How to implement lifestyle changes

Heinrich J Audebert, Dept. of Neurology, Center for Stroke Research Berlin, Charité Berlin, Germany on behalf of

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

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
Stepwise implementation of

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

- Confirmed interest in participating in a support program
- Aftercare only by family physician
- 6-month follow-up FU (88%)

Support program

- Informed consent for participating in a support program
- Aftercare by family physician + outpatient support program with appointments at (3 weeks)
  6 week
  3 month
- 6-month follow-up (78%)

3 groups with increasing intensity
## Outcomes after 6 months

### 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\(^3\)

<table>
<thead>
<tr>
<th>Leistner et al, PLOS one 2010</th>
<th>Standard care</th>
<th>Support program</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=168</td>
<td>N=173</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP according to recommendations</td>
<td>43%</td>
<td>68%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>LDL &lt; 100mg/dl</td>
<td>63%</td>
<td>71%</td>
<td>0.12</td>
</tr>
<tr>
<td>Stopped smoking</td>
<td>50%</td>
<td>79%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>AF patients : INR 2-3</td>
<td>42%</td>
<td>56%</td>
<td>.08</td>
</tr>
<tr>
<td>Physical activity ≥ 2x/w</td>
<td>64%</td>
<td>87%</td>
<td>.02</td>
</tr>
</tbody>
</table>
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
  – ABCD² ≥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
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)
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)
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)
Recruitment period: August 22, 2011 – October 30, 2017
In 7 German and 1 Danish Centers

Support program
- N=1048
  - Withdrawals and lost-to-follow-up
    - N=18
  - N=1030

Conventional care
- N=1050
  - Withdrawals and lost-to-follow-up
    - N=8
  - N=1042

Intention-to-treat analysis
## Baseline characteristics

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

<table>
<thead>
<tr>
<th>1 year follow-up</th>
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<th>p-value</th>
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<tr>
<td>Blood pressure &lt; 140/85 mmHg</td>
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<td>48%</td>
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<td>LDL within target</td>
<td></td>
<td>54%</td>
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<tr>
<td>Oral anticoagulation on target in AF patients</td>
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<td>75%</td>
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<td>Hb1Ac ≤7.5% in diabetic patients</td>
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<td>Smoking cessation</td>
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<td>45%</td>
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<tr>
<td>Physical activity (≥3 times 0.5h per week)</td>
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<td>19%</td>
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Achieving prevention targets

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<tbody>
<tr>
<td>Blood pressure &lt; 140/85 mmHg</td>
<td>59%</td>
<td>48%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL within target</td>
<td>62%</td>
<td>54%</td>
<td>0.001</td>
</tr>
<tr>
<td>Oral anticoagulation on target in AF patients</td>
<td>83%</td>
<td>75%</td>
<td>&lt;0.055</td>
</tr>
<tr>
<td>Hb1Ac ≤7.5% in diabetic patients</td>
<td>80%</td>
<td>71%</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>50%</td>
<td>45%</td>
<td>0.001</td>
</tr>
<tr>
<td>Physical activity (≥3 times 0.5h per week)</td>
<td>33%</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
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</table>
Blood pressure during first 3 years

Blood pressure

mmHg

Baseline 1y Follow-up 2y Follow-up 3y Follow-up

Support program
Conventional care
Physical fitness during first 3 years

Stair climbing test

Watt

1 year FU 2 year FU 3 year FU

Support program

conventional care
First Primary Endpoint

Hazard ratio: 0.92 (0.75 - 1.14)

p = 0.46
Secondary outcome: Disability

Modified Rankin Scale

Conventional Care

- 42% in Modified Rankin Scale 0
- 42% in Modified Rankin Scale 1
- 10% in Modified Rankin Scale 2
- 3% in Modified Rankin Scale 3
- 2% in Modified Rankin Scale 4
- 1% in Modified Rankin Scale 5
- 10% in Modified Rankin Scale 6

Support Program

- 47% in Modified Rankin Scale 0
- 41% in Modified Rankin Scale 1
- 8% in Modified Rankin Scale 2
- 2% in Modified Rankin Scale 3

P = 0.026
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
  • Metabolic 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

[Graph showing cumulative survival for different BMI categories: Very obese (HR 0.36, 95% CI 0.20–0.66), Obese (HR 0.50, 95% CI 0.35–0.71), Overweight (HR 0.69, 95% CI 0.56–0.86), Normal BMI (HR 1.0), BMI not measured (HR 1.20, 95% CI 1.03–1.40), Underweight (HR 2.42, 95% CI 1.55–3.76)].

Doehner ... Audebert et al. Eur Heart J 2013
Associations with different outcomes

Associations 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

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
Weight loss in obese patients with type-2-diabetes

Primary outcome: Major vascular events

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up</td>
<td>9.6y</td>
</tr>
<tr>
<td>Mean age</td>
<td>59y</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>35</td>
</tr>
<tr>
<td>Previous cardiovascular disease:</td>
<td>14%</td>
</tr>
</tbody>
</table>
Weight loss in obese patients with type-2-diabetes

A Weight

B Physical Fitness

Main effect, -4 (95% CI, -5 to -3)
P<0.001

Main effect, 0.6 (95% CI, 0.5 to 0.8)
P<0.001
Weight loss in obese patients with type-2-diabetes

Improved outcomes reported for
- HbA1c
- Urinary continence
- Sleep apnoea
- Depression
- Quality of life
- Mobility