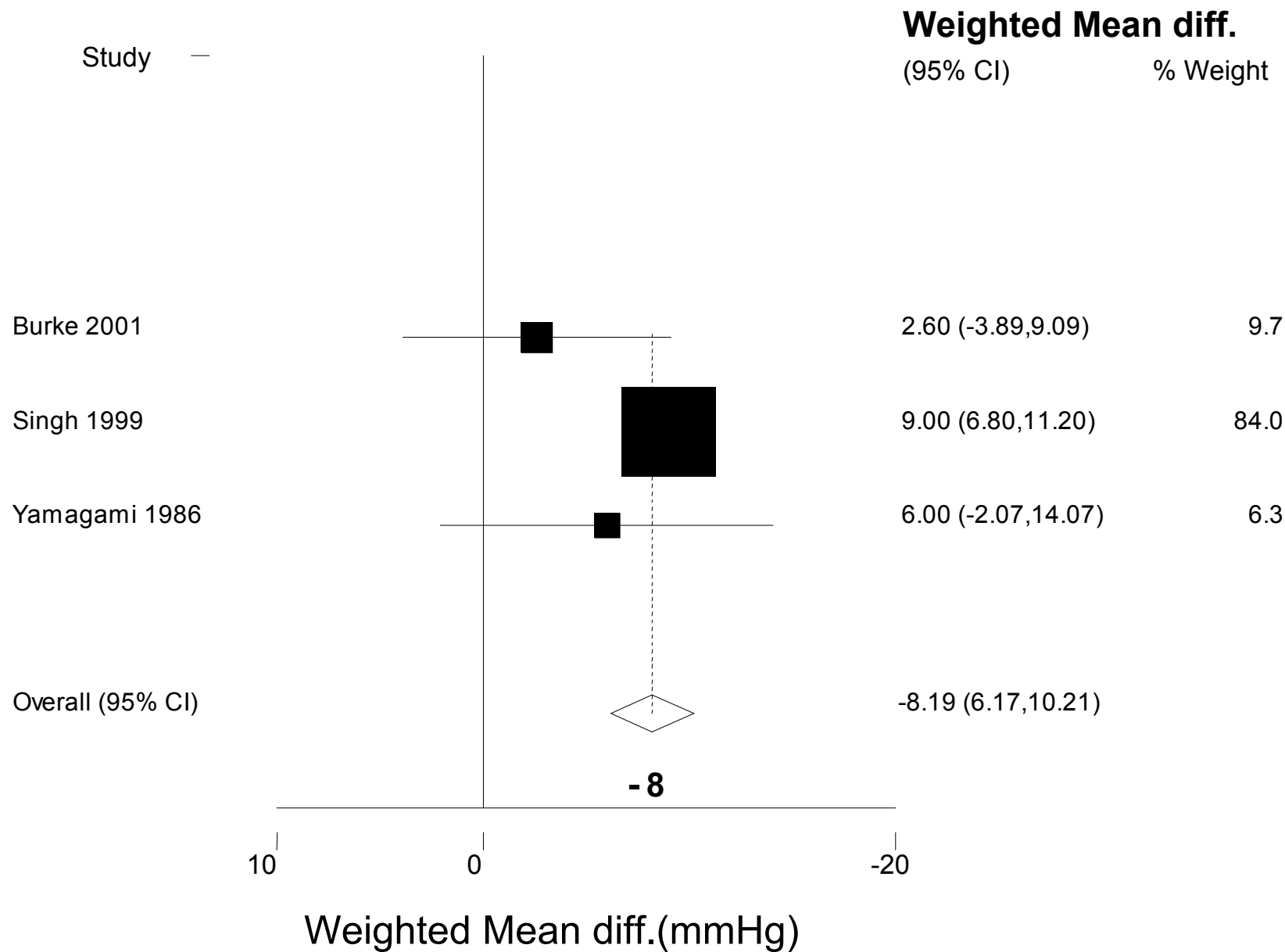
-20

-50

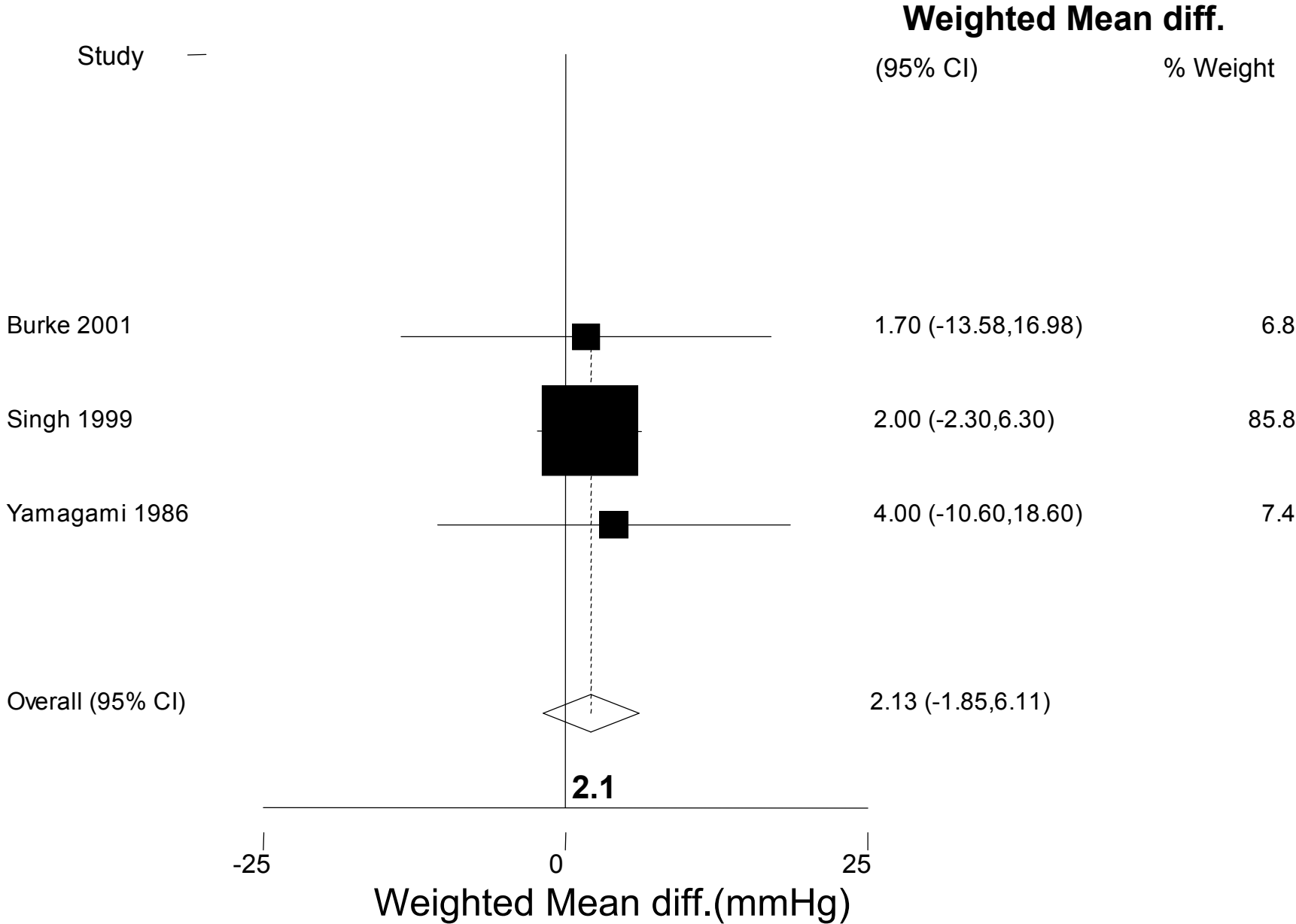
Weighted Mean diff.(mmHg)



Diastolic bp before to after - weighted mean difference in treated group



Systolic bp before to after - weighted mean difference in untreated group



ONE CROSSOVER STUDY

All patients received
both treatments sequentially

CROSSOVER STUDY

Crossover study	N	Patient characteristics	CoQ10 dose (mg/day)	Period (weeks)	Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure (mmHg)		
					Baseline	Final	Diff. SBP	Baseline	Final	Diff. DBP
Digiesi 1990	18	Hypertension WHO stage I/II	100	10	167 ±2.6	156 ±2.3	- 11	103 ±1.2	95 ±1.0	-8

SUMMARY

12 TRIALS

387 PATIENTS

	Studies (n)	Patients (n)	Systolic BP (mm Hg)			Diastolic BP (mm Hg)		
			Baseline	Final	Difference	Baseline	Final	Difference
Open Label Studies	8	214	165 ±8.0	147 ±7.2	-13 ±0.7	97* ±4.7	87 ±4.2	-10* ±0.5
Randomised Controlled Trials		3						
Treatment arm		81	167 ±15.2	151 ±13.7	-17 ±1.5	100 ±9.1	96 ±8.7	-8* ±0.8
Control Arm		74	166 ±15.8	164 ±15.6	+2 ±0.2	101 ±9.6	101 ±9.7	+2 ±0.2
Crossover study	1							
Treatment arm		18	167 ± 2.6	156 ± 2.3	-10	103 ± 1.2	95 ± 1	-8
Control Arm			167 ± 2.6	166 ± 2.4	-0.3	103 ± 1.2	103 ± 1.1	+0.4

* P <0.001

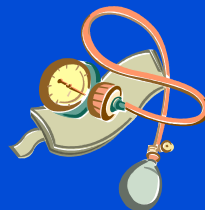
SIDE EFFECTS ?

- Open label studies:
 - Absence of side effects documented: 1
 - Side effects not mentioned :7
- Randomised trials:
 - Absence of side effects documented: 2
 - Side effects not mentioned:1
- Crossover study:
 - Absence of side effects documented: 1

CONCLUSIONS

From 12 studies in 387 patients

- Co-enzyme Q₁₀ reduces
 - systolic blood pressure by 13 to 17 mm
 - diastolic blood pressure by 8 to 10 mm Hg
- Co-enzyme Q₁₀ therapy has no clinically important side effects
- Co-enzyme Q₁₀ therapy may have a role in the routine management of hypertension - especially because of its known additional beneficial effects on the myocardium



CARDIOVASCULAR APPLICATIONS OF COENZYME Q10

Treatment of hypertension
and
Holistic Preparation for Cardiac Surgery



**CLINICAL TRIAL OF CoQ₁₀
AS PREPARATION
FOR CARDIAC SURGERY**

**Coenzyme Q10 therapy before cardiac surgery
improves
mitochondrial function and in vitro contractility of
myocardial tissue**

Franklin Rosenfeldt, Silvana Marasco, William Lyon,
Michelle Wowk, Freya Sheeran, Michael Bailey,
Donald Esmore, Bruce Davis, Adrian Pick,
Mark Rabinov, Julian Smith, Phillip Nagley, Salvatore
Pepe,

**The Journal of Thoracic and Cardiovascular Surgery .
Volume 129, : 25, 2005.**

CLINICAL TRIAL OF CoQ₁₀ IN CARDIAC SURGERY

- Randomised, double blind placebo - controlled trial.
- Elective primary cardiac surgical patients
- Patients (n=62) received CoQ₁₀ (300mg) or placebo (n=59) daily for (14 days average) prior to surgery

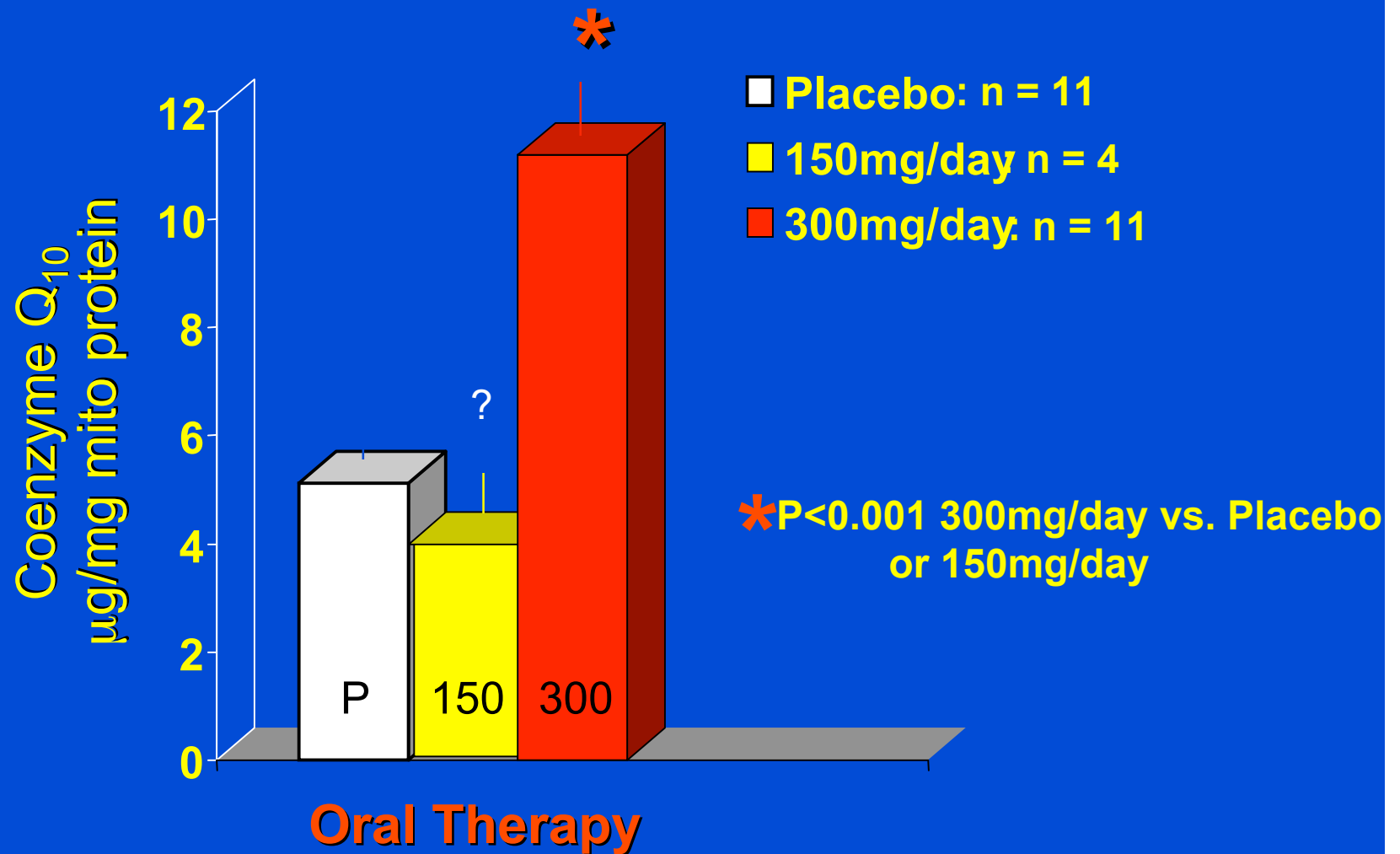
PATIENT DEMOGRAPHICS AND LENGTH OF THERAPY

	Placebo n = 59	CQ ₁₀ n = 62	P Value
Age (years)	68	67	0.31
Male (%)	85	76	0.32
Remote MI (%)	43	31	0.23
LV grade	2.2 ± 0.1	2.1 ± 0.1	0.68
Hypertension (%)	62	57	0.63
Diuretic (%)	21	10	0.13
ACE inhibitor (%)	41	26	0.11
β Blocker(%)	38	50	0.23
Length of treat. (days)	13.5 ± 1.5	14.0 ± 1.1	0.83

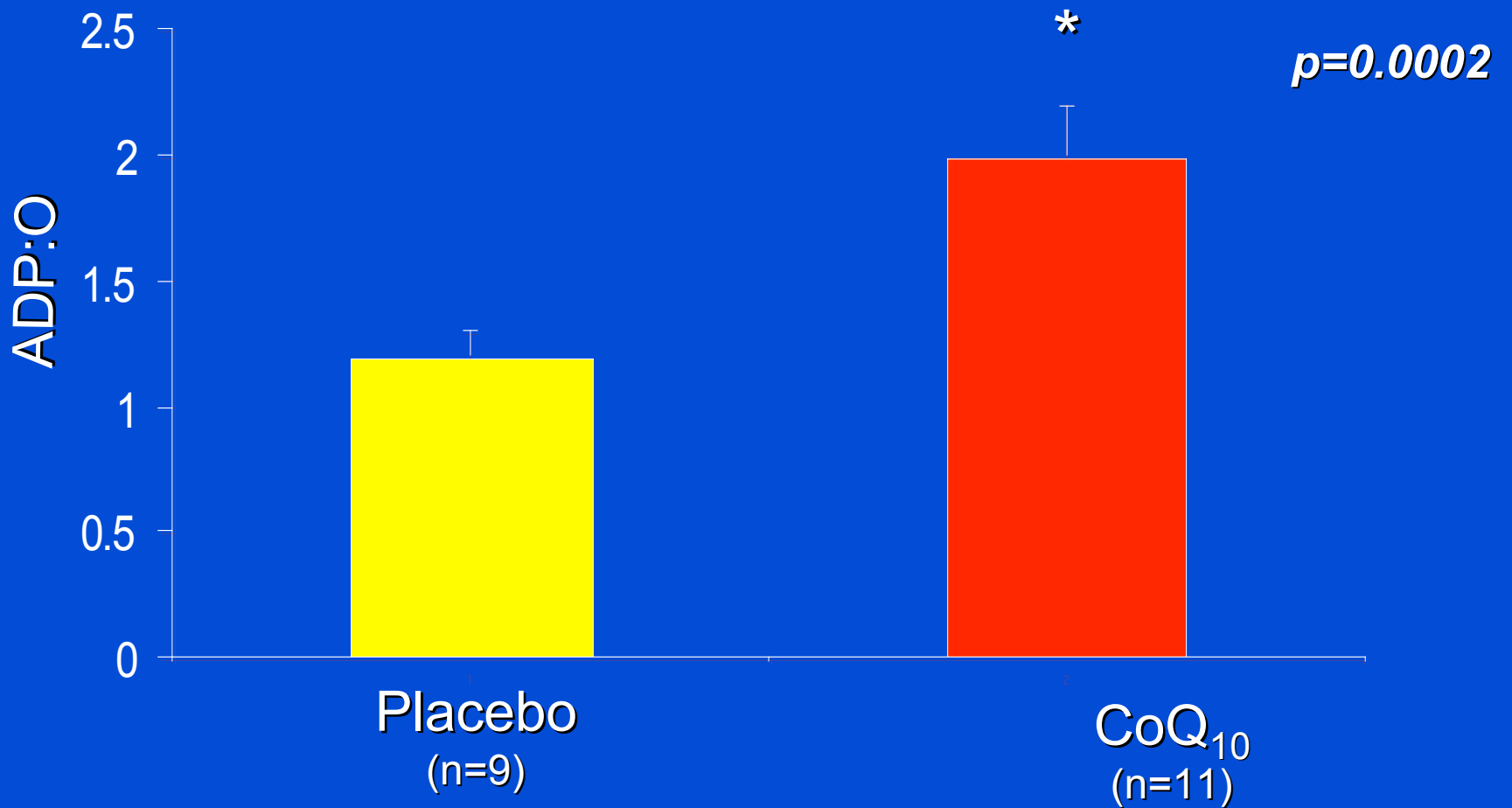
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MITOCHONDRIAL COENZYME Q₁₀

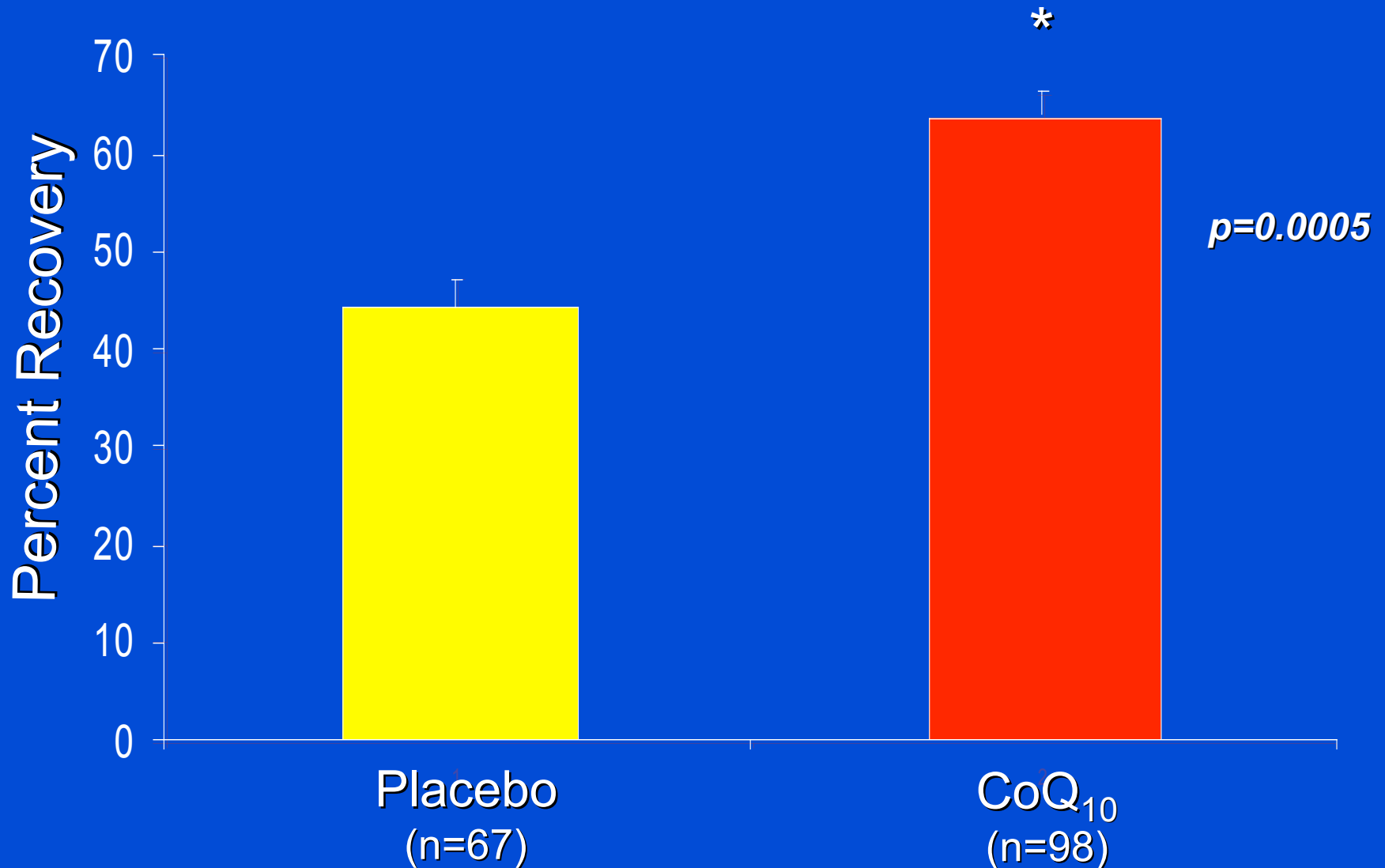


ADP:O EFFICIENCY RATIO

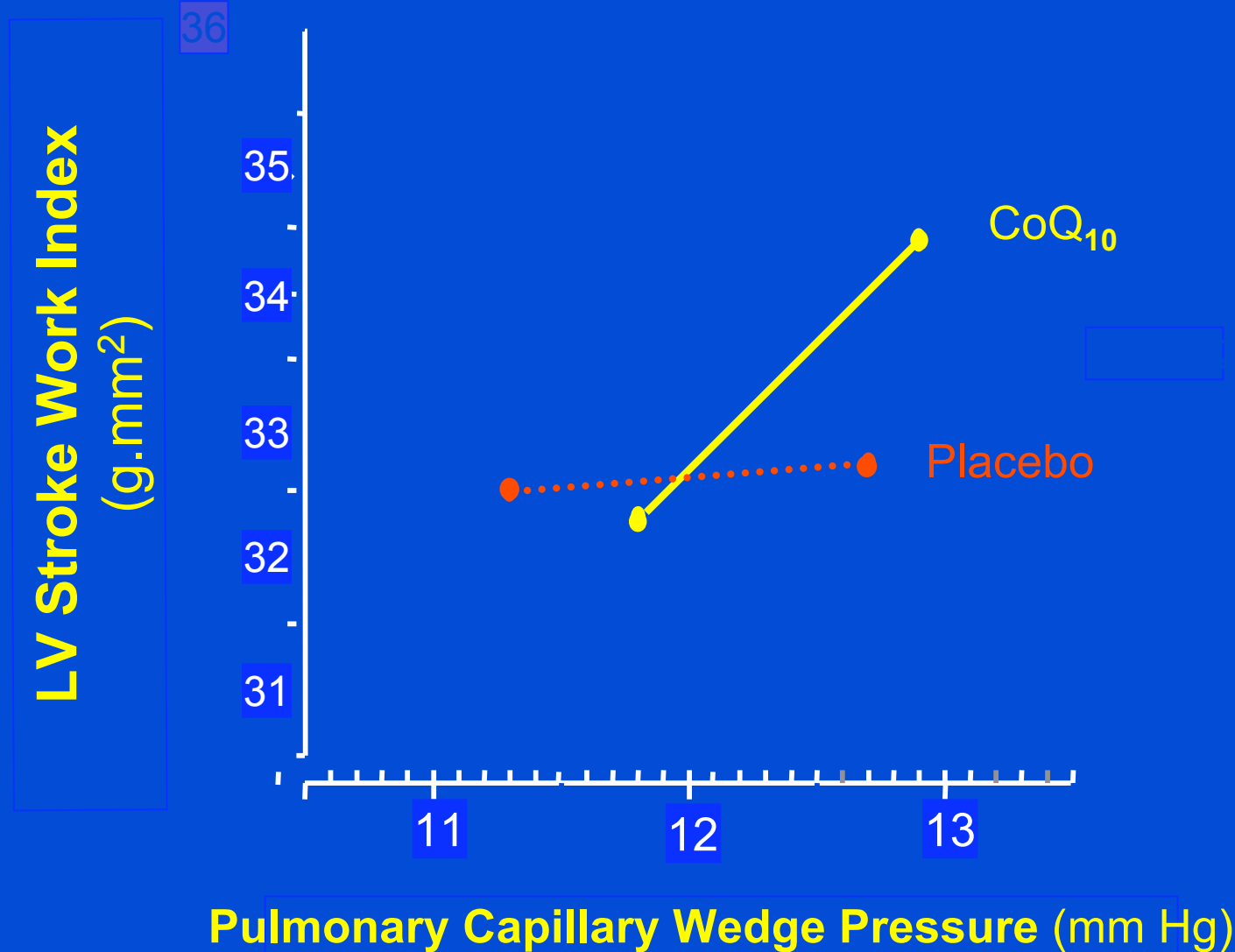


State III oxygen consumption of isolated human mitochondria at 37° C by oxidation of pyruvate (5mM)

RECOVERY OF DEVELOPED FORCE IN MUSCLE STRIPS AFTER HYPOXIA



CARDIAC FUNCTION IMPROVEMENT IN RESPONSE TO CoQ₁₀ MEASURED 4 HRS POSTOPERATIVELY



CONCLUSIONS

CoQ₁₀ therapy before cardiac surgery

1. Increases CoQ₁₀ content of cardiac mitochondria
2. Improves cardiac mitochondrial efficiency
3. Increases tolerance to stress at a myocardial level
4. Improves post-operative cardiac pump function

HOWEVER

1. No significant acceleration in rate of recovery in intensive care and in hospital

~

2. No improvement in postoperative physical or mental quality of life

IMPROVED REGIMEN TO ENHANCE EFFECTS

1. No significant acceleration in rate of recovery in intensive care and in hospital

Add more antioxidants and cellular energisers

2. No improvement in postoperative physical or mental quality of life

Add physical exercise and mental stress reduction

PREOPERATIVE PREPARATION FOR HIGH RISK AND ELDERLY CARDIAC SURGERY PATIENTS

The MPM Program

- Metabolic protection
- Physical Exercise
- Mental preparation

AUGMENTED METABOLIC THERAPY

- Co-enzyme Q₁₀ (300mg)
- Alpha-Lipoic Acid (150mg)
- Magnesium Orotate (1.2g)
- Omega-3-fatty Acids (3g)
- Selenium 200 mcg

(Daily dosage)

PHYSICAL EXERCISE PROGRAMME

Modest pre-operative exercise program
before surgery for at least two weeks
under the supervision of a physiotherapist
Including

- Treadmill walking
- Stationary bicycle
- Light Weights
- Gentle stretching exercises
- Light aerobic exercises

MENTAL PREPARATION

- Teach the patient methods of meditation and relaxation
- Technique that can be learned in four instruction sessions
- Patient Instructed to continue this in their own home

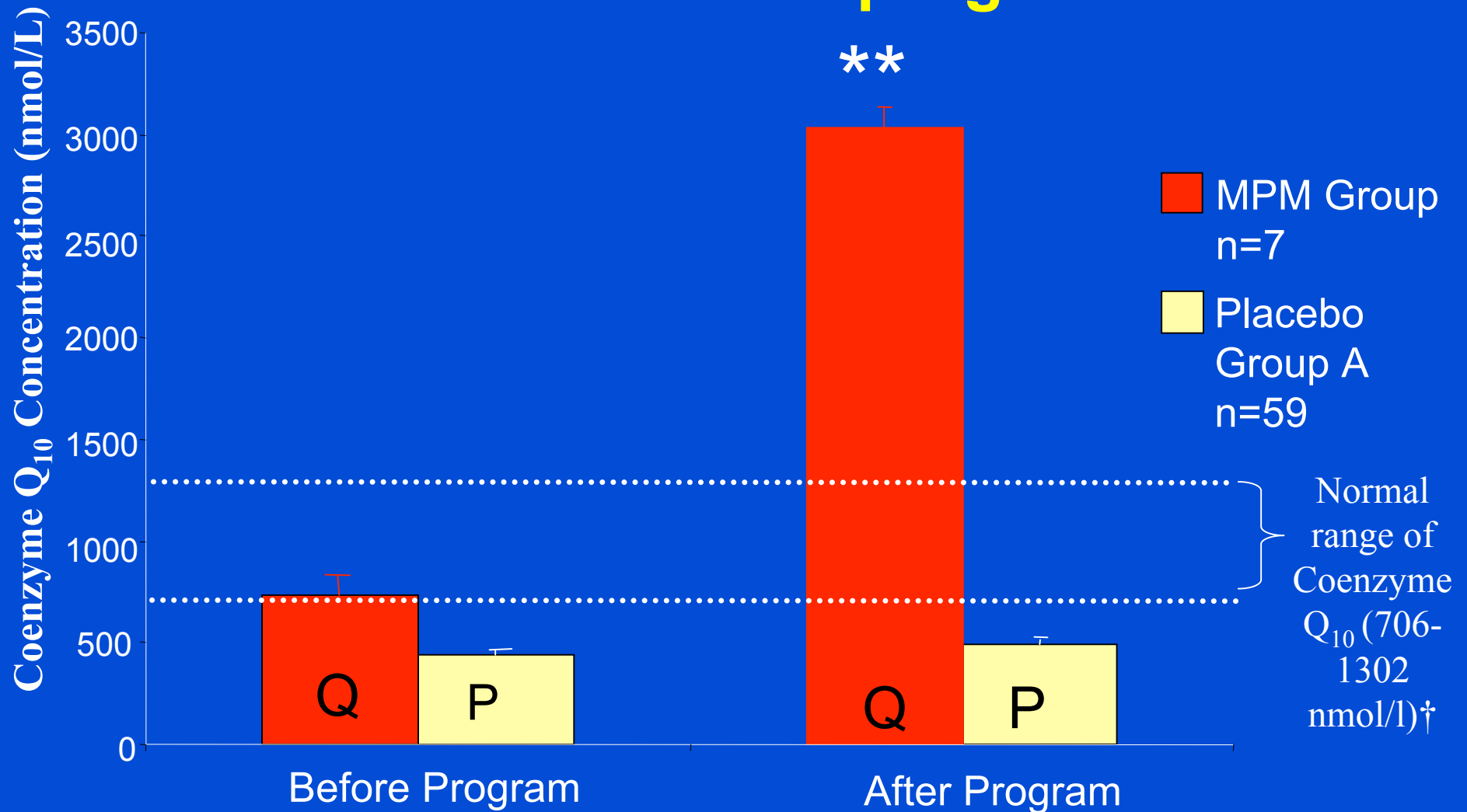
RESULTS OF PILOT STUDY OF MPM PROGRAMME IN PATIENTS UNDERGOING HEART SURGERY

Heart Lung and Circulation (submitted for publication 2005)

PATIENT DEMOGRAPHICS

	MPM Group (n=16)	Control Group A (n=52)	Control Group B (n=74)
Age (years)*	67	68	65
Male %	81	85	74
Operation Type (%)			
CABG	93	93	100
CABG + Valve	7	7	0
Procedure			
Mean number of grafts	3.3	2.9	3.2
NYHA			
I	2	-	-
II	7	-	-
III	5	-	-
IV	2	-	-
* Median			

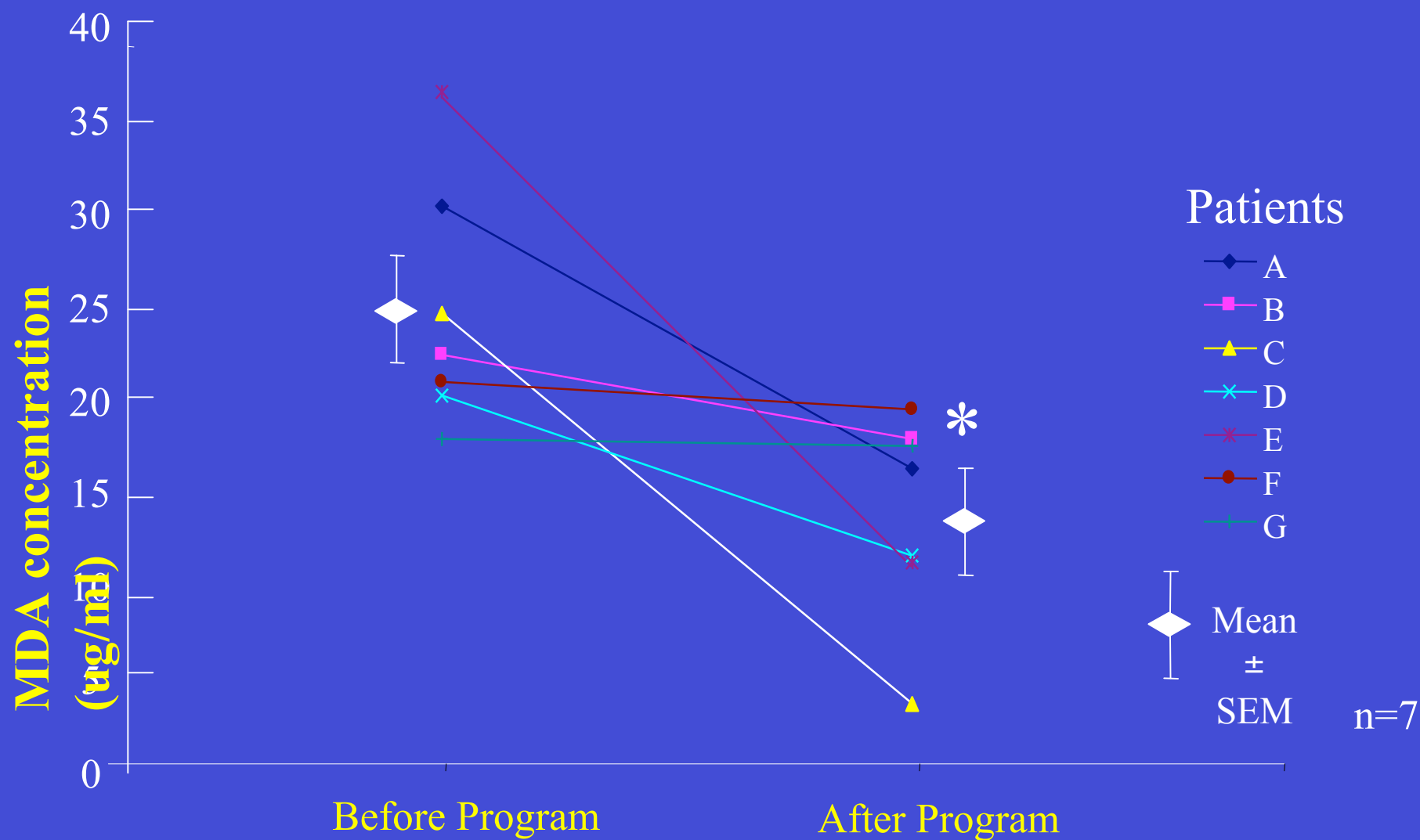
Plasma Coenzyme Q₁₀ levels increased after the MPM program



** p=0.006,

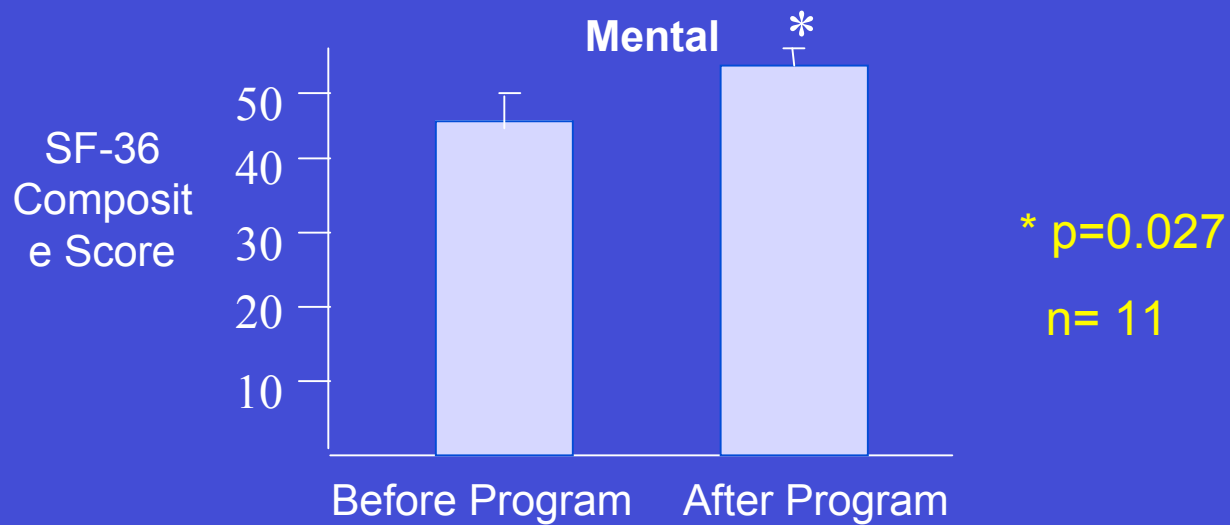
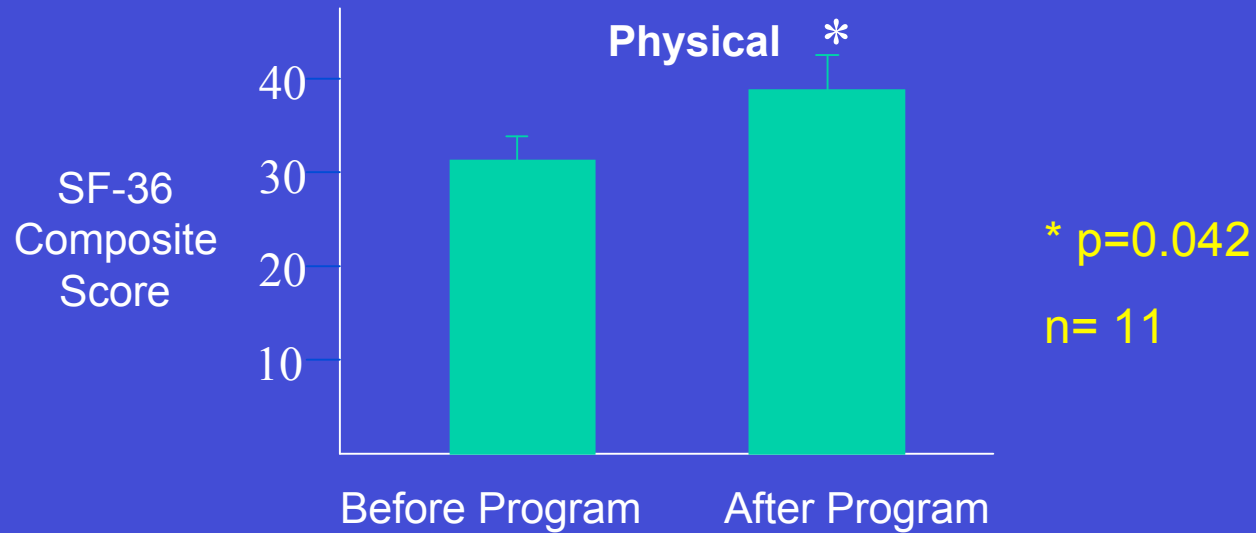
[†] Analytical Reference Laboratory

Serum malondialdehyde levels decreased after the MPM program and before surgery

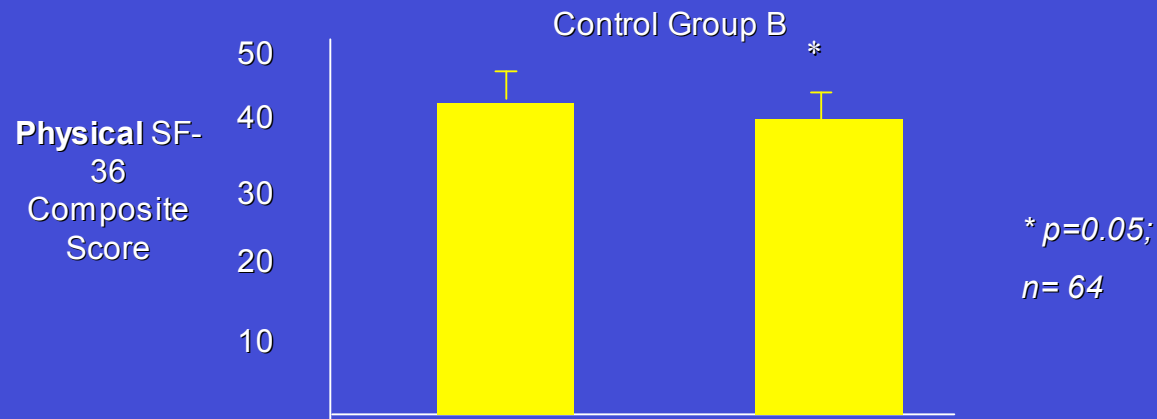
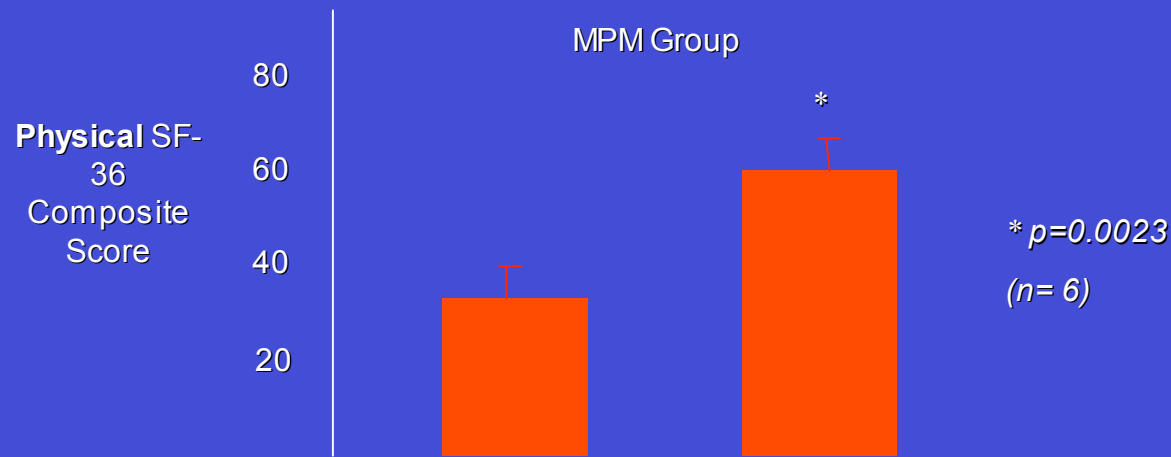


* p=0.0026

BEFORE SURGERY MPM PROGRAM IMPROVED QUALITY OF LIFE



ONE MONTH AFTER SURGERY MPM PROGRAM IMPROVED PHYSICAL QUALITY OF LIFE VS USUAL CARE CONTROL



Before
Surgery

1 month
after surgery

*Control data from Myles et al,
1998*

SUMMARY

Effects of MPM Preoperative Preparation from pilot study

1. Increased antioxidant levels
2. Reduced oxidative stress
3. Improved quality of life before surgery
4. Improved quality of life after surgery

*A PROSPECTIVE RANDOMISED
TRIAL INDICATED*

A prospective randomised clinical trial

**Preparation of patients for major surgery
using a combination of
metabolic, physical and mental therapy**

THE MPM Trial

Study Design

- Prospective randomised placebo-controlled trial
- 2 x 2 Factorial design
- Treatment variables
 - **Augmented Antioxidant therapy**
 - **Holistic therapy: mental and physical**

Primary Outcome Variables

- Mental and physical quality of life (QoL)
 - SF-36 Health Survey Questionnaire
 - Before program, pre-op, 1 month post-op & 6 months post-op
- Oxidative stress
 - Serum malondialdehyde (MDA) levels
 - Urinary isoprostane levels
 - Before program, pre-op & post-op

Secondary Outcome Variables

- Cardiac function (NYHA, 6-minute walk test, haemodynamics)
- Length of ICU stay
- Length of hospital stay
- Stress hormone levels
- Serum Selenium
- Thioredoxin reductase
- Serum troponin I levels
- Blood pressure
- Atrial fibrillation

Sample Size Calculations

	% Change	Sample size per Group
Mental QoL	20	74
Physical QoL	20	74
Serum MDA	20	92

MPM TRIAL

- In progress
- Target 200 (100 per group)
- 50 patients enrolled
- 26 patients completed

INTERIM RESULTS

- Patients separated into 2 groups
 - Rise in plasma CoQ₁₀ level of $\geq 200\%$
 - No rise in plasma CoQ₁₀ level
- Patient randomisation code intact
 - Results of exercise and relaxation therapy not analysed

Patient Demographics

	CoQ ₁₀ Rise (n = 12)	No CoQ ₁₀ Rise (n = 14)	<i>p</i> Value
Age (y)	63.7 ± 15.9	63.6 ± 10.9	0.99
Sex (% male)	83.3	71.4	0.65
Operation % CABG	66.7	64.3	1.00

Plasma Coenzyme Q₁₀

	CoQ ₁₀ Rise (n = 12)	No CoQ ₁₀ Rise (n = 14)	p Value
Baseline (nmol/L)	831 ± 313	960 ± 567	0.49
Pre-Op (nmol/L)	3802 ± 1801	894 ± 410	<0.01
Pre-Op (% Baseline)	464 ± 185	97.6 ± 16.2	<0.01

Normal > 700 nmol/L

Plasma Malondialdehyde (MDA)

	CoQ ₁₀ Rise (n = 12)	No CoQ ₁₀ Rise (n = 14)	<i>p</i> Value
Baseline (μM)	2.67 ± 2.08	1.92 ± 0.92	0.23
Pre-Op (μM)	1.28 ± 1.04	3.24 ± 2.67	0.03
Pre-Op (% Baseline)	52.4 ± 27.4	191 ± 212	0.04

INTERIM CONCLUSIONS

- Increased preoperative CoQ10 levels associated with reduced oxidative stress
- Study continuing and will be reported at the next meeting!

ACKNOWLEDGEMENTS

COLLEAGUES:

Pepe, J.Y.Leong, A. Hadj, D.S.Esmore, S.J.Haas,
H.Krum, K. Ng

GRANTS

National Heart Foundation

Royal Australasian College of Surgeons

COMMERCIAL SPONSORS

Pharma Nord

Tishcon

Blackmore Australia

Urinary Isoprostanes

	CoQ ₁₀ Rise (n = 12)	No CoQ ₁₀ Rise (n = 14)	<i>p</i> Value
Baseline (ng/mmol Cr)	1006 ± 600	1649 ± 1939	0.35
Pre-Op (ng/mmol Cr)	999 ± 632	1216 ± 410	0.40
Pre-Op (% Baseline)	106.7 ± 77.4	95.9 ± 92.8	0.78