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CSB Center for Stroke Research Berlin

How to implement life style changes

INSPiRE

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Background

- Patient after recent stroke or TIA are at high risk of experiencing a recurrent stroke or myocardial infarction
- Risk of new major vascular events can be reduced by evidence based secondary prevention measures
- Quality of secondary prevention is frequently suboptimal in real life
- Mainly elderly patients often have difficulties in changing their habits
- Effective support programs reported in patients with type-2 diabetes and coronary heart disease

Learning from other disciplines

Diabetes


The NEW ENGLAND JOURNAL of MEDICINE

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Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

Peter Gæde, M.D., Pernille Vedel, M.D., Ph.D., Nicolai Larsen, M.D., Ph.D., Gunnar V.H. Jensen, M.D., Ph.D., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

STENO-2-Study (RCT including 160 patients)

- Patients with Type-2 Diabetes and Microalbuminuria (Ø 55y)
- Primary outcome: Major vascular events
- 8 years follow-up

STENO-2-Interventionen und Outcome?

Stepwise implementation of

- o Behavioural modification
- o Pharmacologic treatment focussed on
  - o Hyperglycaemia
  - o Blood pressure
  - o Hyperlipidaemia
- o Aspirin

Results:

- ➢ significant improvement of all prevention targets
- ➢ Significantly fewer
  - ➢ Nephropathy, retinopathy, polyneuropathy
  - ➢ Vascular Events (OR 0.47)

NNT: ~4

Pilot studies in Berlin

2 consecutive cohorts

Standard care	Support program
Confirmed interest in participating in a support program	Informed consent for participating in a support program
Aftercare only by family physcian	Aftercare by family physician + outpatient support program with appointments at (3 weeks) 6 week 3 month
6-month follow-up FU (88%)	6-month follow-up (78%)

3 groups with increasing intensity

Outcomes after 6 months

OPEN ACCESS Freely available online

PLOS ONE

Secondary Prevention after Minor Stroke and TIA - Usual Care and Development of a Support Program

Stefanie Leistner[1*], Steffen Benik[1], Inga Laumeier[1], Annerose Ziegler[1], Gabriele Nieweler[1], Christian H. Nolte[1], Peter U. Heuschmann[2], Heinrich J. Audebert[3]

Leistner et al, PLOS one 2010	Standard care	Support program	p
	N=168	N=173	
BP according to recommendations	**43%**	**68%**	**<.01**
LDL < 100mg/dl	**63%**	**71%**	0.12
Stopped smoking	**50%**	**79%**	**<.01**
AF patients : INR 2-3	**42%**	**56%**	.08
Physical activity≥ 2x/w	**64%**	**87%**	.02

Purpose

Purpose:

To investigate whether a support program for enhanced secondary prevention can reduce the rate of recurrent vascular events.

Design and inclusion

Multicenter, Prospective Randomized Open Trial with Blinded Endpoint assessment (PROBE design)

Study protocol registered in ClinicalTrials.gov (NCT01586702) and in BMC Neurology 2013

Inclusion Criteria

- **Minor stroke** within 14 days from randomisation

  or

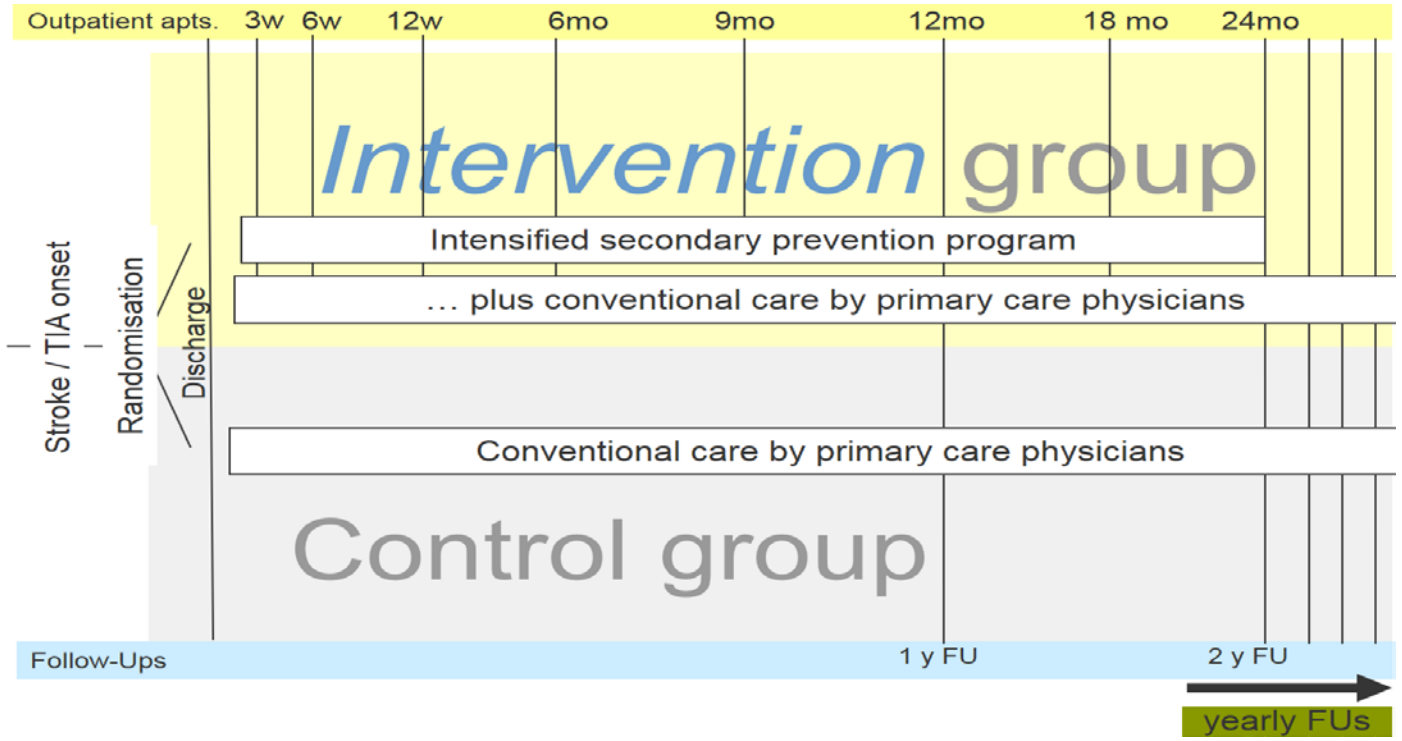
- **TIA** within 14 days from randomisation with
  - DWI lesion in MRI or
  - $ABCD^2$ ≥3
- Age ≥ 18y
- At least one treatable vascular risk factor
- Independent in ADL (mRS ≤2) at time of inclusion
- Being able to attend outpatient appointments

Methods 1: Intervention

In addition to conventional care we applied in 8 outpatient appointments over 2 years

- **Patient empowerment based on Motivational Interviewing**
- Repeated **information** on pathophysiology and individual risk for recurrent vascular events
- **Assessment** of risk factors control and medication intake
- **Feedback** regarding room for improvement and agreement on individual target plans
- Complementary offers (e.g. information on group therapies for physical activity and smoking cessation)

INSPiRE Intervention schedule and sample size



Expected event rate: 6% per year in routine care

Estimated risk reduction: 28% (RRR)

Adherence rate: 90%

Mean FU duration: 3.5 years

Total numbers: 2082 pts. (1041 per arm)

Outcome definitions

Primary outcome

Time to new major vascular events

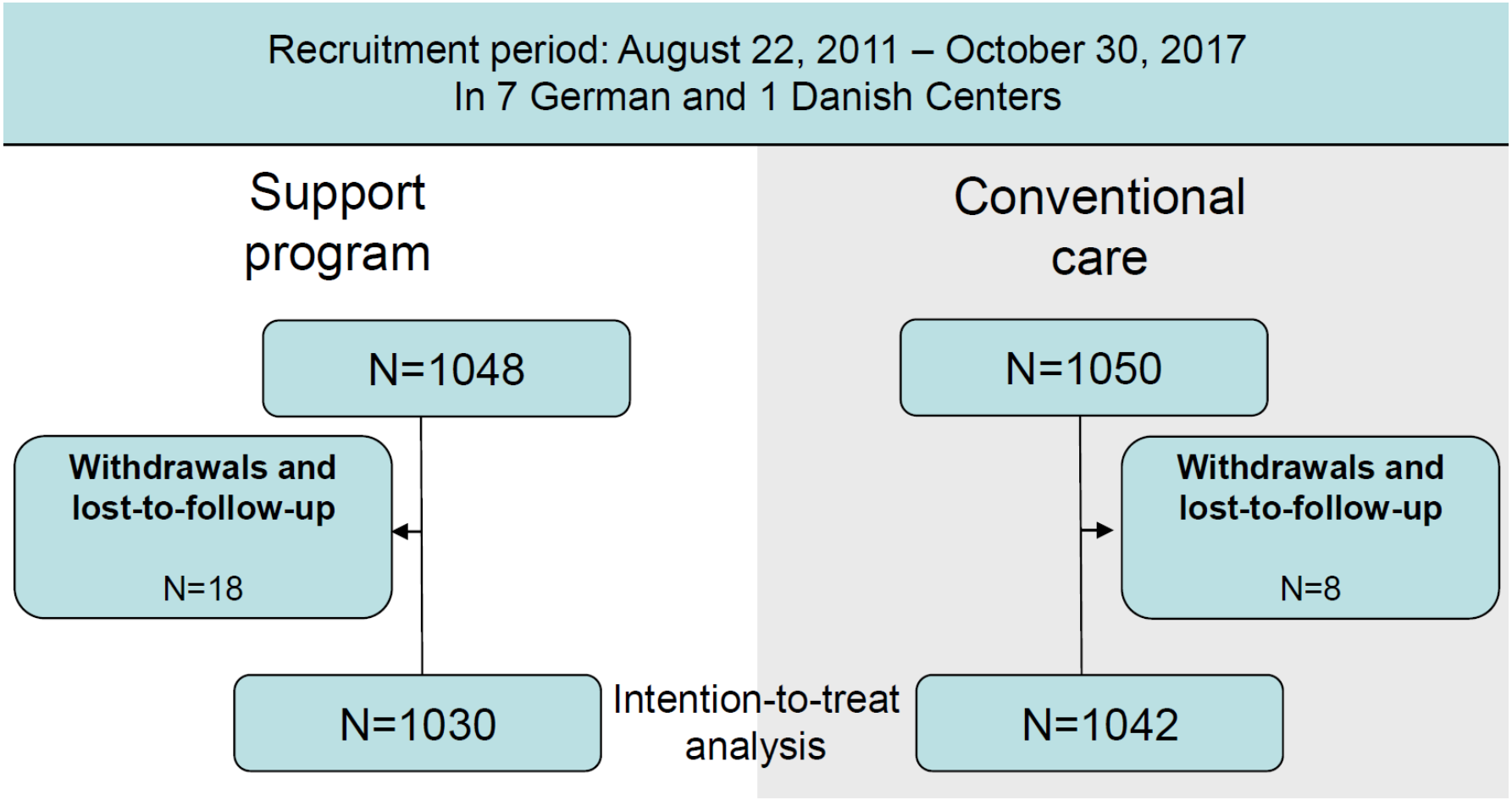
- **Stroke**
- **Acute coronary syndrome**
- **Vascular death**

Adjudicated by clinical event committee unaware of study arm

Secondary outcomes in annual follow-ups:

- Proportion of patients within therapeutic targets
- Intermediary outcomes (Physical fitness)
- Disability (modified Rankin Scale)

Flow-chart


Recruitment period: August 22, 2011 – October 30, 2017
In 7 German and 1 Danish Centers
Support program
Conventional care
N=1048
N=1050
Withdrawals and lost-to-follow-up
N=18
Withdrawals and lost-to-follow-up
N=8
N=1030
Intention-to-treat analysis
N=1042

INSPiRE

Baseline characteristics

	Support program	Conventional care
Age, y, mean ± SD	67.1 ± 10	67.7 ± 10
Female	34%	33%
Arterial hypertension	87%	89%
Diabetes	24%	24%
Atrial fibrillation	17%	17%
Current tobacco use	25%	25%
Index event		
Stroke (with lesion in imaging)	61%	60%
TIA (without lesion in imaging)	40%	39%
Ischaemic monocular blindness	2%	2%
Syst. blood pressure (mmHg), mean ± SD	140 ± 22	139 ± 22
Diast. blood pressure (mmHg), mean ± SD	81 ± 13	80 ± 12
LDL(mg/dl), mean ± SD[#]	124 ± 44	120 ± 42

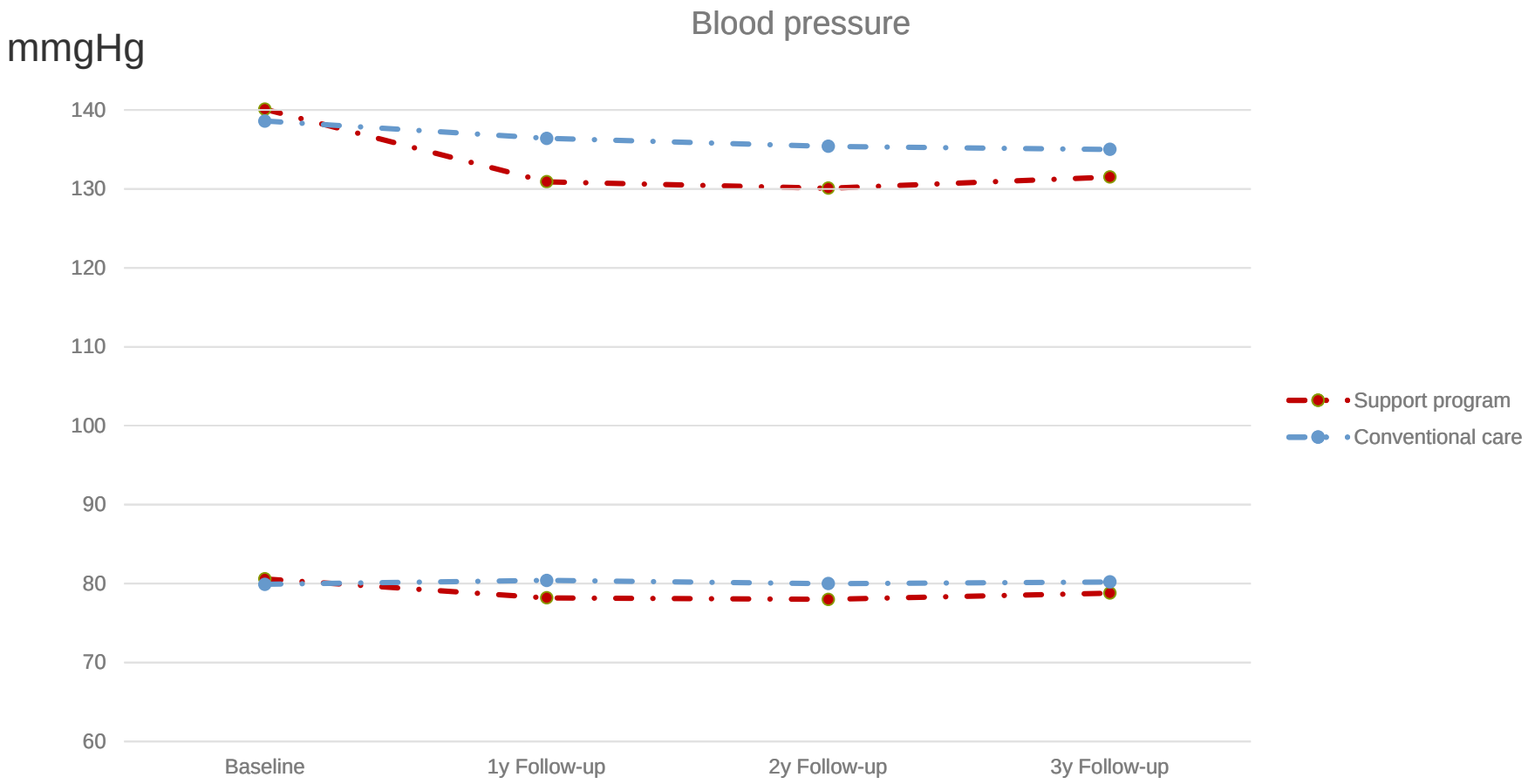
Achieving prevention targets

1 year follow-up	Support program	Conventional care	p-value
Blood pressure < 140/85 mmHg		48%	
LDL within target		54%	
Oral anticoagulation on target in AF patients		75%	
Hb1Ac ≤7.5% in diabetic patients		71%	
Smoking cessation		45%	
Physical activity (≥3 times 0.5h per week)		19%	

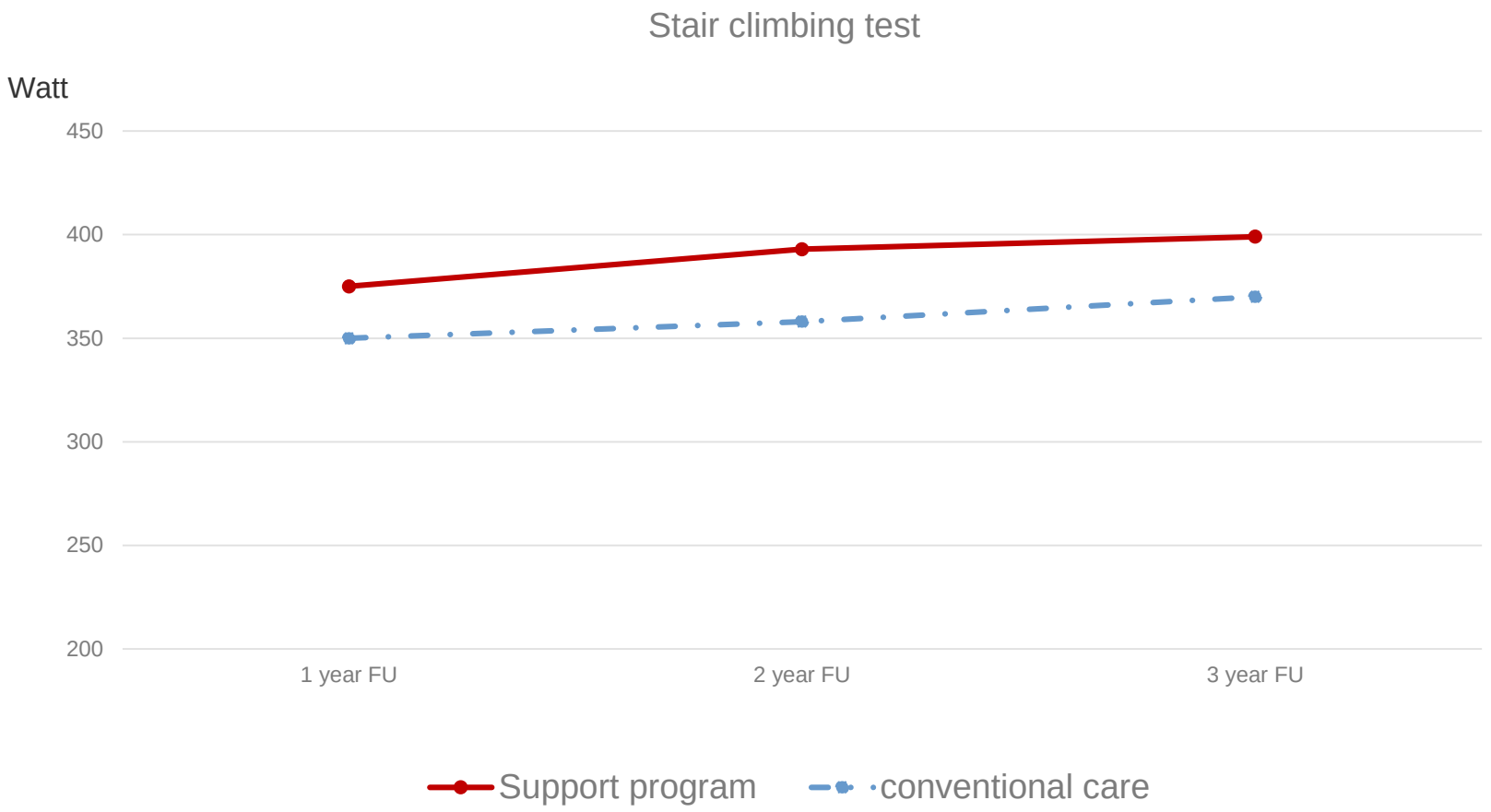
Achieving prevention targets

1 year follow-up	Support program	Conventional care	p-value
Blood pressure < 140/85 mmHg	59%	48%	<0.001
LDL within target	62%	54%	0.001
Oral anticoagulation on target in AF patients	83%	75%	<0.055
Hb1Ac ≤7.5% in diabetic patients	80%	71%	<0.04
Smoking cessation	50%	45%	0.001
Physical activity (≥3 times 0.5h per week)	33%	19%	<0.001

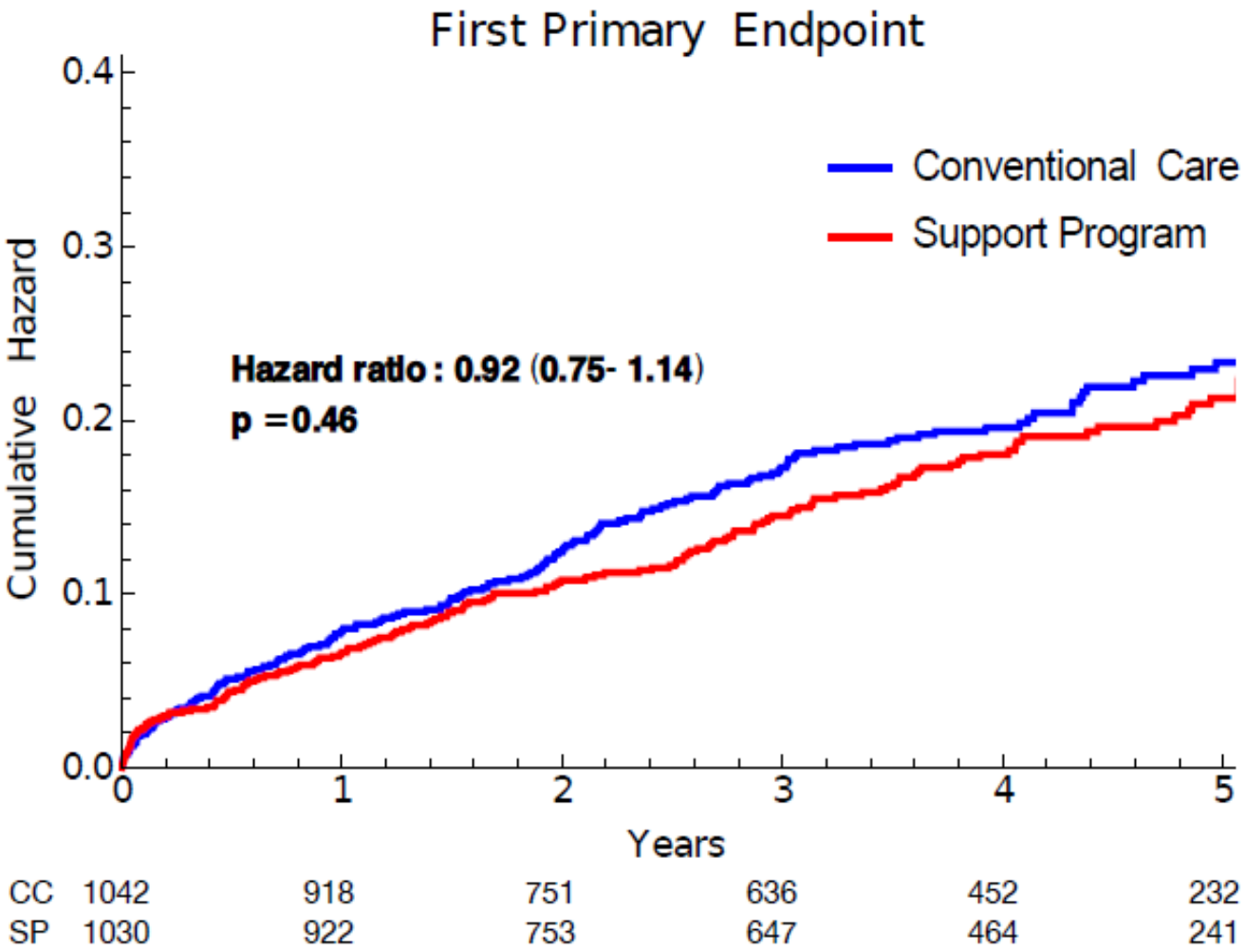
Blood pressure during first 3 years



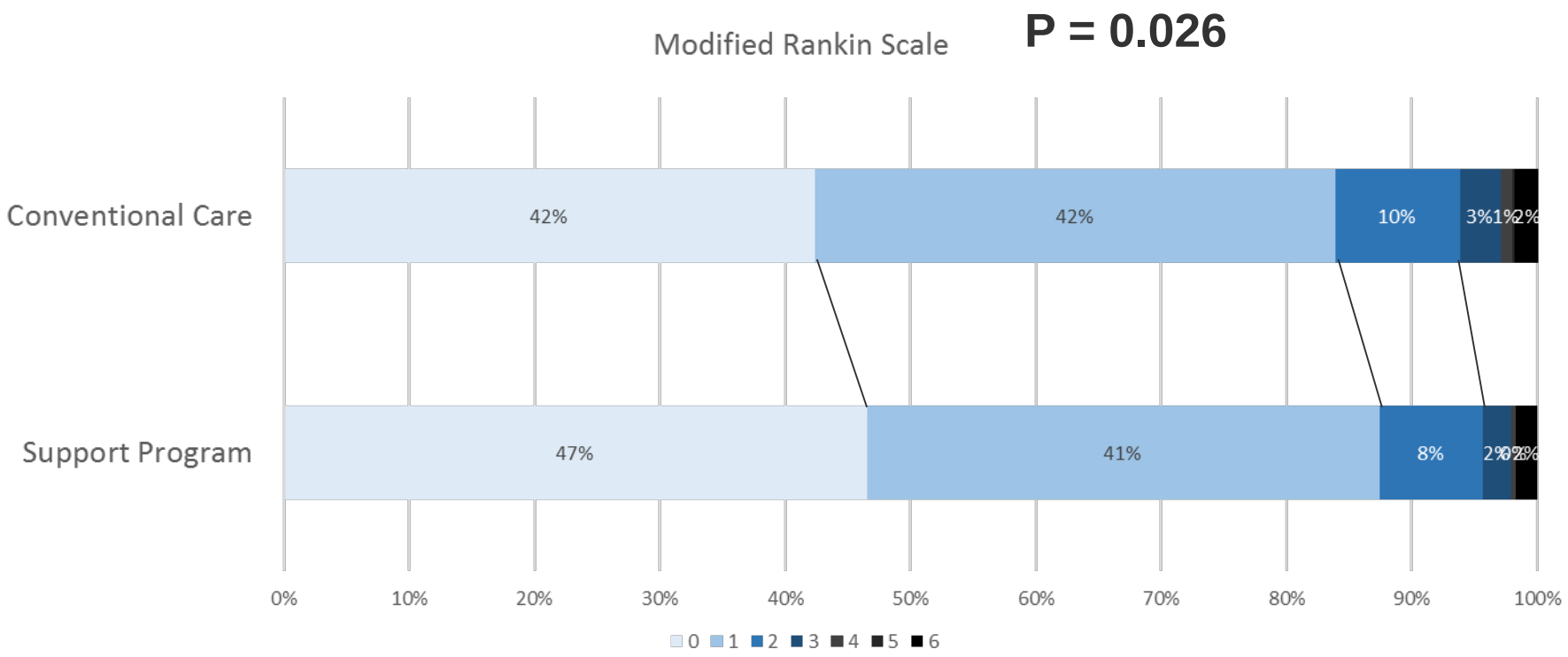
Physical fitness during first 3 years



Primary outcome



Secondary outcome: Disability



Discussion

Possible explanations for partially negative results

- Temporal trends towards better secondary prevention in usual care
- Dilution of effect by ~50% of patients within targets in control group
- Contamination by “optimized” family doctors treating patients of both groups

Limitations of the study

- Conducted in Germany and Denmark ➔ Generalizability?
- Local study personnel not blinded to allocation

Conclusions

Intensified secondary prevention in patients with minor stroke/TIA

- improved achievement of secondary prevention targets
- improved physical fitness
- did not translate to a lower rate of major vascular events
- may have positive effects beyond recurrence risk reduction

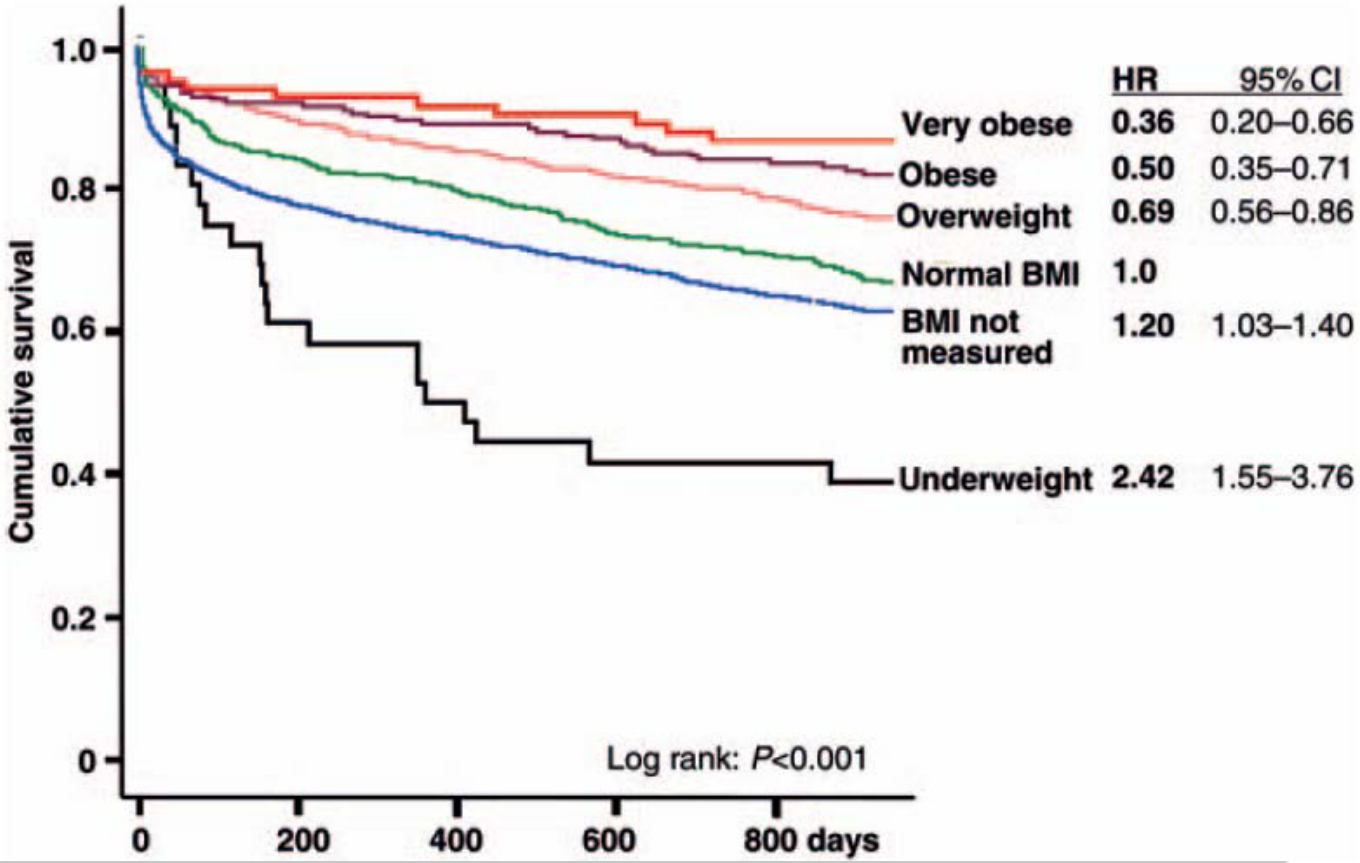
Obesity: Known Facts

- Obesity is a risk factor for
  - Metablic Syndrome
  - Cardiovascular diseases
- Obesity is associated with a better prognosis in some circumstances :
  - Advanced age
  - Oncological patients
  - Cardiac failure

Obesity paradox after Stroke?

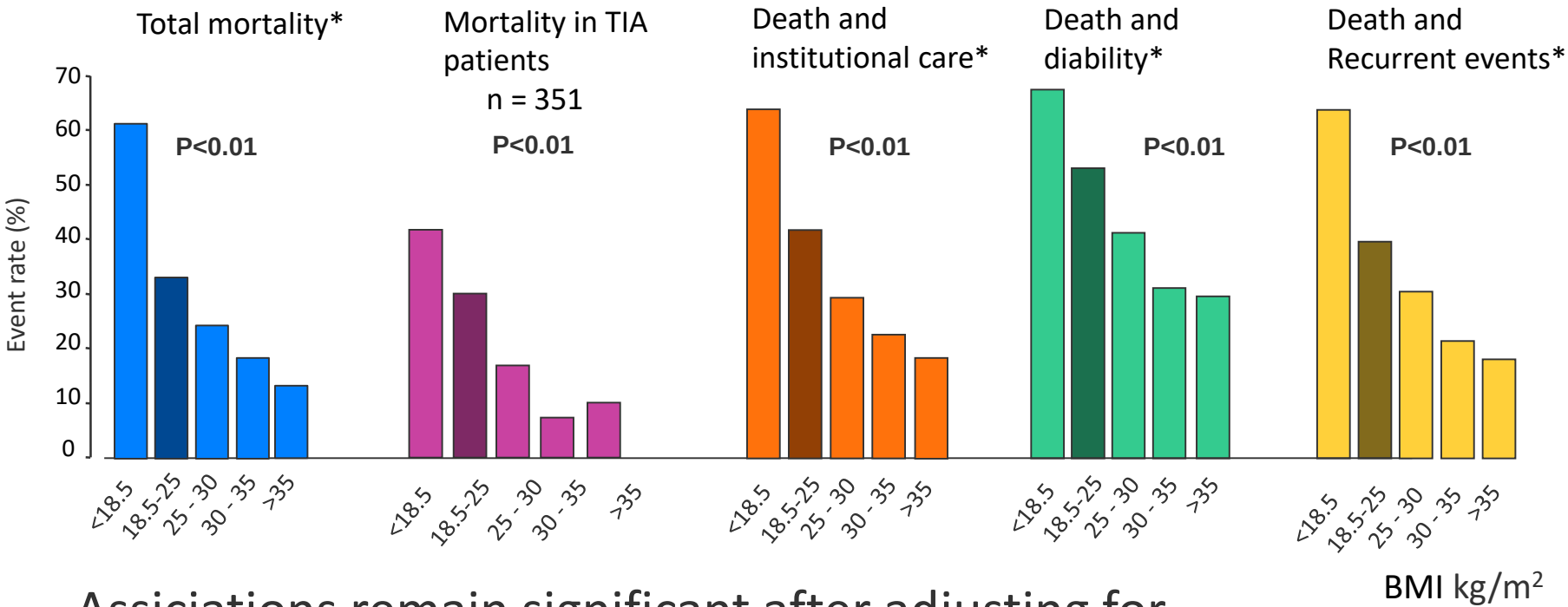
Association between body weight and mortality

- TEMPiS cohort: Patients after Stroke and TIA
- BMI available: N=1,521
- 30 month follow-up



Doehner … Audebert et al. Eur Heart J 2013

Associations with different outcomes

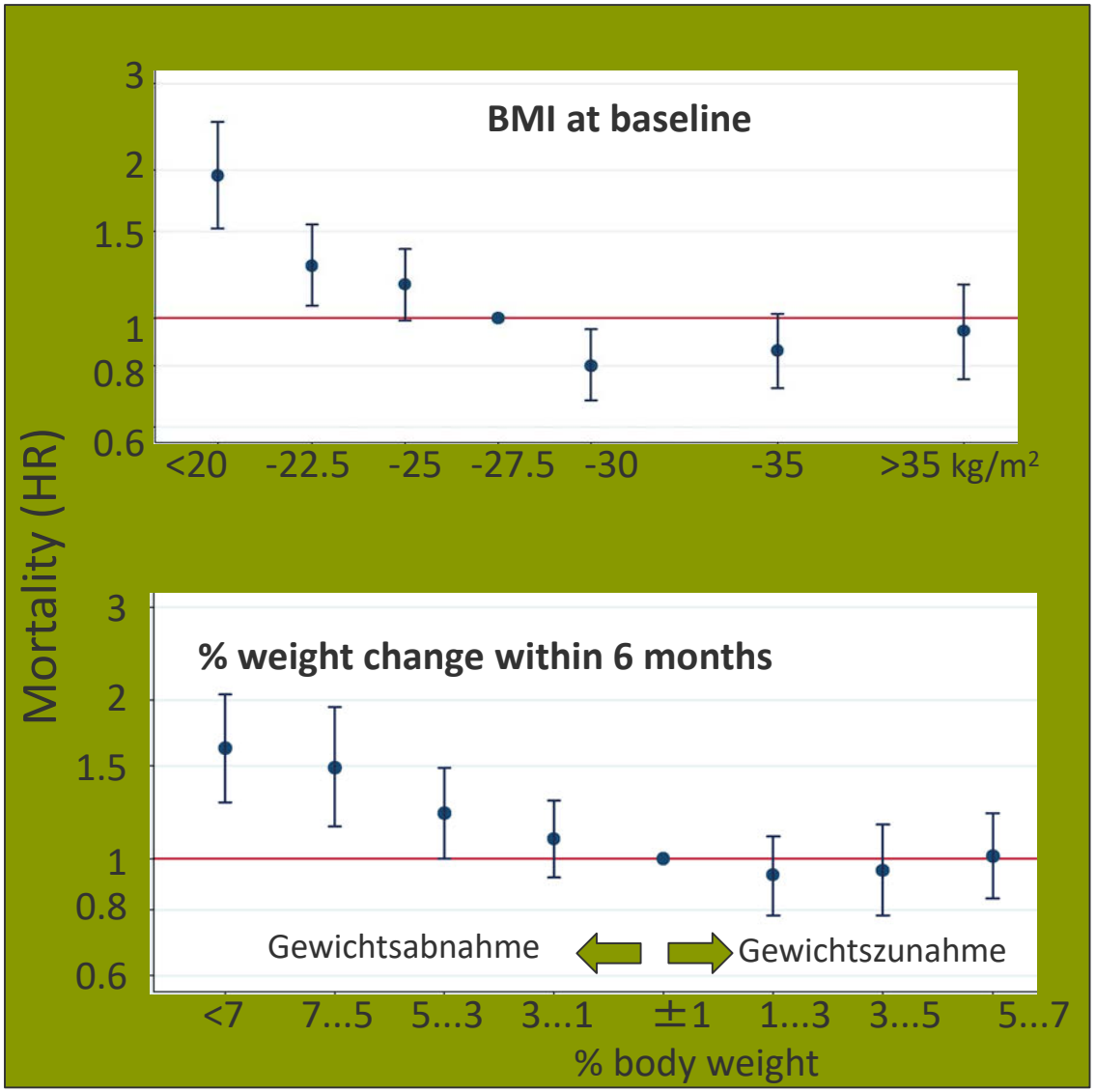


Assiciations remain significant after adjusting for

- Age
- Co-morbidities
- Living in relationship
- Stroke Severity

Doehner, Audebert et al. Eur Heart J 2012

BMI and weight change are predictive in patients with heart failure



CHARM programme
N=6933
FU: 32.90 months

- **High BMI *is no problem***
- **Weigt loss is a problem**

Pocock SJ *et al,* EHJ 2008

Weight loss in obese patients with type-2-diabetes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

Randomized multicenter trial

- Comparison between
  - Intensified program for weight loss
    - ➔ Reduction of daily calorie intake
    - ➔ Enhanced physical activity
  - Control group with structured information on Diabetes including instructural program

JEJM 2013

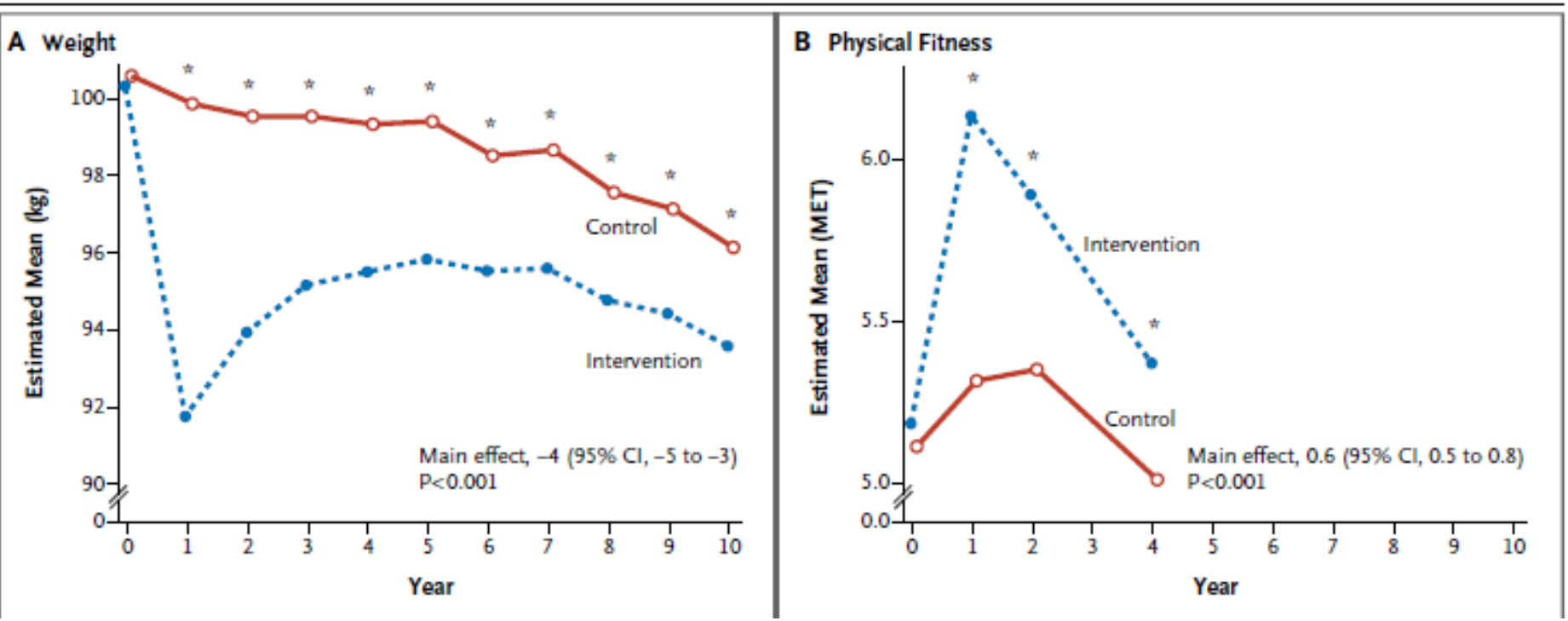
Weight loss in obese patients with type-2-diabetes

Primary outcome: Major vascular events

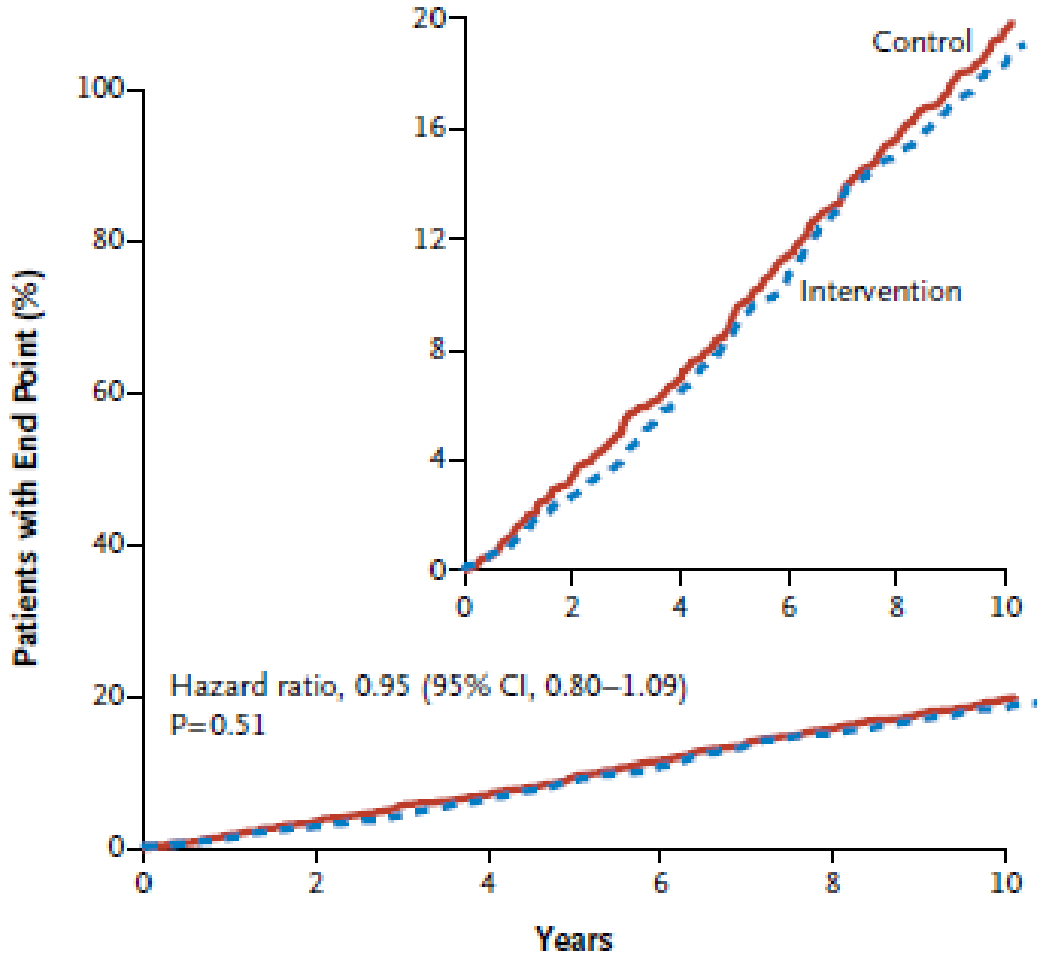
Median follow-up:	9,6y
Mean age:	59y
Mean BMI:	35
Previous cardiovascular disease:	14%

JEJM 2013

Weight loss in obese patients with type-2-diabetes



Weight loss in obese patients with type-2-diabetes



No. at Risk

Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

Improved outcomes reported for

- HbA1c
- Urinary continence
- Sleep apnoea
- Depression
- Quality of life
- Mobility