Definitions

**Stroke**
Sudden onset focal neurological deficit which last more than 24 hours attributable to a vascular defect and has no other identifiable cause

**Dementia**
A syndrome where there is deterioration in memory, thinking, behaviour such that the person is no longer able to perform everyday activities by themselves
Stroke – the importance

- Stroke, 16.9 million new strokes per year,
  - A third are disabled and dependent
  - 2nd commonest cause of death
  - Commonest cause of dependency in adults

Infarct, or ischaemic stroke

Haemorrhagic stroke

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Cerebrovascular disease – the importance

• ‘Silent’ cerebrovascular disease, even bigger issue
  – Up to 45% of 35.6 million dementias
  – Cognitive impairment, mobility problems

Normal

White matter disease

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Dementia

• 47.5 million people have dementia worldwide
• 7.7 million new cases per year
• Affects different people in different ways
• Major cause of dependency and disability amongst older people
• Alzheimer’s disease commonest cause – 60-70% of cases
• Vascular dementia 2nd commonest – 25-45% of all cases
Dementia: historical perspective

1800’s – Blood vessel diseases
1900’s – Alzheimers disease - dominant
1970’s – ‘Multi-infarct dementia’ – vascular
1990’s–2000’s - ‘Vascular cognitive impairment’
2000’s-2010’s: Large variation in diagnosis of dementia and type realised
Now being standardised
Appearance of the brain on imaging helps to diagnose the type - also being standardised
Stroke and Dementia overlap

• “Vascular” dysfunction contributes to Alzheimer’s disease

• Difficult to research, importance of the “whole picture” is not appreciated:
  – Seen by different medical specialties
  – Cause of most vascular dementia unknown
  – Lack of knowledge about disease course
  – Treatment based on assumptions and suboptimal

Many gaps and challenges!
Alzheimer’s dementia and vascular disease

APOe4

Vascular disease is a major risk factor for AD:
• High blood pressure
• Smoking
• Previous heart attack
• Atrial fibrillation
• High cholesterol
• Diabetes
• Obesity
Vascular dementia types

- “multi-infarct dementia”
- Small vessel dementia
- Strategic infarct dementia
- Low perfusion dementia
- Haemorrhagic dementia
- Hereditary vascular dementia
- Alzheimer’s disease with vascular disease

Vascular dementia; vascular cognitive impairment; post stroke dementia/cognitive impairment........
Vascular dementia types

- Multi-infarct
- Small vessel
- Strategic infarct
- Low perfusion
- Haemorrhagic: CAA
- Hereditary
Silent cerebrovascular disease: vicious cycle

Predictors of worsening:
- Worse white matter damage at baseline
- BP, diabetes, cholesterol, smoking
- Less exercise

Worsening:
- Higher risk of stroke
- Higher risk of dementia
- Poor recovery after stroke
- More infarct growth
- More chance of silent lesions
- Worse function, etc, etc
Dementia and Stroke are Interlinked

Stroke leads to dementia:
7-30% in 1\textsuperscript{st} year after stroke

Worse after:
severe stroke, recurrent stroke,
in older people, females
dementia before the stroke

Less with better recovery after stroke

Risk factors:
fewer years of education
diabetes, heart rhythm problem,

But little information about the long term
Dementia after stroke

- 7 - 40% in the 1st year after stroke\(^1\)

1 Pendebury Lancet Neurology 2009;
Cognitive decline predicts Stroke

Cognitive decline predicts stroke:

- 930 men in Sweden without stroke
  - 13 years follow-up
  - Worse performance on a ‘join the dots’ test predicted stroke 3x higher risk in slowest vs fastest test performance
Cognitive decline predicts stroke
Leiden 85+ Study, 480 subjects, 85 years,
In the very elderly, cognition predicts stroke better than vascular risk factors:

![Graphs showing cumulative incidence of stroke over time for vascular risk score and memory test with different risk categories and p-values: 1.86; df=2; P = 0.394 (A) and 11.23; df=2; P = 0.004 (B).](www.strokeassembly.org.uk)


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Prediction of dementia after stroke is difficult

• ‘Dementia’ tests focus on memory – other abilities are more affected

• Tests often too long and tiring
• Patients may not be able to do some tests after stroke
• Don’t account for previous cognitive ability but this is strongest predictor of having cognitive problems after stroke
Cognition after stroke

Among 155 patients with mild stroke, median age 66

Age

Pre-morbid IQ: 0.43

Beck depression index: 0.16

Idyll Zealot Gist Superfluous
Simile Deny Ache Banal
Naïve Depot Beatify Facade
Catacomb Equivocal Gauche Placebo
Détente Heir Aeon Puerperal
Chord Sidereal Quadruped Aver
Rarefied Bouquet Abstemious Rarefy
Topiary Radix Debt Assignate
Capon Thyme Drachma Sidereal
Topiary Prelate Demesne Syncope
Labile Procreate Subtle Gaol
Courteous Gouge Hiatus Psalm
Campanile Leviathan Aisle Cellist
Cerebrovascular disease – stroke and dementia

Acute stroke

‘Covert’ neurology, cognitive symptoms

Small Vessel Disease

‘Silent’ insidious physical decline, dementia, depression
Mobility problems

Where did all this come from???

Why did that dot cause symptoms?
Small vessel disease – stroke and dementia

Acute stroke

‘Silent’ slow decline in cognition, mobility, mood …

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White matter hyperintensities

FLAIR MR image at start

Superimposed Diffusion-Weighted Image

5 patients
weekly scan
16 weeks

Conklin, Silver, Mikulis, Mandell 2014
WMH, where do they come from???

Conklin, Silver, Mikulis, Mandell 2014
WMH, where do they come from???

Conklin, Silver, Mikulis, Mandell 2014
WMH, where do they come from???
Why do some lesions cause stroke symptoms?

Symptomatic lesions more often in the **main motor & sensory paths**

Valdes Hernandez et al IJS 2015; Bailey et al Brain Pathol 2011
Stroke and Dementia: what to do?

Treat vascular risk factors?

- High blood pressure ++
- Diabetes +
- High cholesterol +
- Smoking ++

But! Impact may differ at different ages, e.g., BP may be more important in 40s – 60s than 70s – 90s

But! All common vascular risk factors combined only explain a small proportion of the burden of brain vascular disease, and so far trials of risk factor reduction have been disappointing.

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Trials of blood pressure and lipid lowering

**PODCAST trial** of 83 patients with stroke
Intensive BP lowering did not prevent cognitive decline, even suggestion of adverse effect
Intensive lipid lowering did not prevent cognitive decline but no harm and lipids low anyway

**SPS3 trial** of 3000 patients with lacunar stroke
Intensive vs guideline BP lowering did not prevent recurrent stroke or cognitive decline.

**Various trials**
Mixed results for BP lowering on brain vascular disease on scanning
No effect of statins on brain vascular disease on scanning but may slow cognitive decline
Risk factors: What else???

**Salt**: increases vascular disease on scanning

**Exercise**: linked to reduced brain vascular disease in several studies; helps recovery after stroke

**Diet** – green vegetables help keep the blood vessels healthy???
Other treatment targets?

Week blood vessel lining: strengthen cell junctions

Poor blood vessel function: increase nitric oxide

‘Inflammation’: anti-inflammatory?

Statins, nitrates, pentoxyfiline, cilostazol, dipyridamole, etc
Trials are really difficult

• Need long term treatment and follow-up
  – Expensive
  – Big commitment for patients and families
  – Trial administration is punitive for investigators
• Not enough data on long term outcomes:
  – Recurrent stroke ~3% per year
  – Cognition long term data poor
• Measure other clinically relevant outcomes:
  – Physical – balance, gait problems
• Capture diffuse brain changes – imaging
• Many guideline drugs

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For now?

Apply guideline treatments:
• Lower blood pressure
• Lower lipids
• Use antiplatelet drugs, but not ASA+Clop long term
• Lifestyle advise – smoking, salt reduction, exercise
• Trials of existing agents and novel agents
• More animal data to lead to human trials
Summary

Stroke and Dementia are closely intertwined
– Declining cognition is a warning of stroke
– Stroke is a warning of declining cognition

Large burden of silent cerebrovascular disease – ‘dynamic’

Stopping the burden of cerebrovascular disease from accumulating by:
– better recovery from acute stroke
– reduce ‘silent’ disease build up

Will help prevent vascular dementia
Imaging shows lesions can disappear!
Challenges

• Slowly advancing disorder
  – Long term perspective
• Clinical Trials are really difficult
• Standards for diagnosis needed
• Better understanding of risk factors
• Data on long term outcomes
  – Cognition
  – New strokes
• Different presentations
  – Stroke and dementia doctors need to work together
• *Every Stroke study should collect cognitive data*
• *Every Dementia study should collect vascular risk factor information*