Strategic white matter hyperintensity locations for cognitive impairment in memory clinic patients: a large-scale multicenter study

Mirthe Coenen, PhD candidate
On behalf of the Meta VCI Map Consortium

Department of Neurology, UMC Utrecht, Utrecht, The Netherlands
Introduction

• WMH are a common manifestation of cerebral small vessel disease
• Impact of WMH seems to depend on location
• Only one single study in memory clinic patients (n=200)
Aim

To obtain high WMH coverage to identify strategic WMH locations for cognitive impairment in memory clinic patients
Meta VCI Map consortium

Meta-analyses of strategic lesion locations for Vascular Cognitive Impairment using lesion-symptom Mapping

- >50 cohorts/groups have joined
  - 2950 ischemic stroke patients
  - 3525 memory clinic patients
  - >20,000 population-based subjects

- https://metavcimap.org/
Method

Inclusion criteria
• Memory clinic cohorts
• Patients with any degree of symptom severity and vascular or any kind of neurodegenerative etiology
• MRI: FLAIR and T1 sequence
• Neuropsychological assessment

Image processing
• WMH segmentations
• Spatial normalization
Results

• Combined sample: 3525 patients

• Nearly complete lesion coverage in the supratentorial white matter
Next steps

• Lesion-symptom mapping analyses to identify strategic WMH locations for cognitive impairment
Acknowledgements

Thank you for your attention!

On behalf of the Meta VCI Map consortium

Contact details:

https://metavcimap.org/

Email: m.coenen@umcutrecht.nl
Strategic white matter hyperintensity locations and cognitive functioning in community-dwelling individuals: rationale and design

Floor de Kort, PhD candidate
On behalf of the Meta VCI Map consortium
September 9th 2021
• WMH are a common manifestation of cSVD and a major cause of dementia
• Inter-subject variability
• Cognitive impact WMH likely depends on location
• Map of strategic WMH locations and normative data currently unavailable
Objectives

• To identify **strategic white matter regions** where WMH are most strongly associated with **cognitive performance** in **community-dwelling** individuals

• Obtain **normative data** for total and tract-specific **WMH volumes per decade**

Requires multicenter coordinated effort and data from thousands individuals
Design & Methods

- Large-scale multicohort lesion-symptom mapping study
- Through the Meta VCI Map consortium
- 16 population-based cohorts
- > 20,000 community-dwelling individuals
Harmonization of individual patient data

- Image processing
  - WMH maps
  - Spatial normalization to MNI-152 template

- Cognition
  - Cognitive domains
  - Global cognitive functioning

Analysis

- Lesion symptom mapping
- Establish WMH volumes per decade

Design & Methods

Cognitive domains

<table>
<thead>
<tr>
<th>Cognitive domains</th>
<th>% Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>90</td>
</tr>
<tr>
<td>Attention &amp; Executive functioning</td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
</tr>
<tr>
<td>Visuospatial functions</td>
<td>70</td>
</tr>
<tr>
<td>Language</td>
<td></td>
</tr>
</tbody>
</table>
Concluding remarks

Identification of individuals with excessive WMH in critical white matter regions

Enable individualized approach to interpreting WMH burden and location in relation to cognitive complaints in clinical practice
Thank you for your attention!
On behalf of the Meta VCI Map consortium

Contact details

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Sex differences in white matter hyperintensities are modified by menopause: The Rhineland Study

Valerie Lohner*, Gokhan Pehlivan, Gerard Sanroma-Guëll, Anne Miloschewski, Markus D. Schirmer, Tony Stöcker, Martin Reuter & Monique M.B. Breteler

*Population Health Sciences, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

@ValerieLohner
Background & aim

• In older people, women have more white matter hyperintensities (WMH) than men
• Studies on sex differences in WMH in younger adults are scarce

• There might be a link with menopause, however, previous studies have been underpowered with respect to premenopausal women to explore this

Aim: to investigate sex differences in WMH and the effect of menopause on WMH across the adult life span within the population-based Rhineland Study
**Methods**

### Study population
- N = 2,659 from the population-based Rhineland Study cohort
- Age range: 30 – 95 years

### Menopause
- Self-reported (premenopausal, postmenopausal)

### Vascular risk factors
- Hypertension, diabetes, smoking, history of cardiovascular disease, body mass index, and lipid-lowering medication

### WMH load
- Automatically segmented using an in-house developed algorithm using T1, T2, FLAIR
- WMH / WM volume
- Logit transformed for further analysis

### Statistical data analysis
- Linear regression model, adjusted for age, age\(^2\), and vascular risk factors
- Age*sex interaction
- Stratification for menopausal status
  - Men vs premenopausal women (persons aged ≤ 56 years)
  - Men vs postmenopausal women (persons aged ≥ 45 years)
  - Pre- vs postmenopausal women (age range 45 – 56 years)
Overall sex differences in WMH load

- Mean age 54 ± 13.8 years
- 58% women, of whom 58% postmenopausal
- Median WMH load 0.1% [0.1%; 0.3%]
Overall sex differences in WMH load

- Acceleration with age
- Sex effect changing over the age span (age*sex interaction)
### WMH load across age and sex

<table>
<thead>
<tr>
<th></th>
<th>Estimate [95% CI]</th>
<th>p-value</th>
<th></th>
<th>Estimate [95% CI]</th>
<th>p-value</th>
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<th>Estimate [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premenopausal</strong></td>
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<td><strong>Postmenopausal</strong></td>
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<td><strong>Postmenopausal</strong></td>
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<tr>
<td>women vs men</td>
<td>-0.04 [-0.12 – 0.04]</td>
<td>0.35</td>
<td>women vs men</td>
<td>0.19 [0.12 – 0.26]</td>
<td>&lt;0.001</td>
<td>women vs men</td>
<td>0.23 [0.04 – 0.43]</td>
<td>&lt;0.05</td>
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<td>(reference)</td>
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<td><strong>Age [years]</strong></td>
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</tbody>
</table>

**Notes:**
- WMH load [z-standardised]
- Men, Women premenopausal, Women postmenopausal.
Conclusions

Sex differences in WMH load might be depending on menopausal status

- Premenopausal women = men of similar age
- Postmenopausal women > men of similar age
- Postmenopausal women > premenopausal women of similar age

Underlying effect of menopause remains to be clarified
Different cardiovascular risk factors are related to a distinct white matter hyperintensity MRI phenotype

Jasmin A. Keller, Ilse M. J. Kant, Arjen J. C. Slooter, Simone J. T. van Montfort, Mark A. van Buchem, Matthias J. P. van Osch, Jeroen Hendrikse, Jeroen de Bresser

Jasmin Annica Keller
Department of Radiology
C.J. GORTER CENTER FOR HIGH FIELD MRI
Introduction

• Cardiovascular risk factors ➔ a higher burden of WMH

• Underlying pathological mechanisms are unknown

• Novel WMH markers: type and shape

Previous studies

• WMH shape has shown **distinguishing features** between patients with T2DM and controls

• Irregular shape of periventricular/confluent WMH ➔ **increased risk of ischemic stroke** and mortality
Aim of this study

To study the association between cardiovascular risk factors and WMH shape in cognitively healthy older adults.
Methods: WMH shape analysis pipeline
Results: Demographics

- Cognitively healthy subjects
- Scheduled for major surgery

<table>
<thead>
<tr>
<th>N</th>
<th>155</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71 ± 5</td>
</tr>
<tr>
<td>Female sex</td>
<td>50 (32%)</td>
</tr>
</tbody>
</table>

Vascular risk factors

- Diabetes (type I & II) | 24 (16%)
- Hypertension | 72 (47%)
- BMI (kg/m²) | 27 ± 4
- Hyperlipidemia | 55 (34%)
**Hypertension** is associated with a more complex shape of periventricular/confluent lesions:

- **Convexity**
  
  \( B \ (95\% - CI): -0.12 \ (-0.22 -- 0.03), \ p < 0.01 \)

- **Concavity index**

  \( B \ (95\% - CI): 0.06 \ (0.02 - 0.11), \ p < 0.01 \)

**Diabetes** is associated with higher deep WMH volume

\( B \ (95\% - CI): 0.89 \ (0.15 - 1.63); \ p < 0.02 \)
Discussion

- Hypertension has a direct destructive effect on small vessels in the brain
- Confirms previous results:
  - WMH shape aids differentiation and postulation of pathophysiological mechanisms
- New method:
  - Shape feature calculation
- Cognitively healthy study population
  - Generalizability: major surgery scheduled
Conclusions

Different cardiovascular risk factors are related to a distinct pattern of WMH via different underlying cardiovascular/pathological mechanisms.

Early detection of dementia and personalized treatment.
Thank you for your attention!

Ilse M. J. Kant
Arjen J. C. Slooter
Simone J. T. van Montfort
Mark A. van Buchem
Matthias J. P. van Osch
Jeroen Hendrikse
Jeroen de Bresser
DREAM Trial

Cilostazol in Decreasing pRogression of cerebral white Matter hyperintensities

Prof Vincent Mok
Dr Bonnie Lam
Dr Bonaventure Ip
Division of Neurology
Prince of Wales Hospital
The Chinese University of Hong Kong
Background

- Up to 40% of Chinese aged > 70 years old harbored WMH
- WMH predicts cognitive impairment/ dementia
- Metabolic risk factor control alone may not be sufficient
- Cilostazol has potential effect in reducing gliovascular damage
- Majority of cilostazol trials focused on stroke prevention
- Limited data regarding radiological and cognitive outcomes
Aim and Hypothesis

• Compared to cardiovascular risk factor control alone, cilostazol would slow WMH progression in patients with subclinical SVD

• To determine the efficacy and safety of cilostazol in preventing SVD progression
Methodology

- Single center
- Randomized, double-blind, placebo-controlled study
- Cilostazol 100mg BD vs Placebo
- Treatment:Control = 1:1
- Screening from CU-RISK cohort
Methodology

Inclusion criteria
1) age 65-85 years;
2) Chinese ethnicity;
3) Age-related White Matter Changes (ARWMC) ≥ 2

Exclusion criteria
1) history of clinical stroke or transient ischemic attack;
2) dementia;
3) peripheral arterial disease that necessitated the use of cilostazol;
4) concurrent use of other antiplatelet agents or anticoagulants;
5) contraindications for cilostazol
6) severe medical co-morbidities
7) contraindicated for MRI
Methodology

Data Collection

- Age, sex education level, smoking and drinking status, medications, co-morbidities BP, BMI, CBC, L/RFT, FBG, HbA1c, lipid profile every 52 weeks
- MRI at baseline, 104 weeks
- Cognitive, Gait and Balance tests at baseline, 52 weeks, 104 weeks
Methodology

Primary Endpoint
• Change in WMH volume at 2 years

Secondary Endpoint at 2 years
• CMB
• Brain volumes
• DTI measures (MD and FA)
• MoCA
• NINDS-CSN VCI Neuropsychology Protocol 30-minute battery
• 8-meter walk time
• Single leg stance
Methodology

Sample Size Estimation

• VITATOPS substudy
• 1.66 cm$^3$ difference in median WMH volume change
• 80% power using t-test
• Assumed 20% dropout rate
• 70 subjects per group, i.e. total 140 subjects.
Methodology

Statistical Analysis
- Chi-square tests for categorical variables
- Independent t-test or Mann-Whitney U test for continuous variables
- Normality examination in Kolmogorov-Smirnov test
- Independent t-test for between group comparison
- Paired t-test/ ANCOVA/ Linear Mixed Models for same parameters before and after treatment within the same subjects
- Intent-to-treat population
- 2-sided p<0.05 was considered statistically significant
Results

Recruitment period: October 2014 - January 2019

Assessed for eligibility (n = 1200)

- Excluded (n = 1060)
  - Not meeting inclusion criteria

- Proposed (n = 140)

- Randomized (n = 120)

  - Excluded
    - Screening failure (n = 5)

  - Treatment group (n = 55)
    - Withdrawal due to Adverse Events and Serious Adverse Events (n = 17)
      - Not related (n = 4)
      - Probably related (n = 7)
      - Possibly related (n = 6)
    - Analysed (n = 38)

  - Control group (n = 54)
    - Withdrawal due to Adverse Events and Serious Adverse Events (n = 10)
      - Not related (n = 7)
      - Probably related (n = 1)
      - Possibly related (n = 2)
    - Analysed (n = 44)
## Results – Baseline Comparison

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=54, 49.5%)</th>
<th>Cilostazol (n=55, 50.5%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y; mean ± SD</td>
<td>74.0 ± 4.7</td>
<td>74.0 ± 4.5</td>
<td>0.934</td>
</tr>
<tr>
<td>Female, n(%)</td>
<td>30 (55.6)</td>
<td>26 (47.3)</td>
<td>0.387</td>
</tr>
<tr>
<td>Education, y; mean ± SD</td>
<td>7.1 ± 4.6</td>
<td>9.3 ± 5.4</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>41 (75.9)</td>
<td>31 (56.4)</td>
<td>0.031</td>
</tr>
<tr>
<td>Diabetes mellitus, n(%)</td>
<td>10 (18.5)</td>
<td>10 (18.2)</td>
<td>0.964</td>
</tr>
<tr>
<td>Hyperlipidemia, n(%)</td>
<td>16 (29.6)</td>
<td>13 (23.6)</td>
<td>0.479</td>
</tr>
<tr>
<td>Heart Disease, n(%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>/</td>
</tr>
<tr>
<td>Smoking, n(%)</td>
<td>5 (9.3)</td>
<td>8 (14.5)</td>
<td>0.395</td>
</tr>
<tr>
<td>Drinking, n(%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>/</td>
</tr>
<tr>
<td><strong>Baseline Assessment</strong></td>
<td></td>
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</tr>
<tr>
<td>Gait; mean ± SD</td>
<td>8.1 ± 1.6</td>
<td>8.1 ± 2.2</td>
<td>0.835</td>
</tr>
<tr>
<td>Leg-Stand; mean ± SD</td>
<td>23.1 ± 23.1</td>
<td>20.6 ± 18.1</td>
<td>0.531</td>
</tr>
<tr>
<td>SBP; mean ± SD</td>
<td>138.4 ± 17.1</td>
<td>135.2 ± 14.2</td>
<td>0.305</td>
</tr>
<tr>
<td>DBP; mean ± SD</td>
<td>79.8 ± 11.4</td>
<td>78.3 ± 10.3</td>
<td>0.472</td>
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<tr>
<td>FG level; mean ± SD</td>
<td>5.7 ± 0.9</td>
<td>5.6 ± 1.2</td>
<td>0.723</td>
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<tr>
<td>HbA1c level; mean ± SD</td>
<td>6.1 ± 0.7</td>
<td>6.0 ± 0.7</td>
<td>0.510</td>
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<td>Cholesterol level; mean ± SD</td>
<td>4.9 ± 1.0</td>
<td>4.9 ± 0.9</td>
<td>0.792</td>
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<td>HDL level; mean ± SD</td>
<td>1.5 ± 0.5</td>
<td>1.7 ± 0.5</td>
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<td>Triglyceride level; mean ± SD</td>
<td>1.6 ± 1.7</td>
<td>1.2 ± 0.5</td>
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<tr>
<td>LDL level; mean ± SD</td>
<td>2.6 ± 0.7</td>
<td>2.7 ± 0.8</td>
<td>0.658</td>
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</tbody>
</table>
## Results – Baseline Comparison

<table>
<thead>
<tr>
<th>Metric</th>
<th>PLACEBO (n = 54)</th>
<th>CILOSTAZOL (n = 55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA total score; mean ± SD</td>
<td>21.8 ± 4.0</td>
<td>22.3 ± 4.8</td>
<td>0.314</td>
</tr>
<tr>
<td>NINDS 30 minutes summary z-score; mean ± SD</td>
<td>0.006 ± 0.629</td>
<td>-0.006 ± 0.785</td>
<td>0.193</td>
</tr>
<tr>
<td>HKLLT, total learning; mean ± SD</td>
<td>20.3 ± 6.3</td>
<td>19.2 ± 6.3</td>
<td>0.057</td>
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<td>Symbol Digit Modalities Test, correct hit; mean ± SD</td>
<td>26.5 ± 11.1</td>
<td>29.6 ± 12</td>
<td>0.992</td>
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<tr>
<td>Animal Fluency, correct response; mean ± SD</td>
<td>14.8 ± 3.9</td>
<td>17 ± 10.5</td>
<td>0.239</td>
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<tr>
<td>Geriatric Depression Scale Total; mean ± SD</td>
<td>2.0 ± 2.3</td>
<td>2.6 ± 3.2</td>
<td>0.121</td>
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</table>

<table>
<thead>
<tr>
<th>Metric</th>
<th>PLACEBO (n = 53)</th>
<th>CILOSTAZOL (n = 51)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Parenchyma Vol; mean ± SD</td>
<td>1053.4 ± 76.7</td>
<td>1060.7 ± 84.3</td>
<td>0.834</td>
</tr>
<tr>
<td>Hippocampus Vol; mean ± SD</td>
<td>6.3 ± 0.7</td>
<td>6.00.7</td>
<td>0.027</td>
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<tr>
<td>White Matter Hyperintensity Vol; mean ± SD</td>
<td>21.4 ± 13.7</td>
<td>18.1 ± 9.3</td>
<td>0.179</td>
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<tr>
<td>FA</td>
<td>0.5 ± 0.0</td>
<td>0.5 ± 0.0</td>
<td>0.929</td>
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<tr>
<td>MD*1000</td>
<td>0.8 ± 0.0</td>
<td>0.8 ± 0.0</td>
<td>0.673</td>
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<tr>
<td>PSMD*1000</td>
<td>0.3 ± 0.0</td>
<td>0.3 ± 0.0</td>
<td>0.617</td>
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<th>Metric</th>
<th>PLACEBO (n = 53)</th>
<th>CILOSTAZOL (n = 51)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Brain Parenchyma ratio; mean ± SD</td>
<td>74.7 ± 3.2</td>
<td>73.9 ± 3.1</td>
<td>0.323</td>
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<tr>
<td>Hippocampus ratio; mean ± SD</td>
<td>0.4 ± 0.0</td>
<td>0.4 ± 0.1</td>
<td>0.007</td>
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<tr>
<td>White Matter Hyperintensity ratio; mean ± SD</td>
<td>1.5 ± 1.0</td>
<td>1.3 ± 0.6</td>
<td>0.128</td>
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## Results – Radiological Outcomes

<table>
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<tr>
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<th>PLACEBO (n = 53)</th>
<th>CILOSTAZOL (n = 51)</th>
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<tbody>
<tr>
<td><strong>Absolute Changes (Vol)</strong></td>
<td></td>
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<tr>
<td>Brain Parenchyma; mean ± SD</td>
<td>-6.6 ± 14.2</td>
<td>-8.9 ± 15.1</td>
<td>0.603</td>
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<td>Hippocampus; mean ± SD</td>
<td>-0.1 ± 0.1</td>
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<td>0.212</td>
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<tr>
<td>White Matter Hyperintensity; mean ± SD</td>
<td>2.4 ± 3.7</td>
<td>3.6 ± 3.2</td>
<td>0.077</td>
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<tr>
<td>FA*100</td>
<td>-0.1 ± 0.9</td>
<td>-0.6 ± 1.0</td>
<td>0.024</td>
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<td>MD*100000</td>
<td>-0.2 ± 1.6</td>
<td>0.4 ± 1.3</td>
<td>0.029</td>
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<td>P5MD*100000</td>
<td>2.3 ± 2.8</td>
<td>1.9 ± 2.4</td>
<td>0.417</td>
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<tr>
<td><strong>Absolute Change (ratio)</strong></td>
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<tr>
<td>Brain Parenchymal Ratio; mean ± SD</td>
<td>-0.5 ± 1.1</td>
<td>-0.6 ± 1.3</td>
<td>0.843</td>
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<tr>
<td>Hippocampal Ratio; mean ± SD</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>0.929</td>
</tr>
<tr>
<td>White Matter Hyperintensity Ratio; mean ± SD</td>
<td>0.2 ± 0.2</td>
<td>0.3 ± 0.2</td>
<td>0.073</td>
</tr>
<tr>
<td>MTA ratio</td>
<td>0 ± 0</td>
<td>0.1 ± 0.1</td>
<td>0.078</td>
</tr>
</tbody>
</table>
## Results – Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>PLACEBO (n = 54)</th>
<th>CILOSTAZOL (n = 55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute Change (Yr2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP; mean ± SD</td>
<td>-3.6 ± 20.3</td>
<td>-5.1 ± 20.0</td>
<td>0.449</td>
</tr>
<tr>
<td>DBP; mean ± SD</td>
<td>-1.2 ± 11.8</td>
<td>-2.9 ± 9.3</td>
<td>0.143</td>
</tr>
<tr>
<td>FG level; mean ± SD</td>
<td>0.1 ± 0.6</td>
<td>-0.1 ± 1.6</td>
<td>0.517</td>
</tr>
<tr>
<td>HbA1c level; mean ± SD</td>
<td>-0.1 ± 0.5</td>
<td>0.1 ± 1.3</td>
<td>0.499</td>
</tr>
<tr>
<td>Cholesterol level; mean ± SD</td>
<td>-0.2 ± 0.6</td>
<td>-0.1 ± 0.7</td>
<td>0.648</td>
</tr>
<tr>
<td>HDL level; mean ± SD</td>
<td>0.0 ± 0.2</td>
<td>0.2 ± 0.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Triglyceride level; mean ± SD</td>
<td>-0.4 ± 1.9</td>
<td>-0.2 ± 0.4</td>
<td>0.040</td>
</tr>
<tr>
<td>LDL level; mean ± SD</td>
<td>0.0 ± 0.7</td>
<td>-0.2 ± 0.7</td>
<td>0.365</td>
</tr>
<tr>
<td>Gait; mean ± SD</td>
<td>0.8 ± 1.7</td>
<td>0.8 ± 2.2</td>
<td>0.873</td>
</tr>
<tr>
<td>LegsStand; mean ± SD</td>
<td>1.8 ± 57.5</td>
<td>-2.4 ± 16.2</td>
<td>0.625</td>
</tr>
<tr>
<td><strong>Absolute Change (Cognition) (Yr2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MoCA total score; mean ± SD</td>
<td>0.0 ± 3.2</td>
<td>-1.5 ± 3.3</td>
<td>0.048</td>
</tr>
<tr>
<td>NINDS 30 minutes summary z-score; mean ± SD</td>
<td>0.0 ± 0.4</td>
<td>-0.1 ± 0.6</td>
<td>0.376</td>
</tr>
<tr>
<td>HKLLT, total learning; mean ± SD</td>
<td>2.7 ± 5.5</td>
<td>1.3 ± 5.4</td>
<td>0.394</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test, correct hit; mean ± SD</td>
<td>0.9 ± 5.9</td>
<td>-1.9 ± 4.6</td>
<td>0.045</td>
</tr>
<tr>
<td>Animal Fluency, correct response; mean ± SD</td>
<td>-0.5 ± 3.0</td>
<td>-3.5 ± 12.6</td>
<td>0.186</td>
</tr>
<tr>
<td>Geriatric Depression Scale Total; mean ± SD</td>
<td>0.3 ± 2.3</td>
<td>-0.1 ± 1.2</td>
<td>0.508</td>
</tr>
<tr>
<td>MoCA total score ITT; mean ± SD</td>
<td>0.0 ± 2.9</td>
<td>-0.8 ± 2.9</td>
<td>0.211</td>
</tr>
<tr>
<td>NINDS 30 minutes summary z-score ITT; mean ± SD</td>
<td>0.0 ± 0.3</td>
<td>-0.1 ± 0.5</td>
<td>0.72</td>
</tr>
<tr>
<td>HKLLT, total learning ITT; mean ± SD</td>
<td>2.0 ± 5.5</td>
<td>1.1 ± 4.8</td>
<td>0.714</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test ITT, correct hit; mean ± SD</td>
<td>0.8 ± 5.3</td>
<td>-1.3 ± 4.3</td>
<td>0.063</td>
</tr>
<tr>
<td>Animal Fluency, correct response ITT; mean ± SD</td>
<td>-0.2 ± 3.0</td>
<td>-2.3 ± 10.3</td>
<td>0.39</td>
</tr>
<tr>
<td>Geriatric Depression Scale Total ITT; mean ± SD</td>
<td>0.2 ± 2.1</td>
<td>-0.2 ± 1.2</td>
<td>0.519</td>
</tr>
</tbody>
</table>
## Results – Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>PLACEBO (n=54, 49.5%)</th>
<th>CILOSTAZOL (n=55, 50.5%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>0 (0)</td>
<td>4 (7.3)</td>
<td>0.043</td>
</tr>
<tr>
<td>Ankle Edema</td>
<td>0 (0)</td>
<td>6 (10.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1 (1.9)</td>
<td>1 (1.8)</td>
<td>0.990</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>0.311</td>
</tr>
<tr>
<td>Vascular event</td>
<td>1 (1.9)</td>
<td>1 (1.8)</td>
<td>0.990</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0 (0)</td>
<td>5 (9.1)</td>
<td>0.023</td>
</tr>
</tbody>
</table>
Discussion

Cilostazol treatment did not result in slower progression of WMH compared with placebo group

Cilostazol treatment was associated with worse DTI measures, MoCA and SDMT

1st trial with stroke- and dementia-free patients focusing on WMH progression and cognitive outcomes

Cilostazol treatment group was associated with a lower baseline hippocampal ratio on MRI
Discussion - limitations

- Small sample size
- Lower baseline hippocampal ratio in treatment group
- High dropout rate
  17 (30.9%) of the patients in the cilostazol group and 10 (18.5%) of those in the placebo group
Acknowledgement

Prof. Vincent Mok
Prof. Owen Ko
Prof. Bonnie Lam
Mr. Brian Fung
CUHK Neurology Team
Relation between small vessel function and white matter integrity in patients with CADASIL: ZOOM@SVDs study

Naomi Vlegels, PhD candidate
Department of Neurology, UMC Utrecht, the Netherlands
Small vessel disease on 7T

Unpublished data

Van den Brink, Kopczak, Arts et al. *In preparation*
Aim

To study the association between small vessel function and white matter integrity in patients with CADASIL
## Participants

<table>
<thead>
<tr>
<th></th>
<th>CADASIL n = 23</th>
<th>Reference n = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean±SD</td>
<td>51±10</td>
<td>46±13</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>12 (52%)</td>
<td>6 (46%)</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>7 (30%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Small vessel function measures

- Perforating artery flow and pulsatility
  - Semioval centre
  - Basal ganglia

Diffusion measure

## MRI markers in patients and reference group

Unpublished data

<table>
<thead>
<tr>
<th></th>
<th>CADASIL n=23</th>
<th>Reference n=13</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3T MRI SVD markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PSMD [mm²/s x 10⁻⁴]</strong></td>
<td>4.1 [1.87]</td>
<td>2.1 [0.26]</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>7T MRI small vessel function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Qflow CSO</strong></td>
<td>n=22</td>
<td>n=10</td>
<td></td>
</tr>
<tr>
<td>Blood flow velocity [cm/s]</td>
<td>0.54±0.06</td>
<td>0.63±0.13</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>Pulsatility index**</td>
<td>0.56±0.19</td>
<td>0.37±0.11</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td><strong>Qflow BG</strong></td>
<td>n=21</td>
<td>n=9</td>
<td></td>
</tr>
<tr>
<td>Blood flow velocity [cm/s]</td>
<td>3.07±0.67</td>
<td>4.05±0.83</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Pulsatility index**</td>
<td>0.46±0.12</td>
<td>0.29±0.15</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>BOLD visual stimulus</strong></td>
<td>n=19</td>
<td>n=10</td>
<td></td>
</tr>
<tr>
<td>BOLD amplitude [%]</td>
<td>0.61±0.20</td>
<td>0.82±0.25</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td><strong>BOLD hypercapnic stimulus</strong></td>
<td>n=17</td>
<td>n=11</td>
<td></td>
</tr>
<tr>
<td>CGM BOLD amplitude [%]</td>
<td>2.18±0.72</td>
<td>1.76±0.62</td>
<td>0.054</td>
</tr>
<tr>
<td>WM BOLD amplitude [%]</td>
<td>0.03±0.16</td>
<td>0.16±0.19</td>
<td><strong>0.04</strong></td>
</tr>
</tbody>
</table>
Small vessel function and white matter integrity

Unpublished data

\[ B = -0.42, \ p = 0.038 \]

\[ B = -0.6, \ p = 0.021 \]
Conclusion

• Observed a relationship between impaired small vessel function and decreased white matter integrity in patients with CADASIL.

• Further research is needed to determine causal relationships

Next steps

• Assess relationships in normal appearing white matter and white matter hyperintensities
• Assess relationships in patients with sporadic small vessel disease.
Acknowledgements

Hilde van den Brink
Tine Arts
Geert Jan Biessels
Martin Dichgans
Marco Düring
Alberto de Luca

Anna Kopczak
Benno Gesierich
Laurien Onkenhout
Jeroen Siero
Jaco Zwanenburg

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VASCULAR REACTIVITY IS DECREASED IN EARLY STAGES OF DEMENTIA; A NOVEL MRI MARKER (CASCADE STUDY)

Suzanne E. van Dijk, MSc; Jessie Lak, MSc; Jessy Kauffman, Bsc; Anne Hafkemeijer, PhD; Jeroen van der Grond, PhD; Sanneke van Rooden, PhD

Suzanne E. van Dijk
Department of radiology
LEIDEN UNIVERSITY MEDICAL CENTER
Aim: assess vascular reactivity in a cohort of memory clinic patients independent of the presence of classic radiological CAA markers

Methods

- N=92 (43 controls, 17 SCI, 20 MCI and 12 AD)
- 3T (f)MRI including checkerboard task
- Neuropsychological assessment
BOLD amplitude differences between groups

Univariate GLM, adjusted for age, sex, WMHs, gray matter volume and ≥ 2 lobar (micro)hemorrhages
Associations BOLD amplitude and cognition in memory clinic patients (SCI, MCI and AD)

- **Global cognitive function**
  - BOLD amplitude (%)
  - $p = 0.040$

- **Memory**
  - BOLD amplitude (%)
  - $p = 0.001$

- **Executive functioning**
  - BOLD amplitude (%)
  - $p < 0.001$

- **Language**
  - BOLD amplitude (%)
  - $p = 0.002$
Summary & conclusion

• Vascular reactivity is decreased in both MCI and AD

• BOLD amplitude appears to be the most sensitive parameter to determine differences in vascular reactivity between groups

• BOLD amplitude is associated with cognitive function but not associated with a specific cognitive domain

Conclusion: vascular reactivity is decreased in the early stage of AD, probably caused by amyloid beta deposition in the blood vessels of the brain
CERBROVASCULAR REACTIVITY IN CEREBRAL AMYLOID ANGIOPATHY

Andrew E. Beaudin, PhD | Postdoctoral Scholar
University of Calgary | Cumming School of Medicine
Department of Clinical Neurosciences

VasCog 2021 Virtual Conference
Sept. 8-9, 2021
Cerebral Amyloid Angiopathy (CAA)

BACKGROUND

Charidimou et al. J Neurol Neurosurg Psychiatry, 2012

Cognitive impairment
To assess cerebrovascular reactivity (CVR) across the entire brain using a global vasodilatory stimulus (hypercapnia) and its association MRI markers of CAA and cognitive function.
METHODS

Multicenter Study
- University of Calgary & University of Alberta

Participants
- Patients with probable CAA (according to Boston criteria), mild cognitive impairment (MCI) and Alzheimer disease (AD) and healthy controls

Protocol
- Neuropsychological testing
- 3T MRI
  - T1-weighted high-resolution anatomical image
  - BOLD - Cerebrovascular reactivity (CVR)
    - 2-minute hypercapnic (5% inspired CO₂) challenge
      - % Δ BOLD / mmHg increase in end-tidal CO₂
RESULTS

Grey and white matter CVR is reduced in CAA patients.
RESULTS

Lower CVR in CAA predominantly within posterior brain regions
RESULTS

Lower CVR was associated with lower cognitive performance.
Grey and whiter matter CVR to CO₂ was lower in CAA and AD participants.
  — Impairment showed a predominantly posterior distribution.

Only CAA participants had a lower CVR within the primary visual cortex.

Lower GM CVR was associated with worse cognitive function.

Reduced cerebrovascular reactivity is a core feature of CAA, and its assessment may provide an additional biomarker for disease severity and cognitive impairment.
Acknowledgements

Supervisor:
Dr. Eric E. Smith

U of C Collaborators:
Dr. Richard Frayne
Dr. Bruce Pike
Dr. Brad Goodyear
Dr. Zahinoor Ismail
Dr. Peter Stys

U of A Collaborators:
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Lindsay Litowsky

Funding: