Old age, polymorbidity and stroke, a new epidemy?

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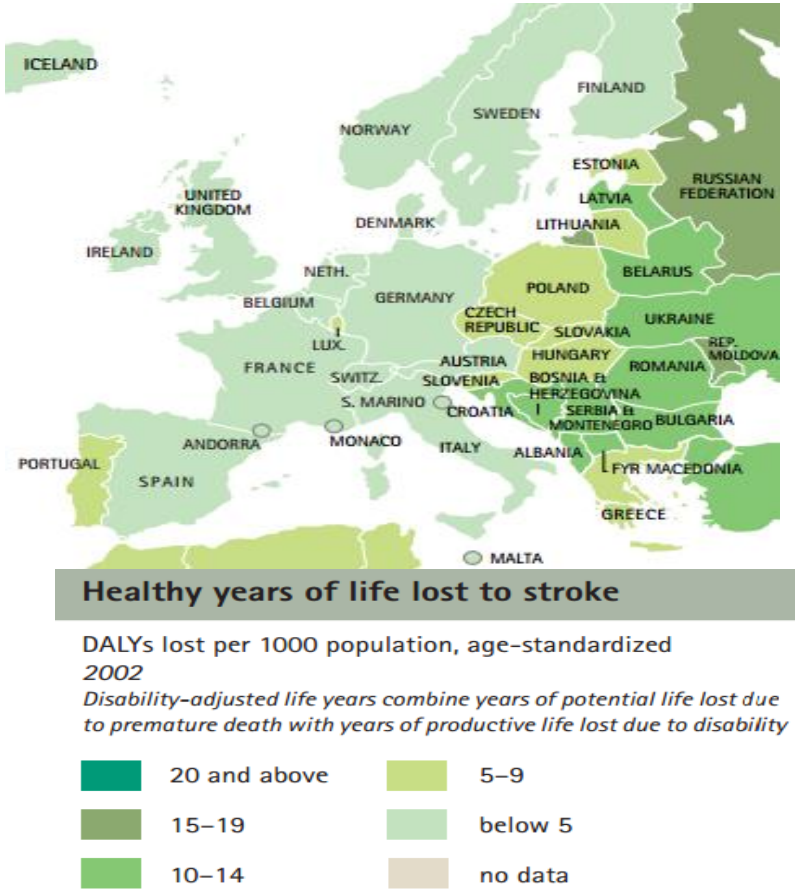
The Global Burden of Stroke

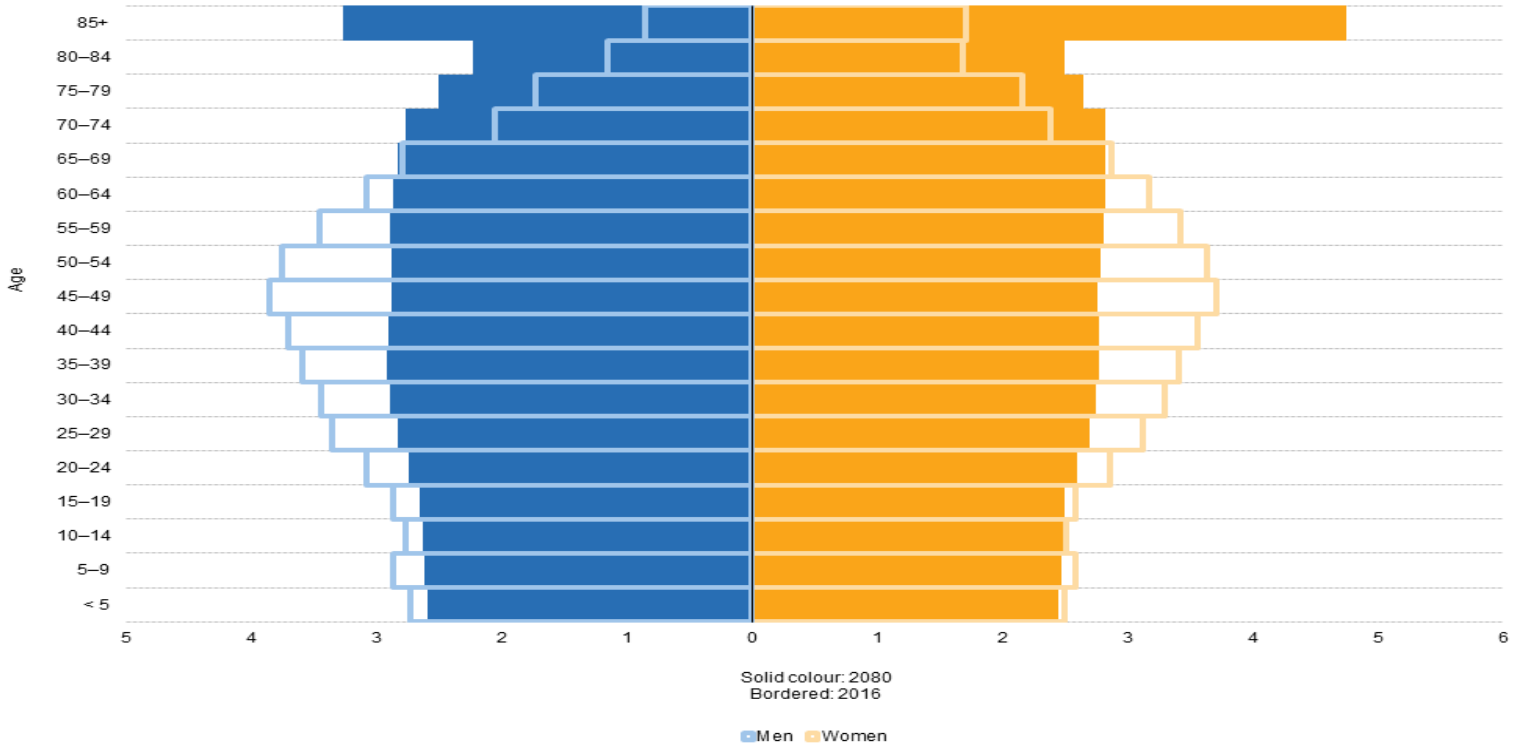
- Each year 15 million people suffer a stroke worldwide
- 6 million die
- 5 million permanently disabled at increased risk of recurrent stroke, depression and dementia

- Stroke 24% increase in global years of life lost between 1990 and 2013
- Moving from 5th to 3rd leading cause



GBD 2013 Mortality and causes of death collaboration, Lancet 2015

EU population pyramid changes 2016-2080



Note: 2016: estimate, provisional. 2080: projections (EUROPOP2015).
Source: Eurostat (online data codes: demo_pjangroup and proj_15npms)

Population projections for the cantons in Switzerland 2015-2045

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
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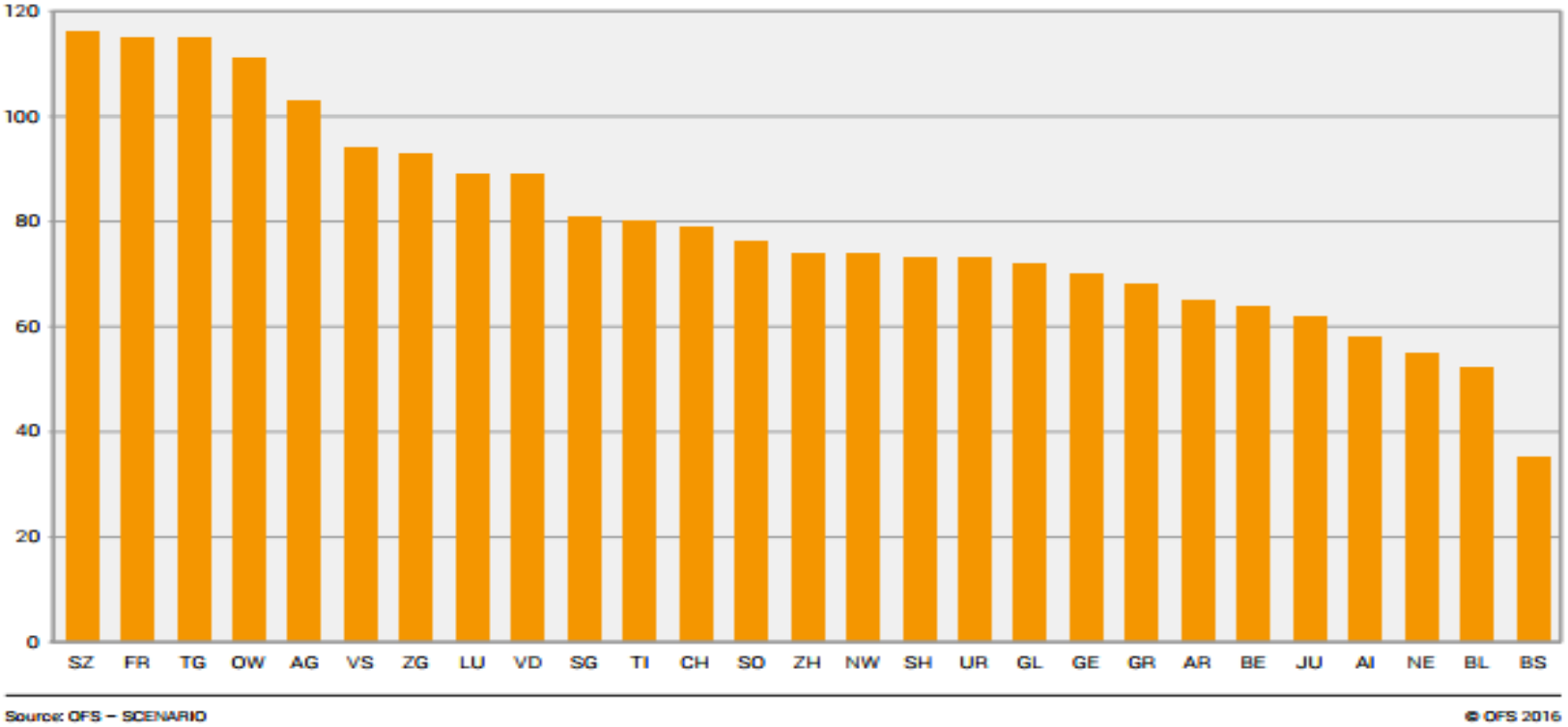
Federal Statistical Office



Source: OFS – SCENARIO

Increase (%) of the permanent resident population ≥65 yrs in the townships from 2015 to 2045

Population projections for the cantons in Switzerland 2015-2045

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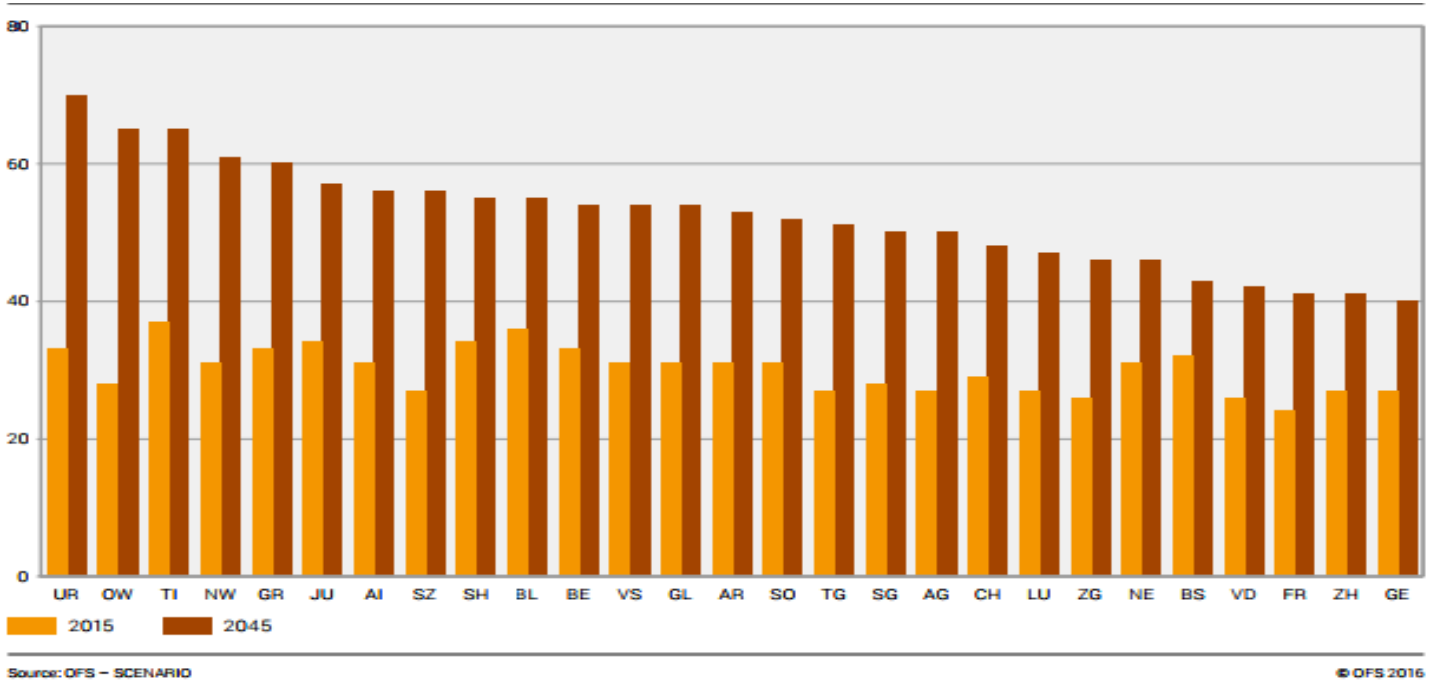
Large increase expected in number of retired people



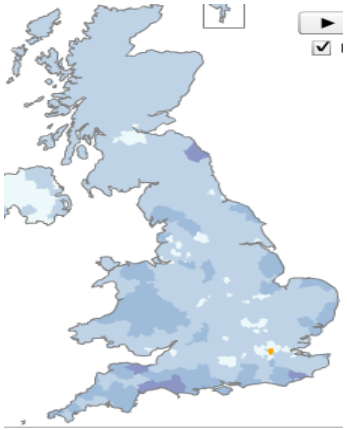
Elderly dependency ratio (number of people > 65 yrs per 100 aged 20-64 yrs) in 2015 and in 2045

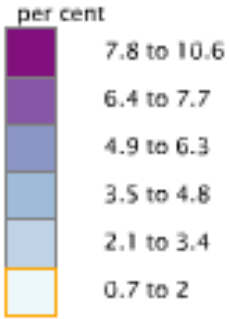
Implications for Stroke Units

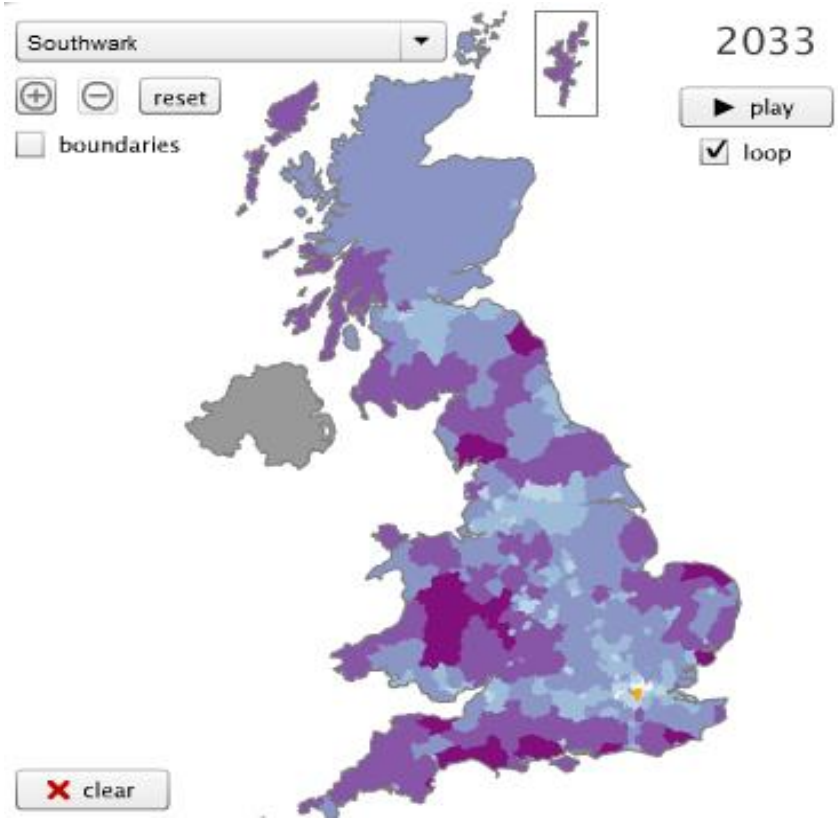
- Age profile of patients presenting with acute stroke will change profoundly
  - population demographics
  - successful prevention in middle age
  - reduced mortality following first ever stroke
- Greater proportion of patients presenting with acute stroke will have disability from previous stroke
- Increasing proportion of acute stroke patients will have multiple comorbidities and disability from other conditions such as dementia
- Oxfordshire comparison of median (IQR) age stroke/TIA patients

OCSP	1981-86	74 (64-80) yrs
OXVASC	2002-03	76 (66-83) yrs

Population 85 years and over: 1992, 2015, 2033



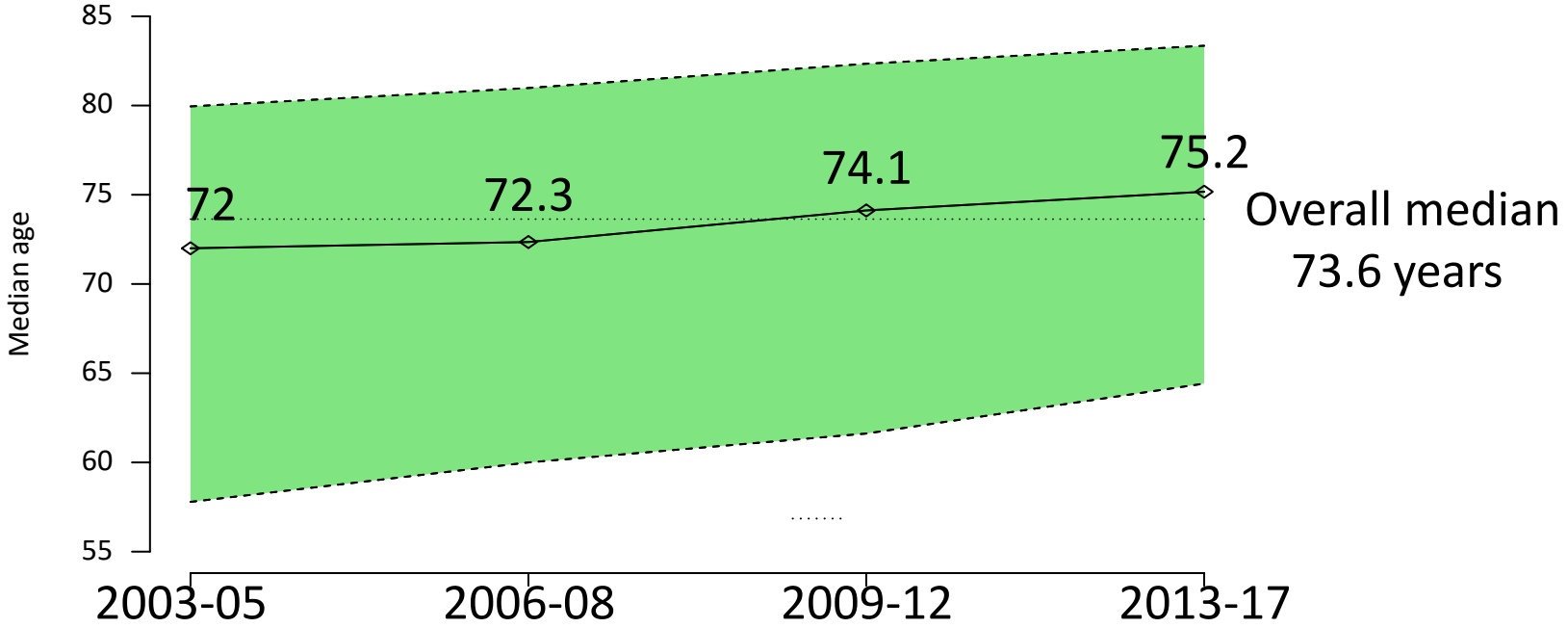




ONS data

Age of AIS at CHUV 2003 → 2017

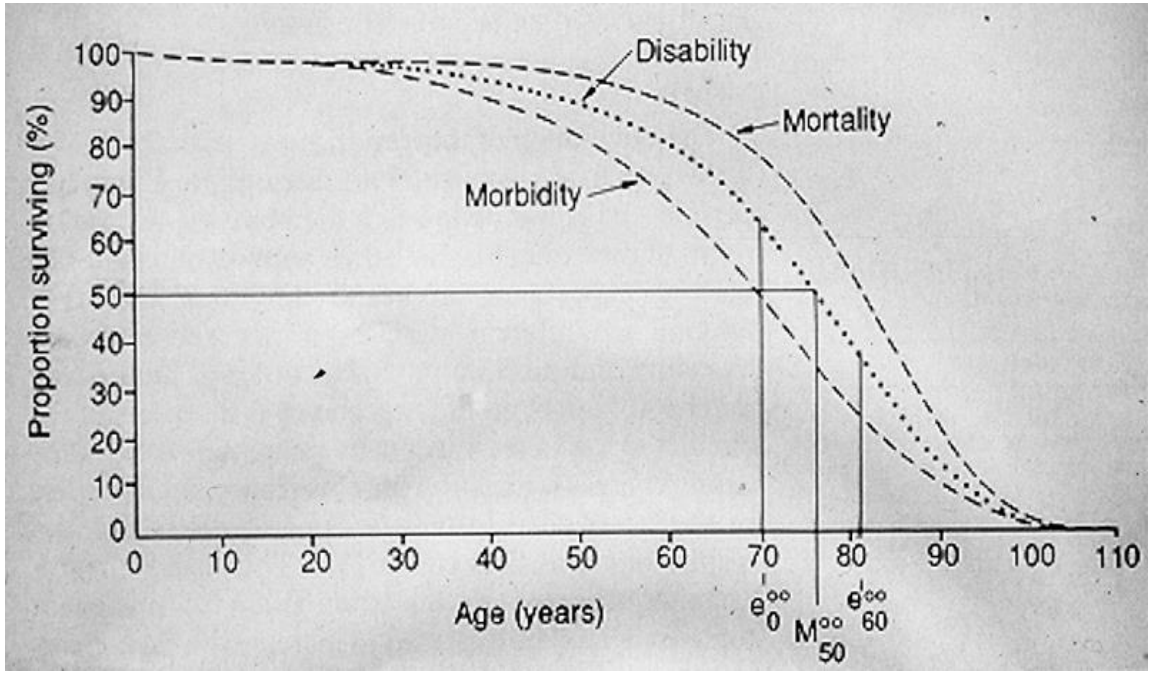
N=4’454 consecutive strokes (median and IQR)



Source: ASTRA *Strambo & Michel, unpublished*

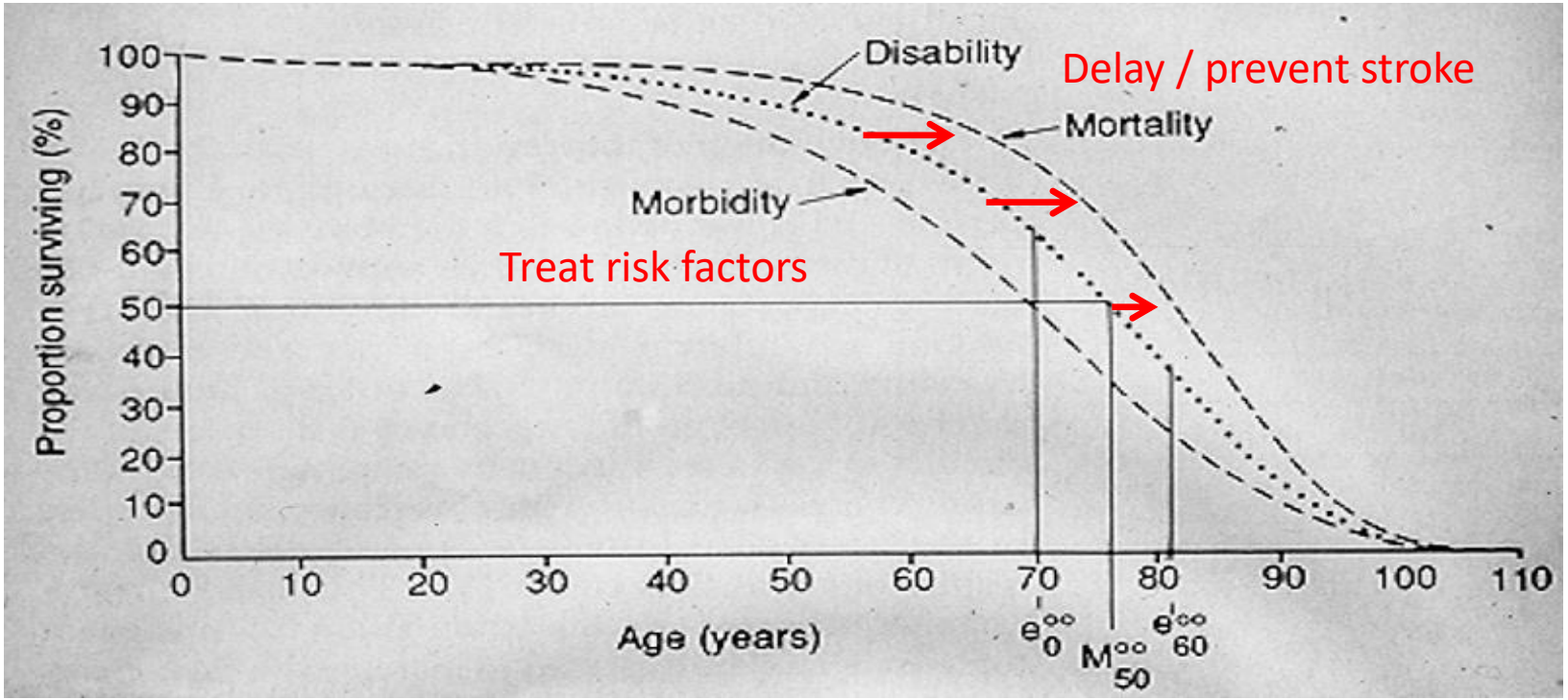
Aims of Treatment in Older People

- Improve quality of life
- Increase life expectancy



Fries et al, NEJM 1980

Primary Stroke Prevention



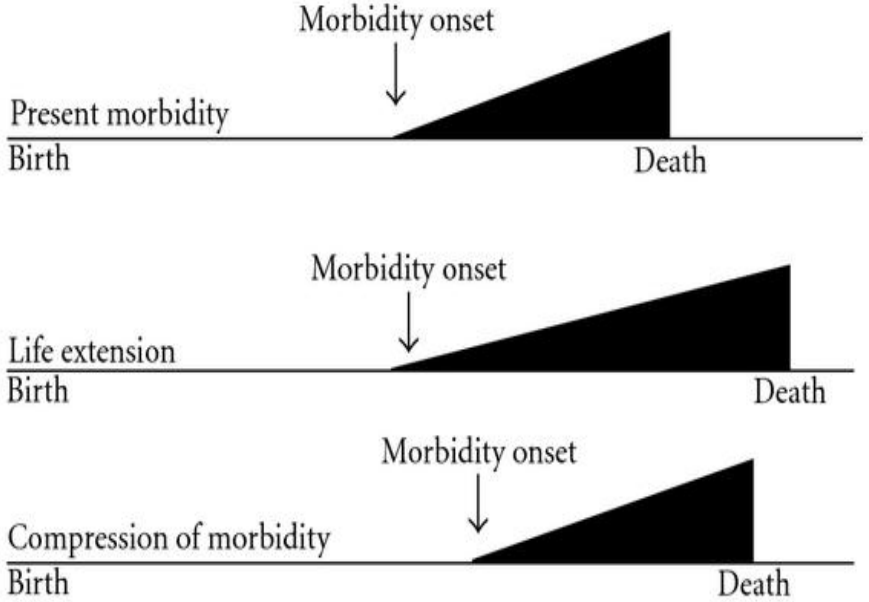
Preventing stroke moves mortality curve and compresses disability mortality curves

Adapted from Fries et al, NEJM 1980

The impact of interventions for stroke on mortality / disability curves

- Hemicraniectomy
- VTE prevention (IPC sleeves)
- Reperfusion therapies in people dependent pre-stroke (mRS 3-5)

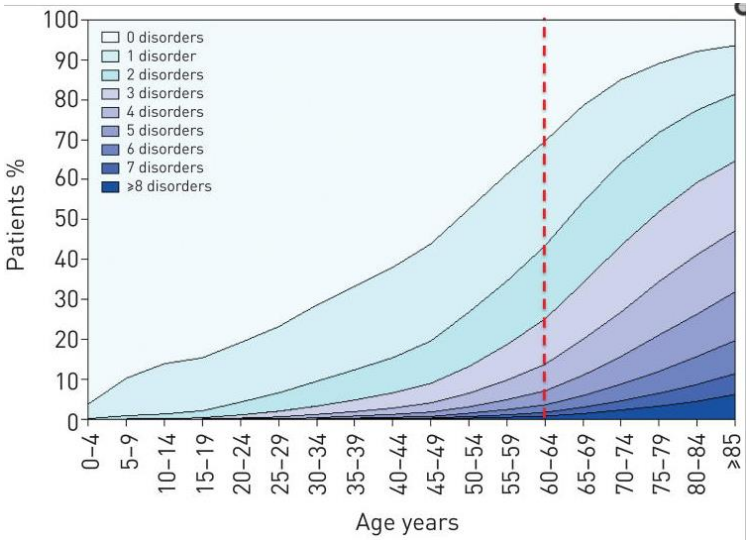
- Hypertension / AF primary prevention
- Reperfusion therapies in people independent pre-stroke (mRS 0-2)



Fries et al, J Aging Res 2011

Co-morbidity Measures

- Comorbidity - the effect of all other diseases an individual patient might have other than the primary disease of interest
- Differences in terminology
  - Cumulative Illness Rating Scale (1968)
  - Cumulative Illness Rating Scale for Geriatrics (1991)
  - The Kaplan-Feinstein Index (1973)
  - Charlson Index (1987)
  - Modified Charlson Index (1992)]
  - Elixhauser Index
  - Index of Co-Existent Disease (1993)
  - Geriatric Index of Comorbidity (2002)
  - Functional Comorbidity Index (2005)
  - Total Illness Burden Index (2007)



Fabbri et al, Lancet 2007

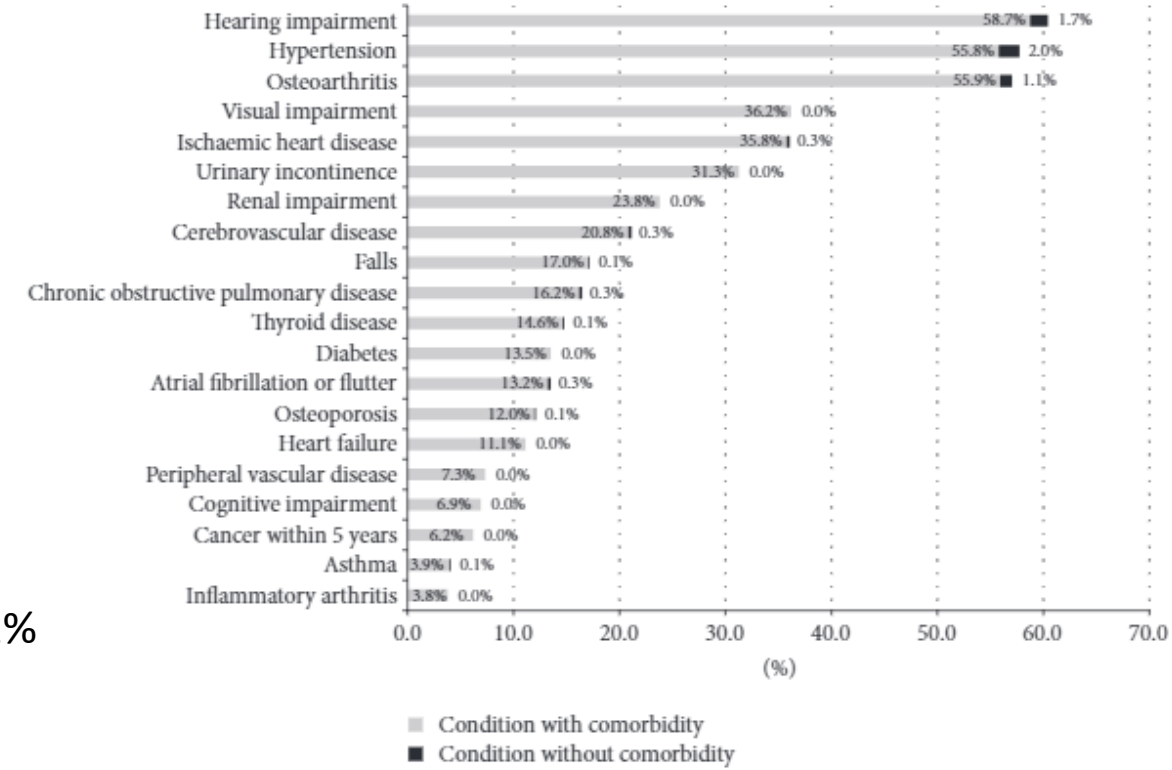
Charlson Comorbidity Index

- Predicts ten-year mortality in population studies
- Conditions are assigned a score of 1, 2, 3, or 6, depending on the mortality risk. Many variations have been produced.

- Scores are summed to provide a total score.
  - Age <40yrs 0 points ; >70 yrs 4 points
  - 1 point: Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes.
  - 2 point: Hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, tumor, leukemia, lymphoma.
  - 3 points: Moderate or severe liver disease.
  - 6 points: Malignant tumor, metastasis, AIDS

Morbidity prevalence in the very old

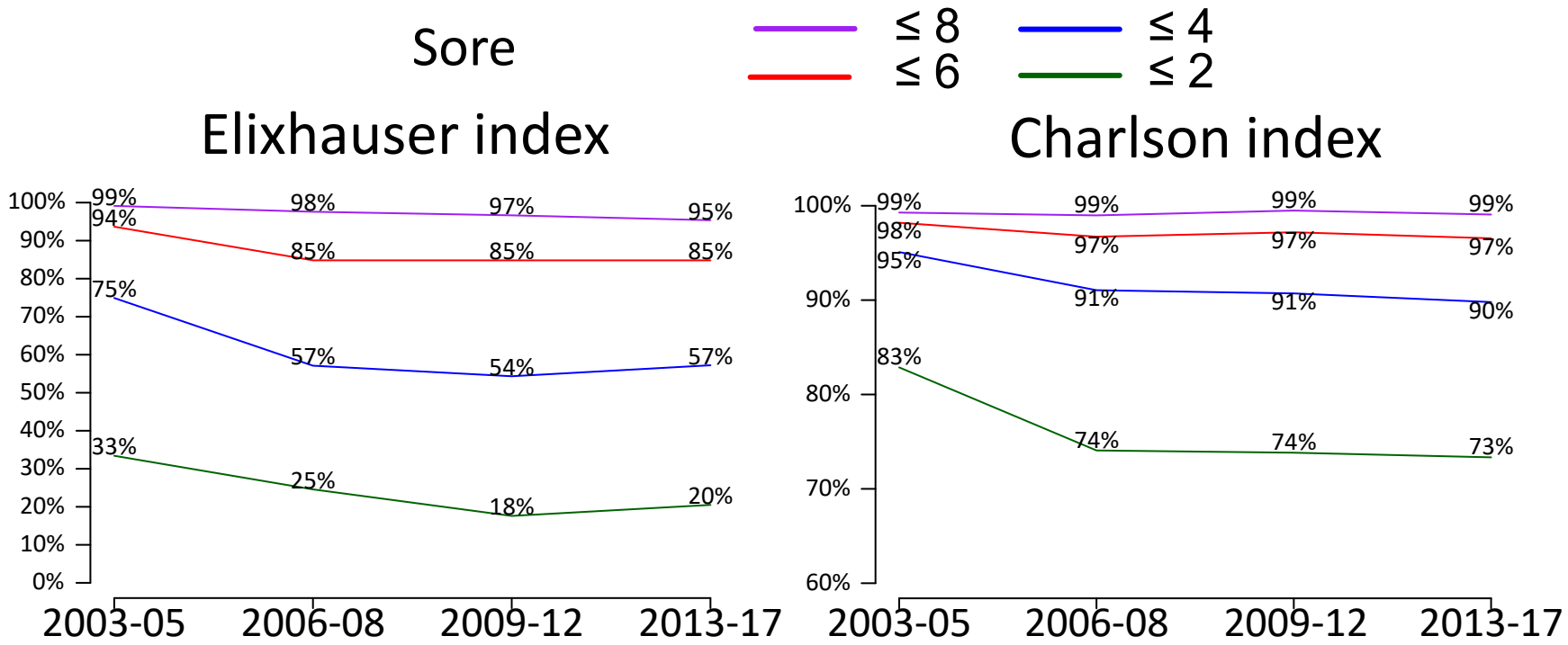
- Newcastle 85+ study population based study
- 710 participants with complete information
- < 1% (n=6) participants had none of the 20 conditions
- 6.5% had one condition
- 8.9% had ≥ 8 conditions
- 92.7% multi-morbidity (≥ 2 conditions)
- Women 93.6% vs. men 91.2% p= 0.22



Collerton et al, Biomed Res International 2016

Comorbidities of AIS at CHUV 2003 → 2017

N=4’268 consecutive strokes



Source: ASTRA Strambo & Michel, unpublished

Frailty

- Syndrome that embodies an elevated risk of catastrophic declines in health and function among older adults
- Increased vulnerability to stressors
- Weakness, slowing, decreased energy, lower activity and unintended weight loss
- Fried Frailty Assessment

  Five domains: Shrinking
  Weakness (grip strength)
  Low energy
  Low physical activity
  Slowness (walking speed)

- *"The sixth age shifts into the lean and slipper'd pantaloon, with spectacles on nose and pouch on side, his youthful hose well sav'd, a world too wide, for his shrunk shank…".* *Shakespeare, As You Like It*

Fried et al, J Gerontol 2001

Walking Speed and Mortality

How fast does the Grim Reaper Walk?

- Concord Health and Ageing in Men Project (CHAMP)
- 1511 males > 7yrs. ROC analysis walking speed and 5 year mortality
- Walking speed of < 2 miles per hour was most predictive of mortality. Likely speed at which the Grim Reaper prefers to ambulate under working conditions.
- No men walking at speeds of > 3 miles per hour or above were caught by Death (n=22, 1.4%). This supports hypothesis that faster speeds are protective against mortality because fast walkers can maintain a safe distance from the Grim Reaper.

Stanaway et al, Br Med J 2011

Rockwood Frailty Index

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

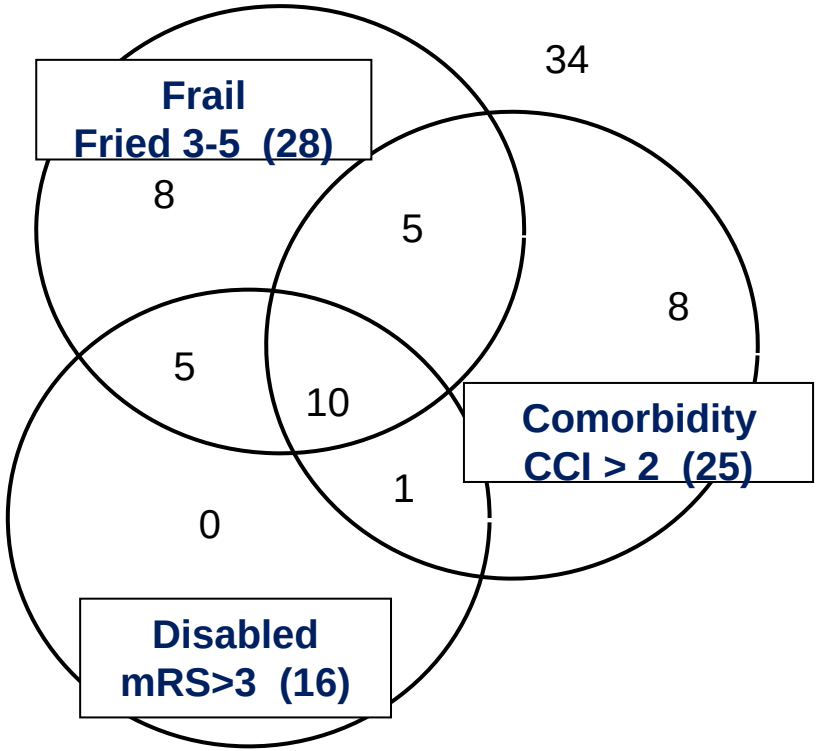
* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

DALHOUSIE UNIVERSITY
Inspiring Minds

Prevalence Frailty Acute Stroke Population

- 71 acute stroke patients within 48 hours admission
- Frailty assessed using adaptation of Fried
- Multivariate model - Frailty independently associated with decline in mRS at 3 months
  (42% vs. 24%)
- Median length of stay;

Frail (3-5)	9 days
Pre-frail (1,2)	6 days
Non frail (0)	2 days



Macleod et al, Int J Stroke 2012 abstract

Pre-stroke frailty, comorbidity and disability prevalence in stroke unit admissions

- 231 stroke unit admissions
- Pre-stroke frailty and comorbidity assessed
- 54% pre-stroke disability mRS >1
- 38% at least one marker pre-stroke frailty

Rockwood Frailty Index

Score	Description
0	Walks unaided, independent with basic ADL*, continent of bowel and bladder, no cognitive impairment.
1	Bladder incontinence only.
2	One or more (two if bladder incontinent) of needing assistance with mobility or basic ADL, cognitive impairment with no dementia, bowel or bladder incontinence.
3	Two or more (three if bladder incontinent) of total dependence for transfers or ≥ 1 ADL, incontinent of bladder and bowel, diagnosis of dementia.

Frearon et al, Stroke 2012

Disability, Frailty and Comorbidity

Frail but not-disabled

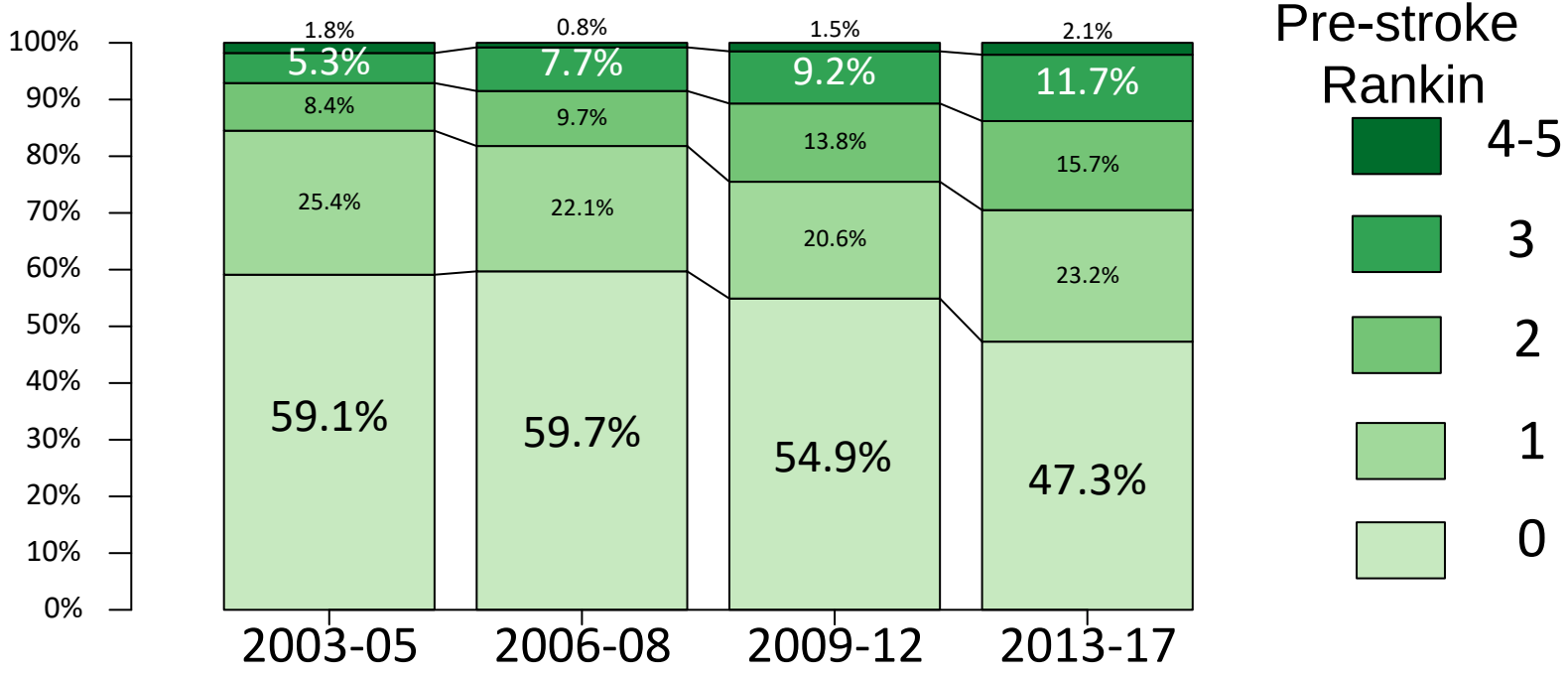
Rockwood Frailty Index	0	1	2	1	0	0	Charlson co-morbidity Index
3	1	1	6	7	9	1	8,9
	4	3	4	3	5	0	
2	0	2	17	10	5	0	6,7
	15	7	15	10	8	1	
1	2	3	7	0	1	0	4,5
	26	12	13	4	3	1	
0	85	27	5	0	0	0	2,3
	36	7	2	1	0	0	
	0	1	2	3	4	5	0,1
	Pre-stroke mRS						

Figure 2. Correlation between prestroke mRS and co-morbidity/ frailty indices. mRS indicates modified Rankin scale.

Frearon et al, Stroke 2012

Pre-stroke mRS in AIS at CHUV 2003 → 2017

N=4’428 consecutive strokes



Source: ASTRA *Strambo & Michel, unpublished*

Pre-stroke disability, dementia and stroke outcome

- Swedish dementia registry.
- Pre-stroke ADLs and mobility were worse in patients with dementia.
- In adjusted analyses, pre-stroke dementia was associated with increased 3-month mortality (OR 1.34; 95% CI 1.18–1.52).
- Patients with dementia independently mobile pre-stroke were more likely to be discharged to a nursing home compared with patients without dementia with the same pre-stroke mobility (37% vs 16%; P < .001).
- In adjusted analyses, pre-stroke mobility limitations were associated with higher odds for poorer mobility, needing more residential assistance, and death

Table 2
Prestroke Dementia in Relationship to Functional and Mortality Outcomes

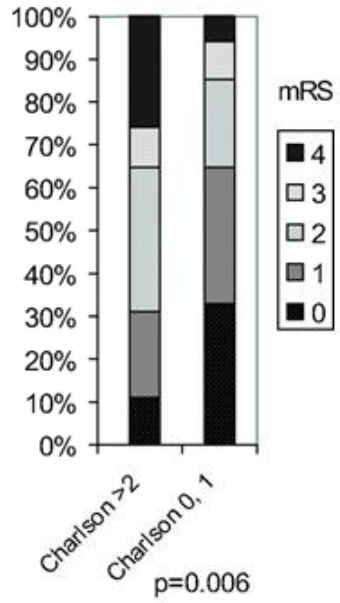
	All	Dementia	No dementia	*P* Value
	n = 9662	n = 1689	n = 7973	
In-hospital deaths	1495 (16%)	287 (17%)	1208 (15%)	.057
Survivors from hospitalization n = 8167				
Place of discharge				
Home	4465 (55%)	457 (33%)	4008 (60%)	<.001
Nursing home	2047 (25%)	712 (51%)	1335 (20%)	<.001
Geriatric rehabilitation	1453 (18%)	210 (15%)	1243 (18%)	.003
Other/still hospitalized	175 (2.1%)	14 (1%)	161 (2.4%)	<.001
Follow-up at 3 mo				
Deaths at 3 mo	2364 (25%)	526 (31%)	1838 (23%)	<.001
Survivors at 3 mo, n = 7298				
Level of residential assistance at 3 mo				
Home without help	3168 (49%)	198 (21%)	2970 (55%)	<.001
Home with help	1811 (29%)	274 (29%)	1537 (28%)	.654
Nursing home	1296 (20%)	458 (49%)	838 (16%)	<.001
Other	84 (1.3%)	12 (1.3%)	72 (1.3%)	.891
Mobility at 3 mo				
Independent	3871 (61%)	343 (37%)	3528 (66%)	<.001
Dependent outdoors	1251 (20%)	1003 (19%)	248 (27%)	<.001
Dependent indoors and outdoors	1188 (19%)	844 (16%)	344 (37%)	<.001

P values obtained from χ^2 tests. Dead at 3 months includes in-hospital deaths and deaths occurring up to 3 months after the stroke. Missing data. Mortality: none; accommodation at discharge 27 (<1%); level of residential assistance at 3 months: 939 (13%); mobility at 3 months: 988 (14%).

Garcia-Ptacek et al, JAMDA 2017

Influence of comorbidity on outcome

- Pre-stroke comorbidity (Charlson Index excluding stroke, hemiplegia) in133 women admitted with acute ischemic stroke (median NIHSS 4 range 0-22) to Duke University Medical Centre, and association with 90 day mRS outcomes. Baseline NIHSS 4.
- 9 deaths, 5 withdrawals 17 lost to follow up.
- Adjusting for NIHSS and age, higher Charlson independently associated with poorer 90 day mRS scores.
- When CI was excluded, coronary disease and diabetes were independently associated with poorer outcome.
- Limitations of study – no pre-stroke MRS assessment, unclear when patients recruited, no mRS 5/6 outcomes



Bushnell et al. Stroke. 2008

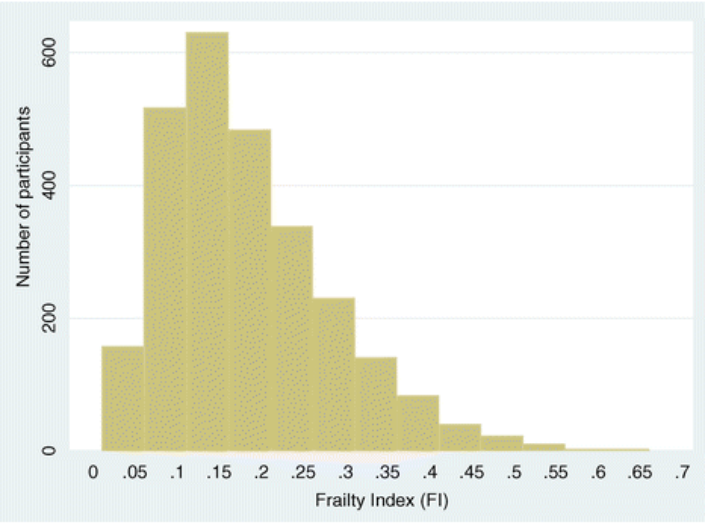
Effects of frailty, comorbidity, disability on outcomes from stroke reperfusion therapies

- Largely unknown – mostly exclude from RCTs. Most published data do not differentiate between comorbidity, frailty and disability.
- Analyses of the impact of single comorbidities on outcomes from iv thrombolysis failed to show major influence
- Reports of outcome from stroke in patients with pre stroke disability (mRS 3 and 4) suggests iv thrombolysis safe
- Single centre study 112 consecutive patients with acute ischemic stroke patients treated with IVT. 3 months outcomes patients with pre-existing disability (21%) had increased mortality (33% v. 14% OR 3.2, 95% CI 1.0-10.1) and worse outcome (median mRS score 3 v. 2, p = 0.03). But no difference in the total proportion of those with an mRS score of 0 1 or, for those with a pre-stroke smRS >1, a return to the pre-stroke mRS (42% v. 41%, p = 0.87)
- No systematic analysis of comorbidity burden on outcomes
- No studies of frailty on impact on efficacy and adverse effects of reperfusion therapy
- Many believe frailty might be associated with an increased risk of sICH

Foell et al, CMAJ 2003

Frailty and stroke prevention treatment

- HYVET study BP lowering > 80 yrs
- N=2,656 with QoL, frailty/co-morbidity assessment - 60 possible deficits
- Benefits of BP lowering present in all groups



Estimated hazard ratios for treatment effect (active treatment versus placebo) and associated 95% confidence intervals, by frailty index

	Stroke		Cardiovascular events		Total mortality	
Frailty index	HR	95% CI	HR	95% CI	HR	95% CI
0.1	0.75	0.40–1.38	0.62	0.42–0.92	0.89	0.63–1.25
0.2	0.66	0.43–1.01	0.60	0.45–0.78	0.84	0.66–1.07
0.3	0.59	0.36–0.96	0.57	0.42–0.79	0.80	0.61–1.04
0.4	0.52	0.25–1.09	0.55	0.34–0.89	0.76	0.50–1.14
0.5	0.47	0.16–1.33	0.53	0.26–1.06	0.72	0.40–1.29
0.6	0.41	0.10–1.65	0.50	0.20–1.27	0.68	0.32–1.48

All models adjusted by age, sex, and interaction between treatment and frailty index, and stratified by region of recruitment.

Warwick et al, BMC Medicine 2015

A difficult case

- 72 yr old lady. Diabetes, hypertension, pseudo obstruction, seizures, cataracts, 2007 R MCA territory ischaemic stroke with residual dense left hemiparesis, left homonomous hemianopia
- Bed bound, hoisted, able to communicate with family and feed herself with right hand. Pre-stroke Modified Rankin Score 5
- Last seen well 0820h. Son went to her room 0900h found unable to speak with right sided weakness
- 0907h Call to ambulance 1006h Arrive at hospital
- Mute, aphasic, R face/arm/leg weakness. NIHSS 25 - new deficits score 7
- 1030h assessed by consultant
- 1040h CT Head – old R MCA infarct, no blood, nil acute left hemisphere

A “poor” outcome

- Discussion with son about quality of life and her likely wishes
- 1055h Treated 165 min since last seen well
- At 24 hr communicating normally. NIHSS 18 no new deficit
- CT – small area haemorrhagic transformation HT1 left parietal cortex
- Discharged home second day following admission. Full resolution.
- Discharge Modified Rankin Score 5

Is the comorbidity epidemic avoidable?

- Our future stroke services need to be designed to manage increasing numbers of people with comorbidity and pre-stroke disability
- Age related comorbidity can be delayed
- Cardiovascular prevention highly effective at preventing premature death and disability from stroke
- Longitudinal studies show strong associations between exercise in middle / old age and avoidance disability
- Animal studies show ageing is modifiable – caloric restriction
- Targets that could delay onset age-related disease – metabolism, inflammation, DNA repair, cell senescence,
- Increasing interest in developing drug therapies that target ageing process rather than single diseases related to ageing

Disability progression—ages 58–79 years: Runners' Club and Community Controls