Ischemic Stroke: Who is at risk?
Implications of white matter disease

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Chairman and Professor
Department of Neurology
Medical College of Georgia
U.S. Stroke Belt

Costs of the “Stroke Belt”
(courtesy of George Howard UAB)"

• What does 648,496 extra strokes mean?
  – Carnage: equivalent to approximately a stroke for everyone over the age of 45 in the combined:
    Raleigh, NC    Columbia, SC
    Atlanta, GA    Nashville, TN
    Montgomery, AL  Jackson, MS
    Baton Rouge, LA  Little Rock, AR
  – Cost in dollars (1968 to 1997):
    – Current estimate of the cost of a stroke is $104,000
    – “Extra” costs associated with the stroke belt: 29-year total $67,443,653,333, or $2.3 billion annually
Poor control of risk factors
Stroke Subtypes

- Hemorrhagic 20%
  - ICH 10%
  - SAH 10%
- Lacunar 20%
- Large vessel (ie carotid) 15%
- Cardioembolic 25-30%
- Ischemic 80%
- Unknown 25%
- Other 3%

About 50% of stroke patients have some degree of disability (mRS 3 or greater) after stroke.
Modifiable Risk Factors for Stroke

- Hypertension
- Smoking
- Diabetes Mellitus
- Obesity
- Heart disease (atrial fibrillation)
- Exercise (lack of)
Risk of Stroke Death According to SBP and DBP in MRFIT


www.hypertensiononline.org
One example of secondary prevention: PROGRESS Trial
Lancet Sept 29, 2001

• Randomised, double blind trial of antihypertensive management in individuals with stroke or TIA

• Two antihypertensive regimens: perindopril; perindopril + indapamide

• Centers in Australia, China, Japan, Europe

• Treated for 4 years
PROGRESS Trial

• 52% hypertensive

• 39% Asian
Two drug treatment consisted of perindopril and indapamide; one drug of perindopril
PROGRESS trial conclusions

• Combination antihypertensive therapy with an ACE inhibitor + diuretic reduces recurrent stroke by about 40% in both hypertensive and non-hypertensive stroke patients

• This combination should be given to stroke patients, irrespective of blood pressure
Relationship Between Cholesterol and CHD Risk: Epidemiologic Trials

MRFIT: Age Adjusted Death Rates from Stroke for 350,977 Men

Simvastatin: Major Vascular Events by Age and Sex

<table>
<thead>
<tr>
<th>Baseline Feature</th>
<th>Simvastatin (10,269)</th>
<th>Placebo (10,267)</th>
<th>STATIN Better</th>
<th>PLACEBO Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 65</td>
<td>831 (16.9%)</td>
<td>1091 (22.1%)</td>
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<tr>
<td>65–69</td>
<td>512 (20.9%)</td>
<td>665 (27.2%)</td>
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<tr>
<td>70–74</td>
<td>548 (23.8%)</td>
<td>620 (27.7%)</td>
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</tr>
<tr>
<td>≥ 75</td>
<td>142 (23.1%)</td>
<td>209 (32.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1666 (21.6%)</td>
<td>2135 (27.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>367 (14.4%)</td>
<td>450 (17.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Simvastatin: Major Vascular Events by LDL and Total Cholesterol

<table>
<thead>
<tr>
<th>Lipid Levels at Entry, mmol/l</th>
<th>Simvastatin (10,269)</th>
<th>Placebo (10,267)</th>
<th>STATIN Better</th>
<th>PLACEBO Better</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt; 3.0 (116 mg/dl)</td>
<td>598 (17.6%)</td>
<td>756 (22.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3.0 &lt; 3.5</td>
<td>484 (19.0%)</td>
<td>646 (25.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3.5 (135 mg/dl)</td>
<td>951 (22.0%)</td>
<td>1183 (27.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.0 (193 mg/dl)</td>
<td>360 (17.7%)</td>
<td>472 (23.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5.0 &lt; 6.0</td>
<td>744 (18.9%)</td>
<td>964 (24.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6.0 (323 mg/dl)</td>
<td>929 (21.6%)</td>
<td>1149 (26.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALL PATIENTS</strong></td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Risk ratio and 95% CI**

- **LDL cholesterol**
  - < 3.0 (116 mg/dl): Risk ratio 0.6 (0.4, 0.9), p = 0.018
  - ≥ 3.0 < 3.5: Risk ratio 0.8 (0.6, 1.0), p = 0.074
  - ≥ 3.5 (135 mg/dl): Risk ratio 1.0 (0.8, 1.3), p = 0.97

- **Total cholesterol**
  - <5.0 (193 mg/dl): Risk ratio 0.4 (0.2, 0.9), p = 0.006
  - ≥ 5.0 < 6.0: Risk ratio 0.8 (0.6, 1.0), p = 0.06
  - ≥ 6.0 (323 mg/dl): Risk ratio 1.0 (0.8, 1.3), p = 0.97

**ALL PATIENTS**
- Risk ratio 0.6 (0.4, 0.8), p = 0.00001

24% SE 3 reduction (2p<0.00001)

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JUPITER – study design

No history of CAD
men ≥50 yrs
women ≥60 yrs
LDL-C <3.36 mmol/L
CRP ≥2.0 mg/L

Visit 1 2 3 4 Final
Week: −6 −4 0 13 3–4 y

Lead-in/ eligibility Randomisation Lipids CRP Tolerability Lipids CRP Tolerability Lipids CRP Tolerability

Rosuvastatin 20 mg (n~8900)
Placebo (n~8900)

CAD=coronary artery disease; LDL-C=low-density lipoprotein cholesterol; CRP=C-reactive protein; HbA1c=glycated haemoglobin

JUPITER - Primary Endpoint
Time to first occurrence of a CV death, non-fatal stroke, non-fatal MI, unstable angina or arterial revascularization

Hazard Ratio 0.56
(95% CI 0.46-0.69)
P<0.00001

NNT for 2y = 95
5y* = 25

Number at risk
RSV  Placebo
8901  8901
8412  8353
3893  3872
1353  1333
538   531
157   174

## JUPITER - Primary Endpoint Components

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo [n=8901]</th>
<th>Rosuvastatin [n=8901]</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>251 (1.36)</td>
<td>142 (0.77)</td>
<td>0.56</td>
<td>0.46-0.69</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><em>(Time to first occurrence of CV death, MI, stroke, unstable angina, arterial revascularisation)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>62 (0.33)</td>
<td>22 (0.12)</td>
<td>0.35</td>
<td>0.22-0.58</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fatal or non-fatal MI</td>
<td>68 (0.37)</td>
<td>31 (0.17)</td>
<td>0.46</td>
<td>0.30-0.70</td>
<td>0.0002</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>58 (0.31)</td>
<td>30 (0.16)</td>
<td>0.52</td>
<td>0.33-0.80</td>
<td>0.003</td>
</tr>
<tr>
<td>Fatal or non-fatal stroke</td>
<td>64 (0.34)</td>
<td>33 (0.18)</td>
<td>0.52</td>
<td>0.34-0.79</td>
<td>0.002</td>
</tr>
<tr>
<td>Arterial Revascularization</td>
<td>131 (0.71)</td>
<td>71 (0.38)</td>
<td>0.54</td>
<td>0.41-0.72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unstable angina†</td>
<td>27 (0.14)</td>
<td>16 (0.09)</td>
<td>0.59</td>
<td>0.32-1.10</td>
<td>0.09</td>
</tr>
<tr>
<td>CV death, stroke, MI</td>
<td>157 (0.85)</td>
<td>83 (0.45)</td>
<td>0.53</td>
<td>0.40-0.69</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Revascularization or unstable angina</td>
<td>143 (0.77)</td>
<td>76 (0.41)</td>
<td>0.53</td>
<td>0.40-0.70</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

**Notes:**
- **HR** – Hazard Ratio; **CI** – Confidence Limit
- **** Rates are per 100 person years;
- † Hospitalisation due to unstable angina;
- *Actual p-value was < 0.00001

The “Polypill”
Wald and Law, BMJ 2003; 326:1419

• Pill consisting of a statin, 3 anti-hypertensives, folic acid, aspirin

• Reduce ischemic heart disease by 88% (CI 84-91%)

• Reduce stroke by 80% (CI, 71-87%)

• Target over age 55 and pre-existing CV disease

• If started at age 55, 1/3 would benefit with 11 years of life stroke and IHD-free
Silent brain infarcts
Rotterdam Scan Study

- Silent infarcts 5X as common as symptomatic infarcts
- Associated with hypertension
- More frequent in women

Rotterdam Scan Study
Prevalence of silent infarcts with age

Vermeer, SE Lancet Neurol 2007;6:611
# Prevalence of MRI-defined silent brain infarcts in general population

<table>
<thead>
<tr>
<th>Study</th>
<th>Country/Location</th>
<th>Sample Characteristics</th>
<th>N</th>
<th>Mean Age (range), years</th>
<th>SBI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helsinki Aging Brain Study (HABS), 1995³</td>
<td>Finland, elderly oversampled, not institutionalised, no neurological disease</td>
<td>128</td>
<td>72 (56-88)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Health Study (CHS), 1997⁰</td>
<td>USA, African-Americans oversampled, not institutionalised, no stroke</td>
<td>3397</td>
<td>75 (65-97)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Atherosclerosis Risk in Communities (ARIC) Study, 1998⁴¹</td>
<td>USA, African-Americans oversampled, no stroke or transient ischaemic attack</td>
<td>1538</td>
<td>63 (55-72)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Rotterdam Scan Study (RSS), 2002⁵²</td>
<td>Netherlands, elderly oversampled, no dementia</td>
<td>1077</td>
<td>72 (60-90)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>National Institute for Longevity Sciences - Longitudinal Study of Aging (NILS-LSA), 2003⁹</td>
<td>Japan, no stroke or transient ischaemic attack</td>
<td>1721</td>
<td>59 (40-79)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Memory and Morbidity in Augsburg Elderly (MEMO) study, 2004⁴⁴</td>
<td>Germany, participants of MONICA survey, not institutionalised, no stroke</td>
<td>267</td>
<td>72 (65-83)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Framingham Heart Study (FHS), 2005⁵⁵</td>
<td>USA, original participants and their offspring, no stroke or dementia</td>
<td>2081</td>
<td>62 (34-97)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Austrian Stroke Prevention Study (ASPS), 2006⁶⁴</td>
<td>Austria, not institutionalised, no stroke or dementia</td>
<td>505</td>
<td>64 (50-75)</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Vermeer, SE Lancet Neurol2007;6:611
Prevalence of MRI silent infarcts in patients with comorbidities

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean age (range), years</th>
<th>SBI (range), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke patients (including cardioembolic stroke)(^{34})</td>
<td>171</td>
<td>69 (26–93)</td>
<td>57 (NA)</td>
</tr>
<tr>
<td>Patients with coronary artery disease(^{35-37})</td>
<td>493</td>
<td>60 (34–84)</td>
<td>32 (17–60)</td>
</tr>
<tr>
<td>Patients with atrial fibrillation(^{38})</td>
<td>72</td>
<td>68 (?)</td>
<td>32 (NA)</td>
</tr>
<tr>
<td>Patients with cardiovascular risk factors(^{39-43})</td>
<td>788</td>
<td>67 (40–93)</td>
<td>39 (21–51)</td>
</tr>
<tr>
<td>Patients with asymptomatic carotid stenosis(^{44})</td>
<td>189</td>
<td>68 (45–82)</td>
<td>23 (NA)</td>
</tr>
<tr>
<td>Patients with hypertension(^{45-58})</td>
<td>1003</td>
<td>69 (40–88)</td>
<td>43 (20–86)</td>
</tr>
<tr>
<td>Patients with diabetes mellitus(^{59-63})</td>
<td>685</td>
<td>62 (41–88)</td>
<td>38 (13–82)</td>
</tr>
<tr>
<td>Patients with chronic renal failure(^{55,64,65})</td>
<td>296</td>
<td>58 (48–74)</td>
<td>51 (25–85)</td>
</tr>
<tr>
<td>Patients with dementia(^{66})</td>
<td>143</td>
<td>73 (?)</td>
<td>33 (NA)</td>
</tr>
<tr>
<td>Patients with depression(^{67-69})</td>
<td>131</td>
<td>63 (50–76)</td>
<td>46 (39–49)</td>
</tr>
<tr>
<td>Patients with migraine(^{70})</td>
<td>295</td>
<td>48 (30–60)</td>
<td>8 (NA)</td>
</tr>
<tr>
<td>Patients with sickle cell disease(^{71,72})</td>
<td>94</td>
<td>24 (16–44)</td>
<td>30 (20–36)</td>
</tr>
</tbody>
</table>

Table 2: Prevalence of MRI-defined silent brain infarcts (SBIs) among selected populations

Vermeer, SE Lancet Neurol 2007;6:611
BELIEVE IT OR NOT, THIS 91-YEAR-OLD NUN CAN HELP YOU BEAT ALZHEIMER'S

A landmark study of the disease sheds new light on:

- WHAT CAUSES IT
- HOW TO PREVENT IT
Hypertension, stroke, and dementia

• Nun Study (102 college-educated women aged 76 to 100) showed that small lacunar infarcts in thalamus, basal ganglia, and subcortical white matter increased risk of dementia (OR of 20.7)

• For a given amyloid load, lacunar infarcts increase the clinical expression of dementia (Snowdon JAMA 1997;277:813)
Neuropathological Alzheimer: Prevalence of Clinical Dementia

Adjusted OR for clinical dementia

No brain infarcts: 1
>1 large neocortical infarct: 6.7
1-2 lacunes in BG, thalamus or DWM: 20.7

Snowdon DA et al., JAMA 1997;277:813-7
White matter lesions in the brain

• Term “leukoaraiosis” introduced meaning “rarefaction of the white matter”

• Manifestation of “small vessel disease”

• Associated with cognitive decline, lacunes and other strokes, mood disorder (depression), falls, urinary incontinence
• Between ages of 60 and 90, 95% of subjects have white matter lesions in some region

• Increase with age - Of subjects aged between 60–70 years, about 13% were completely free of subcortical white matter lesions and 32% were free of periventricular matter lesions, whereas for subjects aged between 80–90 years these percentages were 0 and 5, respectively.

• More common in women than men
LeukoAraiosis and DISability Study (LADIS)

• Multicenter (11 centers) European collaboration started in 2000

• Longitudinal, cohort study, age 64 to 85

• 639 patients, mean age 74.1 yrs, 45% males

• Determine whether white matter changes are an independent predictor of functional decline
Modified Fazekas Score

Grade 1 (mild changes): single lesions <10 mm and/or areas of “grouped” lesions <20 mm in any diameter;
Grade 2 (moderate changes): single hyperintense lesions 10 to 20 mm
Grade 3 (Severe): single and confluent >20 mm
Severity of WM lesions predicts progression to cognitive disability

LADIS Study Group BMJ 2009
• Severe WMC more than doubles the risk of transition from an autonomous to a dependent status after 3 years of follow-up.

• Severity associated with depression with deep and fronto/temporal lesions more strongly associated than periventricular

• Severity associated with gait problems and falls

• Associated with atrophy of corpus callosum and this atrophy predictor of cognitive decline
LADIS Study: Protective effect of physical exercise
Verdelho A, Stroke 2012;43:3331

• 639 patients followed for 3 years with cognitive and neuropsychological testing

• Physical exercise defined as 30 minutes per day, 3 days per week

• Physical exercise reduced risk of cognitive impairment (hazard ratio 0.64; 95% CI, 0.48–0.85) and dementia (0.61; 95% CI, 0.38–0.98) independent of age, education, white matter lesion intensity, etc
The “Alzheimerization” of Dementia

• Not all “Alzheimers” is Alzheimers

• Vascular dementia is an under-recognized cause of dementia

• “Vascular cognitive impairment” is common and will increase due to aging population
R. J. HARWELL

BORN 1914
GAVE UP SMOKING 1959
GAVE UP BOOZE 1973
GAVE UP RED MEAT 1983
DIED ANYWAY 1991
Summary

• “Clinical strokes” are just the tip of the iceberg; for every “clinical stroke,” there may be 5 silent strokes.

• Silent strokes are common, affecting up to 20% of the population by age 65.

• White matter lesions are associated with cognitive decline, lack of independence, gait problems, depression, and falls.

• Lacunes and WML are related.

• Physical exercise may reduce risk of cognitive decline in patients with WML.