The clinical epidemiology of acute ischaemic stroke and its long-term health economic outcomes

Thesis submitted for degree of D.Phil. in Clinical Neurosciences

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To my parents,

Padmaja and Genesh

Who taught me love, kindness, and perseverance, and

Whom I continue to learn from with each passing year

To my grandmothers,

Thankom

Who taught me the meaning of audacity, and

Saroamma,

Whose kind spirit left us too soon

To my grandfather,

Cheriyil Gangadhara Kurup

Whose memories led me to neuroscience

THESIS ABSTRACT

The clinical epidemiology of acute ischaemic stroke and its long-term health economic outcomes

Aravind Ganesh, St John's College, University of Oxford

Submitted for the degree of D.Phil, Trinity Term 2017

This thesis examines 5-year clinical and health-economic outcomes of ischaemic stroke, and their relationship to short-term post-stroke disability, as captured by the 3-month modified Rankin Scale (mRS) – the favoured primary outcome measure in acute stroke trials. I used data from the Oxford Vascular Study (recruited 2002-2014), a population-based prospective cohort for which I followed patients in-person and via medical records until 15-May-2017.

I demonstrate that 3-month mRS strongly predicts 5-year post-stroke disability and mortality, including in clinically-relevant groups (treatable major strokes, atrial fibrillation-related strokes, and lacunar strokes), reaffirming its use as a trial outcome measure. About one in four patients experience functional recovery between 3-12 months post-stroke, and mortality follow-up beyond 1-year by stroke trials can show translation of early disability gains into lower mortality. Contrary to previously reported apparent sex-differences, I find no evidence of worse outcomes in women after accounting for differences in age and pre-stroke mRS. I find that late recovery between 3-12 months occurs more often in lacunar strokes, supporting the focus of restorative therapies in this group, but highlighting that uncontrolled studies cannot assume that improvements after 3-months are treatment-related.

In addition, I demonstrate that like death/disability, outcomes of institutionalization, post-stroke dementia, health/social-care costs, and quality-adjusted life expectancy (QALE) also show meaningful differences with each step up the mRS ladder. Consequently, ordinal analysis of the 3-month mRS (capturing transitions across the scale's range) better predicts long-term outcomes than dichotomous approaches, which also foster high exclusion rates of relevant patient segments from trials owing to their pre-morbid disability. However, the mRS should be weighted in ordinal analyses, as different state transitions carry different implications for long-term outcomes. Using 3-month mRS-stratified data for clinical endpoints, care costs, and QALE, I derive mRS weights that could be used for meaningful ordinal analyses, clinical prognostication, and cost-effectiveness analyses of stroke therapies.

DECLARATION

I certify that this thesis entitled “The clinical epidemiology of acute ischaemic stroke and its long-term health economic outcomes” was performed whilst I was a full-time postgraduate student at the University of Oxford.

I declare that this thesis is of my own composition, and the research contained herein is my own original work under the supervision of Professor Peter Rothwell. No portion of this work has been submitted in support of an application for any other degree.

CANDIDATE CONTRIBUTION

The Oxford Vascular Study (OXVASC) is supervised by Professor Peter Rothwell and the day-to-day patient ascertainment, assessment, and follow-up are performed by clinical fellows and research nurses.

This thesis uses data from patients recruited from 2002-2014, followed until 15-May-2017. I participated in OXVASC as one of five full-time clinical fellows from 2014-2017. Over the first two and a half years of my fellowship, I was responsible for patient ascertainment and assessment for the study. I participated in the study's clinical service on a day-to-day basis, assessing and ascertaining upwards of ten referrals of suspected stroke or transient ischaemic attack (TIA) per week, in addition to carrying out clinical follow-up appointments for patients to review investigations, optimize their secondary prevention, evaluate and manage post-stroke complications. I also helped provide clinical supervision for the research nurses who also performed many of the follow-up assessments, including home assessments for several patients. As part of these appointments, I also gathered data for OXVASC using several standardized forms that are appended at the end of this thesis. The data on functional recovery in OXVASC, particularly with respect to assessments using the mRS, Rivermead Mobility Index, and Barthel Index, had not previously been collated or cleaned in detail, so I performed much preparatory work on existing data and collected a large amount of new data. I also gathered and cleaned 5-year institutionalization and healthcare utilization data for the entire cohort of 1,425 3-month survivors of ischaemic stroke that are used in the bulk of this thesis, reviewing various hospital and primary care records, and collating data from in-person or telephone appointments.

Over the course of my DPhil, I assessed and followed-up a significant proportion of patients whose data are used in this thesis, but I would like to acknowledge the invaluable help of other clinical fellows and research nurses in this process. All the data extraction and data entry in this thesis are my own, and I also performed most of my own statistical analyses. I acknowledge the help of the study statisticians, Ms Rose Wharton and Dr Ziyah Mehta, for their advice and assistance with data analysis; of epidemiologist Dr Christel Renoux for her guidance and assistance with the analyses of sex-differences for Chapter 3; of health economist Dr Ramon Luengo-Fernandez for the analysis of healthcare costs and quality-adjusted life expectancy reported in Chapters 5 and 6; of Dr Sergei Gutnikov for his support with database management and data extraction in OXVASC; and of Professor Peter Rothwell for his advice in the preparation and revision of the thesis chapters.

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PUBLICATIONS, PRESENTATIONS, AND AWARDS

The work in this thesis has led to the following publications, presentations, and awards:

Publications

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- Ganesh, A., S.T. Pendlebury, R.M. Wharton, R. Luengo-Fernandez, P.M. Rothwell, on behalf of OXVASC. “Three-month modified Rankin Scale score predicts 5-year post-stroke dementia and institutionalization outcomes: a population-based prospective cohort study”. Stroke 2018;49(Suppl 1):A154.
- Ganesh, A., R. Luengo-Fernandez, R.M. Wharton, S.A. Gutnikov, L.E. Silver, Z. Mehta, P.M. Rothwell, on behalf of the Oxford Vascular Study. “Time course of evolution of disability and cause-specific mortality after ischemic stroke: implications for trial design”. Journal of the American Heart Association 2017;6(6) pii:e005788.
- Ganesh, A. “Residual poststroke disability is another opportunity to reduce long-term morbidity and mortality”. CMAJ 2017;189(35):E1120.
- Ganesh, A. and C. Renoux. “Letter by Ganesh and Renoux regarding article, ‘Sex differences and functional outcome after intravenous thrombolysis’”. Stroke 2017;48(11):e329.
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- Ganesh, A., R. Luengo-Fernandez, P.M. Rothwell, for OXVASC. “Ordinal analysis of the modified Rankin Scale predicts 5-year disability, death, and healthcare costs better than either dichotomy: informing acute stroke trials”. International Journal of Stroke 2017;12(4S):4.
- Ganesh, A., R. Luengo-Fernandez, P.M. Rothwell, on behalf of OXVASC. “Risk of selection bias and misrepresentation of stroke populations with dichotomous analyses of the modified Rankin Scale in stroke trials”. International Journal of Stroke 2017;12(4S):13.
- Ganesh, A., R. Luengo-Fernandez, R.M. Wharton, S.A. Gutnikov, L.E. Silver, Z. Mehta, P.M. Rothwell, on behalf of the Oxford Vascular Study. “Time-course of functional recovery after acute ischaemic stroke and its relationship to cause-specific mortality: Implications for follow-up of stroke trials” (Abstract). Neurology 2017;88(16): Supplement S19.004.
- Ganesh, A., R. Luengo-Fernandez, R.M. Wharton, S.A. Gutnikov, L.E. Silver, Z. Mehta, P.M. Rothwell, on behalf of the Oxford Vascular Study. “One-month modified Rankin Scale (mRS) predicts five-year disability, death, quality-of-life, and healthcare costs in ischaemic stroke: a prospective cohort study” (Abstract). Stroke 2017;48(Suppl 1):A166.

Presentations

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costs better than either dichotomy: informing acute stroke trials". *2017 Canadian Stroke Congress (CSC)*. September 11, 2017. Calgary, Canada.

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- Ganesh, A., R. Luengo-Fernandez, R.M. Wharton, S.A. Gutnikov, L.E. Silver, Z. Mehta, P.M. Rothwell, on behalf of the OXVASC. "Performance of the ordinal versus dichotomized modified Rankin Scale in predicting 5-year death, disability, and healthcare costs after ischaemic stroke: implications for clinical trials". *The 3rd European Stroke Organization Conference (ESOC).* May 18, 2017. Prague, Czech Republic.
- Ganesh, A., R. Luengo-Fernandez, R.M. Wharton, S.A. Gutnikov, L.E. Silver, Z. Mehta, P.M. Rothwell, for OXVASC. "Time-course of functional recovery and cause-specific mortality after ischaemic stroke: implications for trial design and interpretation". *The 3rd ESOC.* Prague, CR.
- Ganesh, A., R. Luengo-Fernandez, R.M. Wharton, S.A. Gutnikov, L.E. Silver, Z. Mehta, P.M. Rothwell, on behalf of OXVASC. "Time-course of functional recovery after acute ischaemic stroke and its relationship to cause-specific mortality: Implications for follow-up of stroke trials". *The 69th American Academy of Neurology Annual Meeting.* April 25, 2017. Boston, MA.
- Ganesh, A., R. Luengo-Fernandez, R.M. Wharton, S.A. Gutnikov, L.E. Silver, Z. Mehta, and P.M. Rothwell, on behalf of OXVASC. "One-month modified Rankin Scale predicts 5-year disability, death, quality-of-life, and healthcare costs in ischaemic stroke: a prospective cohort study". *International Stroke Conference.* February 23, 2017. Houston, Texas.
- Ganesh, A., R. Luengo-Fernandez, R.M. Wharton, S.A. Gutnikov, L.E. Silver, Z. Mehta, and P.M. Rothwell, on behalf of OXVASC. "One-month modified Rankin Scale predicts five-year disability, death, and healthcare costs in ischaemic stroke: implications for outcome measurement in hyperacute stroke trials". *The 2nd ESOC.* May 12, 2016. Barcelona, Spain.
- Ganesh, A., R. Luengo-Fernandez, R.M. Wharton, S.A. Gutnikov, L.E. Silver, Z. Mehta, and P.M. Rothwell, for OXVASC. "Health economic and clinical outcomes in thrombectomy-eligible acute ischaemic strokes". *The 2nd ESOC.* May 10, 2016. Barcelona, Spain.

Awards and Recognitions

- **American Academy of Neurology Resident Scholarship** 2018
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- **Junior Investigator Award, International Stroke Conference (ISC)** 2017
  Awarded for the paper: "Late functional recovery after lacunar stroke" based on my thesis
- **Top Breakthroughs, Canadian Stroke Congress (CSC)** 2017
  Recognizing the four top abstracts at CSC (for: "Ordinal analysis of the modified Rankin Scale predicts 5-year disability, death, and healthcare costs better than either dichotomy")
- **Best of Speciality Conferences, American Heart Association Scientific Sessions** 2017
  Recognizing top papers presented at ISC (for: "One-month modified Rankin Scale score predicts five-year disability, death, quality-of-life, and healthcare costs in ischemic stroke")
- **Best of Cerebrovascular Disease, American Academy of Neurology (AAN)** 2017
  Recognizing the four top-scoring stroke papers at the AAN annual meeting (for: "Time-course of functional recovery after acute ischaemic stroke and its relationship to cause-specific mortality")
- **Thomas Willis Postgraduate Research Prize, University of Oxford** 2017
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- **Junior Investigator Award, International Stroke Conference (ISC)** 2016
  Awarded for thesis project: "One-month modified Rankin Scale score predicts five-year disability, death, quality-of-life, and healthcare costs in ischemic stroke"

TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION

1.1 CHAPTER ABSTRACT

In this Chapter, I provide the clinical and scientific context for the work presented in the core chapters of this thesis (Chapters 2 to 6). First, I review the current state of short-term outcome measurement in acute ischaemic stroke trials, which forms the basis of how we decide whether stroke therapies are effective, and discuss how the modified Rankin Scale (mRS) measured at 3-months has come to be the most favoured outcome measure. Next, I briefly review the current literature on functional recovery and disability outcomes after stroke, highlighting uncertainties about late recovery beyond 3-months, and specific uncertainties regarding differences in outcome between men and women, and between lacunar and non-lacunar strokes. I further review the current knowledge and uncertainties regarding how short-term post-stroke disability, as captured in stroke trials (using the 3-month mRS), translates into long-term clinical and health economic outcomes: specifically long-term disability, mortality, health/social care costs and institutionalization, post-stroke dementia, and quality of life. I highlight the paucity of high-quality, population-based data to inform this question. Such disability-stratified data are crucial to guide clinical prognostication and cost-effectiveness analyses as well as the design, analysis, and interpretation of acute stroke trials. Such data is also essential to demonstrate the predictive validity of the mRS as an outcome measure for ischaemic stroke.

Therefore, in this thesis, I will use data from the Oxford Vascular Study (OXVASC), a population-based, prospective cohort study of ischaemic stroke, to examine the time-course of functional recovery and cause-specific mortality over 5-years of follow-up after ischaemic stroke, and relate this to 3-month mRS (Chapter 2). I will seek to clarify uncertainties regarding differences in stroke outcomes in men versus women (Chapter 3), and in long-term functional recovery in lacunar versus non-lacunar strokes (Chapter 4). I will also further examine the relationship between 3-month mRS and 5-year outcomes of death, disability, dementia, institutionalization, health/social care costs, and quality-of-life to inform the debate regarding how the mRS should be analyzed when it is used as a primary outcome measure in stroke trials (Chapters 5 and 6).

1.2 OUTCOME MEASUREMENT IN ACUTE ISCHAEMIC STROKE TRIALS

Over the last decade, marked improvements have been observed in the treatment and management of acute ischaemic stroke. These have come about through a series of multi-faceted interventions like increasing public awareness of stroke symptoms,[1, 2] rapid ambulance protocols,[3] and the reorganization of hospital systems of care around specialized stroke units and hyper-acute reperfusion services.[4, 5] Much of this change has been driven by the findings of large-scale, multi-centre, randomized controlled trials demonstrating the efficacy of rapid intravenous thrombolysis with alteplase,[6] hemicraniectomy for malignant middle cerebral artery (MCA) infarctions,[7] and stroke unit care.[8] Most recently, mechanical thrombectomy or endovascular therapy, in addition to intravenous thrombolysis, has been shown to be a highly efficacious but time-sensitive treatment for acute ischaemic strokes with proximal occlusion in seven randomized controlled trials,[9-15] prompting further systemic changes in the delivery of stroke care.[16, 17]

In addition to stroke-related mortality, stroke-related disability and functional decline is a grave concern for patients and carers, and as such stroke trials have sought to demonstrate a reduction in death and/or dependency outcomes, with treatments like thrombolysis having demonstrated a positive effect on the latter rather than the former.[18] Proving efficacy requires robust measures to capture post-stroke recovery and functional status. A 2006 systematic review of functional outcome measures in stroke trials identified 47 different outcome measures that had been used over time.[19] However, there were clearly three favourites – the modified Rankin Scale (mRS) was the most prevalent (64.3% of studies from 2001 to 2006) followed by the Barthel Index[20] (BI, 40.5%) and the National Institutes of Health Stroke Scale (NIHSS, 27.8%). The mRS was the most commonly used primary outcome, followed by the NIHSS and the BI. Of the remaining variety of outcomes, only the Scandinavian Stroke Scale (SSS) and the Glasgow Outcome Scale (GOS)[21] were used in >5% of trials, but even these featured as the primary outcome measure in <5% of trials. The National Institute of Neurological Disorders and Stroke Common Data Elements (NINDS CDE) group selected the mRS, NIHSS, BI, and European Quality-of-Life scale[22] as the most relevant outcome measures for use in acute stroke, with conditional support for the Functional Independence Measure (FIM) and GOS.[23] The BI and mRS were recommended as primary outcome measures for activities of daily living (ADLs) or functional status. The 90-day mRS has been recommended as the primary outcome measure for acute stroke trials by the European Stroke Organization (ESO) Outcomes Working Party.[24, 25]

Overall, the modified Rankin Scale (mRS) has emerged as the preferred method to measure stroke-related disability[26, 27] and has become the preferred outcome measure in acute stroke trials.[28, 29] The Rankin Scale was first published in 1957 by Dr John Rankin

(1923-1981)[30] in a Scottish Medical Journal paper describing early rehabilitative stroke medicine, using a grading system that assigned patients to one of 5 disability grades (1-5).[31] Sixty years later, the most frequently used modification of the scale adds two addition categories: 0 for no symptoms, and 6 for dead.[32] This “modified” Rankin Scale is a 7-point ordinal scale (Table 1). The Oxfordshire version focuses more on handicap, adding lifestyle restrictions and removing the emphasis on ambulation.[33]

A key determinant of the quality of an outcome measure is its validity – simply put, the degree to which it measures the concept it was intended to measure.[34] The mRS has good construct validity, reflecting aspects of stroke recovery that are directly important to the daily activities and quality of life of patients, aligning closely with the interests of stroke survivors, and capturing more information on quality of life than either the NIHSS or BI.[35] The mRS also has good convergent validity, corresponding well to other established measurements of stroke outcome and disability. Scores on the mRS are strongly correlated with those on the NIHSS and BI. For example, in 9,275 patients from the Virtual International Stroke Trials Archive (VISTA), the 3-month mRS had a Spearman rank correlation with the BI of –0.94 (negative since lower scores on the BI and higher scores on mRS indicate worse outcomes), and with the NIHSS of 0.91.[36] Importantly, the mRS also shows good clinical sensitivity or responsiveness. The different categories of the mRS distinguish clinically important states without a floor or ceiling effect; on the other hand, the BI suffers from both and the NIHSS also appears to have a ceiling effect.[24] The distribution of final outcomes on the BI is U-shaped, rendering it insensitive to subtle change between populations and forcing dichotomized analysis, and the NIHSS has a bimodal skewed distribution of final scores, whereas the mRS shows a more even distribution with enough categories to offer at least 95% of the discriminatory power of a continuous scale.[24]

The unique value of the NIHSS lies in documenting baseline neurological impairment from stroke and initial changes in the patient’s condition. Its item profiles, particularly at 24-hours, are individually associated with 3-month functional outcome and mortality in acute stroke patients including those receiving thrombolysis.[37] However, it is not considered an ideal primary outcome measure given that in addition to its poor statistical properties, it lacks meaning for patients, and does not closely reflect health or social care costs or quality of life. It thus appears to be best suited as a measure of stroke severity, versus stroke-related disability or functional status.[38] The BI is also limited by its reliance on motor function and basic activities of daily living (e.g. walking, dressing, grooming) whilst ignoring instrumental activities of daily living (e.g. meal preparation, shopping, handling money), quality of life, and cognitive function, which can be accommodated within the broad categories of the mRS.[24] However, the BI has excellent inter-rater reliability for standard administration after stroke[39] and remains an important outcome measure in stroke, particularly for rehabilitation

studies, although the same BI label is ascribed to several different forms of the scale.[40] A 20-point version of the standard 10-item scale has used in many studies,[41] but a 100-point version (scoring 0 to 100 with 5-point increments) has been used in several multicentre stroke trials and has been proposed as the uniform version of the BI in stroke trials.[40] There have been recent attempts to further reduce the items in the BI (down to 3) to minimize redundancy and enhance ease of use.[42]

The acceptance of 90-day status as captured in the mRS as the favoured post-stroke outcome measure is further reflected in the fact that various scales have been devised to predict this outcome. Examples include the SOAR (Stroke subtype, Oxfordshire Community Stroke Project, age, and pre-stroke mRS),[43, 44] modified-SOAR (adds initial NIHSS to improve early mortality prediction),[45] DRAGON (dense middle cerebral artery sign, pre-stroke mRS, age, glucose, onset-to-treatment, NIHSS),[46] and ASTRAL (Acute Stroke Registry and Analysis of Lausanne)[47] scales. A recent comparative analysis of eight different prognostic scales using individual patient-level data from VISTA (Virtual International Stroke Trials Archive) found that ASTRAL was most accurate at predicting 90-day mRS>2.[48]

Despite its currently favoured standing, the mRS also has its limitations. The mRS may have lower internal reliability than the NIHSS and BI as it combines motor and cognitive components with environmental and historical elements, and mixes impairment, disability, and handicap.[49] Whether or not a patient resumes their usual activities can depend on factors unrelated to stroke, like social interest, psychological motivation, and legal permissions.[24] Indeed, functional outcome measures like the mRS are not disease-specific; the disability captured does not necessarily reflect post-stroke disability alone and can be heavily influenced by the patient's co-morbidities and their sequelae. Functional decline is a common presentation of many disease states, particularly in older adults.[50] Pre-stroke mRS is thus itself a robust predictor of post-stroke outcomes like mortality, length of stay, post-stroke complications, and institutionalization, over and above any influence of the pre-stroke mRS on care pathways.[51, 52] The aforementioned SOAR and DRAGON scales' inclusion of the pre-stroke mRS represents an important acknowledgement of this contribution of pre-morbid disability to post-stroke death/dependency outcomes.

There also remain concerns about the external reliability of the mRS, with inter-observer studies similar to the design of large-scale trials demonstrating significant inter-observer variability.[25] To address these challenges, training programs for mRS assessment have been developed.[53] Standardized assessments for the mRS have also been developed, including a Structured Interview for the mRS and the Rankin Focused Assessment.[54-56] However, despite the availability of such training and structured interviews, there remains substantial inter-observer variability in the mRS grades awarded, even among experienced

researchers.[57, 58] Furthermore, an overly reductionist approach to mRS assessment can compromise its strength of having a global approach to patient ability, potentially losing important information about the patient's functioning in the unique context of their own lives that may not be captured by a focus on certain activities of daily living.[59] When used as the primary outcome measure in acute stroke research, it is recommended that the mRS be assessed at 3-months (90-days) after stroke onset or later, and that the interview be conducted by a trained rater involving both the patient and relevant caregivers.[24] Direct mRS interview with patients is preferred as there can be substantial inter-observer variability with proxy mRS assessments, some of which may have questionable validity;[60] an accurate mRS cannot be derived from standard hospital records.[61] To achieve further improvements in inter-observer reliability – and thereby potentially reduce study sample sizes – the central adjudication of mRS assessments in stroke trials, using recorded and (as needed) translated interviews scored by a committee, has been proposed.[62]

There is also debate in the stroke community as to whether ordinal (shift) or dichotomized analysis (mRS 0-1 versus 2-6 or 0-2 versus 3-6) is the ideal choice when using the mRS as a primary outcome measure.[63] It has been argued that ordinal analysis – assessing changes across the full range of the mRS – is statistically more powerful, more robust to variation in case mix among different trials, and better reflects the potential importance of functional gains at any level of the mRS.[24] A key aspect of this issue is what constitutes a clinically relevant shift in mRS. In examining the published short-term cost data, it would seem that any improvement in mRS would translate into healthcare savings within the 3-months after stroke.[64, 65] While this may appear to favour ordinal analysis, a typical ordinal approach would treat all state-transitions as equal, which can be a major limitation if improvements in different parts of the scale are unequal in their implications for long-term outcomes (this topic is explored in greater detail in Chapters 5 and 6). Long-term data on clinical and health economic outcomes from high-quality population-based studies can help inform this debate by examining whether there are meaningful differences in long-term outcomes going from each level of the mRS to the next – supporting ordinal analysis – or only between certain groupings of mRS levels (e.g. mRS 0-2 vs 3-6), supporting dichotomous analysis and/or a mixed approach. Such data could also help with the selection of the ideal binary cut-off when using a dichotomous outcome i.e. in choosing what would constitute a "good" outcome.[66] Central to this discussion, therefore, is another key aspect of validity – predictive validity, the prognostic value of an outcome measure, or the extent to which it translates into long-term outcomes of interest.[67]

In summary, the mRS, typically measured at 3-months post-stroke, is the most commonly used primary outcome measure in acute stroke trials, with easily understood grades

describing the range of global disability, good construct validity and convergent validity, and avoidance of major floor or ceiling effects, but with some concerns about reliability and an ongoing debate about how it should be analyzed in stroke trials. To explore the predictive validity of the mRS and inform the question of how it should be analyzed, a key component of this thesis (specifically Chapters 2, 5, and 6) will involving examining the relationship between 3-month mRS and 5-year clinical and health economic outcomes of disability (functional recovery), death, dementia, institutionalization, health/social care costs, and quality-of-life. This work will use data from the Oxford Vascular Study (OXVASC) – a population-based, prospective cohort study in Oxfordshire, the methodology of which will be presented first in Chapter 2, with additional details provided where relevant in the subsequent chapters.[68]

In the subsequent sections of Chapter 1, I will briefly review the current literature regarding these long-term outcomes, their relationship to early post-stroke disability (per measures like the 3-month mRS), and/or uncertainties regarding how they evolve over time.

SEARCH STRATEGY

To examine the relationship between the following long-term post-stroke outcomes and early post-stroke disabilities (particularly as captured on the mRS) in the narrative review presented in this Chapter, the electronic databases Medline/PubMed and EMBASE were searched using the terms “stroke” AND “disability” OR “Rankin Scale” in combination with the following additional AND terms, based on the outcome of interest, further limited to studies of humans in the English language:

1. “Recovery” OR “Rehabilitation”: This gave 9,129 results of which 46 were included in section 1.3 after removing duplicates, title search, abstract search, and full review.
2. “Mortality” OR “Death”: 11,737 results of which 11 were included in section 1.4.
3. “Economic$” OR “Cost$” OR “Institutionalization” OR “long-term care”: 2,953 results of which 39 were included in section 1.5.
4. “Dementia”: 1,127 results of which 22 were included in section 1.6.
5. “Quality of life” OR “Utility”: 3,215 results of which 19 were included in section 1.7.

To be included in this Chapter, studies needed to: (1) involve stroke patients, (2) include some assessment of functional status or disability within 3 months of stroke, and (3) report the outcome of interest for these patients beyond the 3-month period. The literature search is up-to-date as of 18 August 2017.

1.3 FUNCTIONAL RECOVERY AND RELATIONSHIP TO EARLY DISABILITY

The enduring burden of long-term disability in stroke patients has been reported in many cohort studies, with the overall proportion of functionally disabled (mRS>2) patients being about 31-36% at 1-year and 5-years after ischaemic stroke in the Oxfordshire Community Stroke Project (OCSP),[69] OXVASC,[70] the Auckland Stroke Outcomes study,[71] and the Perth Community Study.[72] Whereas major strides have been made in hyper-acute reperfusion therapies for ischaemic stroke like thrombolysis and endovascular therapy, the advancement of restorative treatments, aimed at promoting further functional recovery, has been slow. This is partly because evaluating the efficacy of restorative therapies is complicated by several barriers to patient recruitment (resulting in small-scale studies),[73] trial design, and analysis, including variable patterns of stroke care and concomitant behavioural training, longer time-windows than acute therapies, social/personal factors affecting subject retention, and fluctuating behaviour of participants.[74] Selection of appropriate patients is particularly challenging. Enrolling patients with too severe injuries can prevent the detection of any treatment effects owing to their limited capacity for neuroplasticity. However, choosing the right patients – and deciding whether or not a restorative therapy is effective – requires a sound understanding of the determinants of long-term functional recovery, particularly in relation to the known clinical characteristics of the patient such as their demographics, stroke subtype, and their short-term disability.

The time course of long-term functional recovery after stroke is an important consideration in this regard, and there have been a few studies examining this. The Copenhagen Stroke Study involved 1,197 acute stroke patients in a Copenhagen stroke unit and performed weekly examinations of neurological impairment (using the SSS) as well as functional disability (using the BI) at the time of admission through to the end of rehabilitation, with the evaluations repeated at 6-months.[75] The time-course of functional recovery was strongly correlated to the initial stroke-related disability (1-week BI), with milder strokes recovering faster. Overall, functional recovery was completed in 12.5 weeks from stroke onset in 95% of the patients, with 80% attaining their best BI score within 6-weeks. The results of this 1995 publication have highly influenced the conventional teaching that a reliable prognosis can be made in stroke patients within 12-weeks or 3-months post-stroke.[75] However, these hospital-based results may not apply to all patients in the community and it is uncertain whether further recovery might occur in a subset of patients beyond 6-months. A longer study with 1-year follow-up found that there was no significant neurological improvement in patients between 3 and 12-months post-stroke, with only slight improvements in quality-of-life scores, but included only MCA-territory stroke patients who were admitted to hospital; therefore, the results may not be generalizable to the entire stroke population.[76]

Clarifying the time-course of functional recovery in stroke is particularly important to inform the timing of the primary outcome assessment in clinical trials – a critical issue when seeking to identify beneficial stroke treatments. The NINDS CDE group has recommended that acute stroke studies intended to demonstrate durable clinical benefit should assess disability outcome at 90 days, but have also encouraged evaluation of outcomes beyond this time point.[23] However, excessive delay of outcome measurement may allow more confounding events unrelated to stroke to accumulate, attenuating potential treatment effects.[24] On the other hand, assessing the outcome too early could miss beneficial treatment effects if many patients are still in the process of recovery and their distribution is unequal in treatment and control arms. Therefore, in Chapter 2, I will seek to further clarify the time-course of long-term functional recovery after stroke by examining 1-year and 5-year mRS outcomes in relation to 3-month mRS in ischaemic stroke survivors.

Functional recovery after stroke is driven partly by structural and functional neuroplasticity within surviving neural elements.[77] Comorbidities like diabetes, extent of peri-ventricular white matter disease, and prior stroke are known to adversely affect recovery,[78-80] and genetic factors such as polymorphism of brain-derived neurotrophic factor may also account for inter-individual variability in post-stroke neuroplasticity.[81, 82] The influence of sociodemographic factors on functional recovery is less certain; it can be challenging to distinguish true biological or physiological differences from apparent differences related to confounding by comorbidities or socioeconomic factors like insurance coverage, educational level, household income, etc. that influence access to healthcare or rehabilitation services. For instance, whether increased age contributes to poorer recovery outcomes remains a controversial topic,[83-87] but there is compelling evidence from a multi-centre prospective cohort study that the influence of age on recovery may be minimal after adjusting for factors like functional and cognitive status at admission and social situation.[88] Similarly, it has often been argued that women are less likely to achieve functional independence and more likely to be disabled than men, although there does not appear to be a clear biological mechanism to explain such a difference.[89-91] Clarifying such uncertainties regarding differences in long-term functional recovery outcomes among key patient groups is essential to inform accurate clinical prognostication (including in relation to short-term outcomes like 3-month mRS), as well as potential policy decisions and further research into mechanisms of recovery. Therefore, in Chapter 3 of this thesis, I will examine one aspect of this issue by assessing for potential sex differences in the severity and prognosis of ischaemic stroke between men and women, whilst carefully taking pre-morbid differences (particularly functional status) into account.

In addition, although the extent of the initial injury is known to strongly influence the capacity for neuroplasticity,[92] it is unclear how different locations and subtypes of stroke differ in their

long-term recovery trajectories. An important unanswered question is how lacunar and non-lacunar strokes differ in their capacity for long-term functional recovery, especially beyond the typically studied trial endpoint of 3-months. The efficacy of restorative therapies is often evaluated in less-disabled patients, often with small subcortical (lacunar) strokes and isolated motor deficits, since enrolling patients with too severe injuries and associated cortical issues like aphasia or neglect can interfere with behavioural training and patient retention,[74] and potentially prevent detection of treatment effects.[93, 94] These studies are often uncontrolled, assuming that improvements seen beyond 3-months are treatment-related. However, recent insights into mechanisms of white-matter recovery – which remain relatively understudied[95] – suggest that there may be slower, time-dependent neuroplasticity mechanisms at play in these patients that facilitate recovery over longer periods of time than we have anticipated. These mechanisms include cortical activation and network modulation,[96, 97] contralesional cortical structural reorganization,[98] enhanced inter-hemispheric connectivity,[99] remyelination with gradual clearance of peri-lesional extracellular matrix components,[100] as well as modulation of recently-described “axo-myelinic” synapses as a means for injured axons to signal companion glia for metabolic support or alter myelin properties.[101] Recent MRI studies have also shown that stroke lesions disappear or shrink over 1-year in almost half of lacunar stroke patients,[102] and diffusion-tensor imaging studies have demonstrated that the axonal remodeling process initially gives rise to poorly-organized, randomly-oriented axons in the first few months post-stroke, followed by a gradual organization into single direction-oriented fibers.[103]

However, to date, the only convincing evidence of differences in recovery among stroke subtypes is that Total Anterior Circulation Infarcts (TACIs) unsurprisingly fare worst.[104, 105] Some studies have suggested that certain lacunar stroke syndromes might have a greater capacity for recovery; for instance, a 2003 study of 1,473 consecutive stroke patients by Arboix and colleagues found that dysarthria-clumsy hand syndrome was the only variable significantly associated with in-hospital recovery.[106] Other studies have found no significant differences in recovery at discharge in cortical or subcortical strokes.[107-109] Few studies have examined recovery beyond the acute or in-hospital phase; some found no differences[110, 111] whilst others suggested that lacunar strokes fare worse,[112-114] but were limited by small sample size and/or retrospective design. For example, a study by Smith and colleagues that serially assessed outcomes (including the BI) until 24-weeks post-stroke and reported no differences in recovery patterns, only included 25 patients with lacunar syndromes.[110] Therefore, in Chapter 4 of this thesis, I will seek to clarify the late functional recovery trajectories of lacunar versus non-lacunar strokes. If lacunar strokes indeed have a greater capacity for recovery beyond 3-months, then trials of restorative therapies that enroll these patients would need to be appropriately randomized and controlled.

1.4 LONG-TERM MORTALITY AND RELATIONSHIP TO EARLY DISABILITY

Death in the first 30 days after stroke is driven by three major causes – the direct effects of extensive brain injury like brain edema with transtentorial herniation, which peaks in the first week; secondary complications of stroke like pneumonia, pulmonary embolism, and sepsis which peak towards the end of the second week; and cardiac disease which causes deaths throughout the first month.[115, 116] Over the longer-term, at 1-year and beyond, the most frequent causes of post-stroke death are respiratory infections and cardiovascular disease.[117] Prior studies have found an association between life-threatening post-stroke complications and markers of severe disability. Early evidence came from OCSP, in which 51% of 30-day post-stroke deaths were due to complications of immobility (pneumonia, pulmonary embolism).[116] Examining complications over 30-months after stroke, a multi-centre study of 311 consecutive stroke inpatients found that functional dependency – as assessed using the FIM within 1-week of stroke – was significantly associated with the medical complications of infections and pressure sores.[118] These findings make it biologically plausible that stroke-related disability hastens long-term mortality.

Nine observational studies have previously examined the relationship between early stroke disability and long-term mortality, with key methodological limitations and conflicting results. In the Copenhagen Stroke Study, the BI at 1-week did not predict 6-month survival as well as impairment on the Scandinavian Stroke Scale, while in another single-ward study the BI did not predict 1-year mortality.[75] The Perth Community Stroke Study found that post-stroke disability on the BI (< 20/20) significantly predicted 5-year death, but the timing of the BI assessment varied considerably.[119] The remaining six studies examined the predictive value of the mRS for long-term mortality. A prospective admissions-based study at the University of Rome that only included minor strokes (30-day mRS ≤2), found that mRS of 2 was associated with a HR of 3.4 for 10-year mortality.[120] A Rochester-based retrospective medical record review of cause-specific mortality over 10-years or more after first ischaemic stroke, found that mRS of 4 or 5 was associated with higher mortality.[117] The Swedish Riks-Stroke study reported HRs of 1.7, 2.5, and 3.8 respectively for 3-year mortality for 3-month mRS of 3, 4, and 5 compared to 0-2.[121] However, it was limited by its register-based design and the consequent absence of initial or follow-up clinical evaluations, with the mRS being determined using a questionnaire mailed to the patients, which meant that the mRS could be determined for less than 70% of the registry patients. The self-report method also has only 76% accuracy.[122] A higher quality of evidence was provided by the Athens Stroke Registry, which examined the effect of the 3-month mRS on long-term survival in 3-month stroke survivors, and found that patients with worse mRS scores had higher mortality, after adjusting for comorbid risk factors (relative mortality risk increases of 18%, 55%, 80%, 157%, and 472% respectively for mRS 1 through 5 versus 0).While the study suffered from

the selection bias of only recruiting inpatients to a single centre, an important strength was that mRS was determined using a personal or phone interview and was missing only for 3.6% of patients. Interestingly, the initial stroke severity assessed using the SSS was not associated with survival beyond 3-months after adjusting for the mRS. This suggests that the 3-month mRS is a stronger predictor of long-term survival than initial stroke severity. Conflicting evidence was provided by a Japanese study of consecutive inpatients with ischemic stroke, in which mRS at discharge was associated with 3-year mortality on univariate analysis, but this association was seen on multivariate analysis only for cardioembolic stroke.[123] In addition to the limitations of intrinsic selection bias from the admission-based recruitment and the inconsistent time-from-event for evaluation of functional outcome, the mRS was missing for 18.9% of patients.

The most compelling evidence to date was provided in a combined analysis of three prospective cohorts in the UK – OCSP, the Lothian Stroke Register, and the First International Stroke trial – consisting of 7,710 ischaemic stroke patients registered between 1981 and 2000 and followed up for a maximum of 19 years.[124] In the combined mortality analysis of 6-month survivors, the median length of survival among functionally independent and dependent patients was 9.7 years and 6.0 years respectively. Functional independence remained a significant predictor in each cohort after adjustment for relevant comorbidities in a Cox regression model. However, only the OCSP cohort was assembled within a community-based incidence study, raising the issue of selection bias for the assembly of the other two cohorts that limited their ability to reliably evaluate long-term mortality outcomes for all ischaemic stroke. The scope of selection bias was greatest for the randomized International Stroke Trial. 17% of the Lothian cohort patients also ended up being excluded owing to missing mRS data. Furthermore, the disability assessment in the First international stroke trial was performed using “two questions” instead of the mRS.[125]

In summary, there remains a paucity of data from high-quality population-based studies to examine the predictive value of early stroke disability (3-month mRS) with respect to long-term mortality. In addition to the methodological weaknesses detailed above, studies to date have generally not accounted for the patient’s pre-morbid disability status or systematically assessed the causes of death, making it difficult to infer how much of the mortality effect is due to stroke-related disability versus that from confounding comorbidities. I will examine the time-course of cause-specific mortality after ischaemic stroke in OXVASC in Chapter 2, and further explore the relationship between 5-year mortality outcomes and the 3-month mRS in Chapters 5 and 6.

1.5 LONG-TERM CARE COSTS AND INSTITUTIONALIZATION AFTER STROKE

The healthcare cost for patients is known to increase sharply following a stroke. A health economic analysis of the Rochester Stroke Registry found that total costs in the year after stroke were 3.4 times those for the previous year.[126] A 2006 health economic analysis of the OXVASC cohort also demonstrated that hospital costs increase following a stroke compared to premorbid resource use, owing to hospitalizations linked to the index stroke as well as subsequent vascular events.[127] Most cost-analysis studies conducted to date have focused on the short-term, in-hospital costs of stroke, with the majority of these studies being retrospective analyses of different inpatient care databases of varying sizes.[128, 129]

There is some evidence that both the Barthel Index (BI) and the mRS are good predictors of acute stroke-related care costs.[130] The 90-day mRS was found to be closely related to hospitalization and institutional care home stays within the first 90-days after stroke, with weaker relationships found for the NIHSS and Barthel Index in the GAIN International trial.[64] Similarly, the Erlangan Stroke Project found that patients with good function – defined as a score of 95-100 on the Barthel Index at 3-months – accrued the lowest healthcare costs in the first 3-months after ischemic stroke, whether in an institution or not.[131] A study of 1,717 stroke patients from the GAIN International trial evaluated the mean duration of stay in the patients' own home over the first 90-days since stroke (90-day "home time") for different categories of the 90-day mRS (0 through 6), and found significant differences across all the categories with the exception of mRS 4 to 5.[65] These data have helped validate how 90-day functional disability measures in stroke reflect costs accrued up to that time point.

There have been a few population-based studies that have gathered longer-term cost data for patients for 12-months or more post-stroke.[132-140] In particular, previous work from the North East Melbourne Stroke Incidence Study (NEMESIS) cohort has shown the high lifetime costs of ischaemic stroke, demonstrating that basing lifetime cost estimates on 1-year data significantly underestimates the cost of stroke compared to 5-year data.[136] Outpatient and community care accounted for most of these costs. The 10-year cost outcomes of NEMESIS, albeit with a small sample of 283 participants, have demonstrated that the overall average annual direct costs at 10 years for first-ever ischemic stroke were comparable to those for survivors between 3-5 years, indicating that 5-year outcomes indeed provide a robust estimate of lifetime costs in this disease.[137] In addition to consistently demonstrating the high lifetime costs of ischemic stroke, studies like NEMESIS that have also included hemorrhagic stroke patients have shown that the longer survival and higher risk of recurrent events in ischemic stroke means that patients on average tend to use more resources over a longer period of time.[137] Previously published 5-year cost outcomes of stroke in the OXVASC study have also shown that although annual hospital

costs are highest in the first year after stroke, they remain higher than pre-morbid levels for survivors in subsequent years.[138] Institutionalization after stroke is another relevant long-term outcome, closely tied to the costs of care. Population-based studies in Oxford, London (UK), Perth (Australia), Auckland (New Zealand), and Erlangan (Germany) have observed rates of institutionalization in nursing-home or residential-care settings of 9-15% at 5-years post-stroke.[70, 71, 141-143] Higher rates exceeding 40% have been reported by studies that have recruited only hospitalized stroke patients with generally more severe strokes.[144-146]

Although costing studies in medicine often describe a single aggregate cost of a disease state, this approach is less helpful for diseases like stroke that have a range of potential disability outcomes (as reflected in the different mRS scores). Cost data stratified by disability are necessary for accurate cost-effectiveness analyses of stroke therapies, since potential savings are expected to be driven by reduced disability and associated long-term health and social care costs.[147] However, a recent systematic review of stroke costing studies in the published literature between 2004 and 2015 found that 13 studies incorporated the cost of stroke relating to an mRS score but only four studies reported costs by individual mRS categories.[148] The authors highlighted the need for more real world data investigating health economic outcomes in stroke, looking at not only short-term but also long-term costs across the full range of mRS scores. That being said, in the included studies, the costs consistently increased with increasing mRS scores, indicating that the mRS is a strong predictor of post-stroke care costs.[148]

Most of the included studies in the review only examined direct (typically hospital-based) medical costs, and did not examine costs beyond 1-year post-stroke: five studies recorded costs until discharge,[149-153] five till 90-days,[64, 154-157] and five for 6-18 months post-stroke (two studies included costs for multiple time-periods).[156-160] Costs of stroke are of course highly dependent on the duration of follow-up used, with costs relating to intervention, acute rehabilitation, and associated hospital costs being concentrated in the acute phase (usually the first 3-months) and then plateauing,[156, 160] whereas longer-term, social care costs like institutionalization or home-care costs, social services assistance, and productivity losses become more significant over subsequent years.[148] However, hitherto published long-term costing studies have generally not examined the relationship of these costs to post-stroke disability.[132] It is conceivable that 3-month mRS may not predict long-term (e.g. 5-year) costs as well as it predicts shorter-term costs owing to accumulation of non-stroke-related disability (and associated higher costs) in patients with initially lower mRS scores and/or earlier death (and lower costs) in more disabled patients. That being said, the OXVASC study previously demonstrated that 1-month mRS predicts 5-year institutionalization (>35% of patients with mRS of 3-5 institutionalized by 5-years versus <10% with mRS 0-2),

suggesting that short-term disability likely remains a strong predictor of long-term care costs.[70] Similarly, the Erlangan Stroke Project found that urinary incontinence on the BI at 7-days conferred a four-fold higher risk of 12-month institutionalization in consecutive inpatients.[161]

In summary, capturing health and social care costs across a longer time horizon (>1 year), in relation to short-term mRS outcomes, remains an important unmet need to elucidate the health economic impact of ischaemic stroke and the long-term cost-effectiveness of stroke therapies. In Chapters 5 and 6, I will examine the relationship between 3-month mRS and 5-year institutionalization and health and social care costs.

1.6 POST-STROKE DEMENTIA AND RELATIONSHIP TO EARLY DISABILITY

Cognitive impairment is a well-recognized long-term complication of ischaemic stroke that progresses to dementia in up to a third of patients.[162, 163] Ischaemic stroke may facilitate the onset of vascular dementia and/or aggravate prior cognitive decline, through the activation of both neurodegenerative and vascular mechanisms of damage, and the onset of cognitive decline may become apparent immediately after the stroke or there may be a delay.[164] Post-stroke dementia is a major contributor to post-stroke dependency[165, 166] and mortality.[167] The systematic study of post-stroke dementia and its risk factors is complicated by substantial heterogeneity among studies in terms of setting, evaluation of pre-stroke dementia (and inclusion/exclusion of such patients), whether first-ever and/or recurrent strokes were included, attrition on follow-up, and the method by which dementia was diagnosed.[168-170]

With respect to the means of diagnosis, cognition assessments are infrequently used in stroke research,[171] and there is substantial variation in the measures used in different settings; some commonly-used tools are not validated or appropriate for use in stroke,[172] many brief screening assessments are specific but not sensitive,[173] and even relatively brief tools have substantial incompletion rates.[174] Tools like the Addenbrooke's Cognitive Examination-Revised, Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and the Rotterdam-CAMCOG (Cambridge Cognitive Examination) appear to have similar accuracy for the detection of post-stroke dementia or multi-domain cognitive impairment with no test being clearly superior and no evidence that tools that take longer to administer perform better.[175] The MoCA offers a short assessment time, and the adapted cut-off of 22/30 versus the conventional 26/30 appears to improve specificity without compromising sensitivity.[175] As for informant cognitive assessments, there are few high-quality data but the IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) appears to have similar test properties as other screening tools for dementia and is a specific but insensitive prognostic tool.[176] When used in older adults, the 16-item version

of the IQCODE carries lower test burden without loss of accuracy;[177] in the hospital setting, it is helpful specifically for ruling out those without evidence of cognitive decline.[178]

Notwithstanding such methodological challenges, a systematic review and meta-analysis of 73 cohort studies of post-stroke dementia in 7,511 patients found that predictors of post-stroke dementia included demographic characteristics (older age, low educational attainment, pre-stroke cognitive decline and disability), vascular risk factors (diabetes, atrial fibrillation), and the number of strokes (prior stroke, multiple infarcts, recurrent strokes).[179] However, many of the predictors were related to the initial stroke itself – left hemisphere location, dysphasia, infarct volume, post-stroke complications (incontinence, early seizures, acute confusion, hypoxic ischaemic episodes, and hypotension), as well as stroke severity, as captured in measures of neurological impairment like the NIHSS, SSS, Canadian Neurological Scale (CNS), or European Stroke Scale (ESS).[179] A recent VISTA analysis of demographic and clinical variables associated with post-stroke cognitive impairment (defined as a MMSE score ≤26) in 5,435 patients found that in addition to age, stroke severity, hypertension, diabetes, and type of event (ischaemic stroke, haemorrhagic stroke, TIA), the severity of the presenting stroke and the presenting symptom (in particular, leg paralysis and aphasia) was associated with cognitive impairment at 1-year and 3-years after stroke.[180] At present, no specific biomarkers have been shown to reliably discriminate patients at risk of post-stroke dementia from those with better prognosis or to discriminate Alzheimer's Disease dementia from post-stroke dementia.[181] As the overlap between the traditionally divided classifications of vascular dementia and Alzheimer's Disease becomes better elucidated, the role of small-vessel disease and radiological features like medial temporal lobe atrophy (traditionally considered reflective of Alzheimer's Disease) in the evolution of post-stroke cognitive impairment is also being examined. For instance, a recent analysis of 234 patients with stroke or TIA in VISTA found that small-vessel disease features were associated with medial temporal lobe atrophy (seen in 44% of the patients), and that this atrophy – rather than small-vessel disease markers – was most associated with post-stroke cognitive impairment.[182] Psychological symptoms that influence cognition, like depression and anxiety, are often not tested in stroke patients, but prior studies have found a high prevalence (around a quarter) of anxiety and depression in this population.[183]

Although the relationship between post-stroke functional status measures like the 3-month mRS and post-stroke dementia outcomes is less well described, the prediction of post-stroke dementia by stroke severity suggests that 3-month mRS is also likely to be a strong predictor. Quantifying this relationship can better inform clinical prognostication as well as cost-effectiveness analyses of stroke therapies. In Chapter 6, I will also evaluate the relationship between 3-month mRS and 5-year post-stroke dementia outcomes.

1.7 QUALITY OF LIFE AND RELATIONSHIP TO EARLY DISABILITY

Quality of life (QOL), besides just the quantity of survival, is now recognized as an important component of evaluating the outcomes of diseases like stroke. A number of measures have been developed to measure QOL, but the selection of appropriate instruments for stroke has been hindered by the relative absence of stroke-specific measures that are also patient-centered and psychometrically robust.[184] The Newcastle Stroke-Specific Quality of Life Measure (NEWSQOL) is a patient-derived, interviewer-administered measure that was devised by identifying 11 relevant quality-of-life domains through interviews with stroke patients, which include: feelings, activities of daily living/self care, cognition, mobility, emotion, sleep, inter-personal relationships, communication, pain/sensation, vision, and fatigue. It has acceptable reliability and validity.[185] Other stroke-specific measures include the Frenchay Activities Index,[186] the Niemi QOL scale,[187] Ferrans and Powers QOL Index–Stroke Version,[188] the Stroke-Adapted Sickness Impact Profile [SA-SIP30],[189] and the Stroke Impact Scale (recently shortened).[42] The European QOL scale (EQ-5D), albeit not a stroke-specific measure, has been found to be a valid quality-of-life measure after stroke.[190]

It would seem intuitive that higher levels of disability in stroke are associated with a poor quality of life. In addition to the care needs necessitated by higher levels of disability, such patients would also likely forgo such aspects of life as employment and leisure. Indeed, the 3-year POISE (Psychosocial Outcomes In Stroke) study in 20 Australian stroke units found that independence in activities of daily living at 28-days (per the Frenchay Activities Index) was the strongest predictor of return to paid work within 12-months of stroke.[191] Combining life expectancy data with quality-of-life assessments could therefore provide a richer reflection of the long-term outcomes after stroke, particularly in relation to the 3-month mRS. Quality-adjusted life-years (QALYs) provide such a combined estimate of both length and quality of life. Quality-adjusted life expectancy (QALE, expressed in QALYs) can be an especially powerful means to analyze clinical trial results in stroke, being intuitively understandable and applicable to a wide range of treatments.[192] Although the duration of disability and life years lost due to premature death linked to disability are critical aspects of stroke outcome, current stroke trial outcome measures like the 3-month mRS are single-time-point snapshot metrics that do not take these long-term sequelae of the disease into account. Since QALYs are explicitly designed to reflect both premature disease-related mortality and limited scope in remaining life years, long-term data in this regard from high-quality population studies can help better inform the interpretation of stroke trials. However, none of the aforementioned studies examining the relationship between early disability and long-term mortality in stroke have examined the QOL for the years lived by the survivors at each level of disability.

The calculation of QALYs requires reliable mortality data for a given health state, reliabile measurements of patients' health-related QOL on at least two occasions, and accurate health utility estimates. Health utility estimates define and assign preference weights to each possible health state using a scale of <0 to 1, with 0 equivalent to death, 1 representing perfect health, and negative values representing states deemed worse than death. They may be derived using diverse QOL measures like the European Quality of Life Scale (EQ-5D),[190] Health Utilities Index (HUI),[193] or the Assessment of Quality of Life (AQoL),[194] using a variety of methods (standard gamble, time-tradeoff, visual analogue scale)[195] from various populations. Value sets are typically collected from the general population. For example, EQ-5D responses were converted into utilities using UK population tariffs developed in the 1990s,[196] when a sample of health states was valued using the time-trade-off method by 3,337 members of the general public,[14] and regression equations were fitted to obtain a tariff for all 243 possible EQ-5D health states, generating tariffs ranging from -0.59 to 1.[196] In a 2010 analysis of data from the OXVASC study, mRS scores were mapped to EQ-5D scores in stroke/TIA survivors and then to utilities using utility values for these 243 possible EQ-5D health states.[197]

Owing to sociocultural differences in views and values, health utilities can vary considerably from country to country (and would likely vary considerably among different groups within each country). Therefore, whilst the application of a single value set to international populations is commonly practiced, it is limited by between-country differences in health-related QOL as well as differences in healthcare costs, available social support, and perceptions of disability.[198] Recently, the VISTA collaborators used EQ-5D data to calculate health utilities stratified by 3-month mRS, applying published value sets for different countries to generate these utilities and thereby describing expected variability when applying diverse value sets to international populations. Importantly, the authors demonstrated that the 3-month mRS scores accounted for 65-71% of the variation in the generated utilities.[198] Although the application of country-specific value sets improves the relevance of generated utilities for a given country, it can be challenging for pooling international data for analysis.

Despite the paucity of high-quality QALE data for different mRS levels from population studies, a couple of efforts have been made to extrapolate this information from extant sources. A 2010 study analysed the NINDS rtPA trials using a disability-adjusted life year (DALY) metric and projected that rtPA treatment would generate 1,280 DALYs per 1,000 patients treated.[192] This study used the mRS-specific mortality HRs published by the aforementioned Riks-Stroke (Swedish) and Lothian Stroke Register (Scottish) studies,[121, 124] and was further limited by seeking to apply this data to clinical trial findings performed in the United States population. Age-specific life expectancy data from the 2004 US life table,[199]

and disability weights generated from a 9-member panel of stroke experts for each mRS level[200] were used to calculate, respectively, the years of life lost (YLL) and years of healthy life lost because of living with disability (YLD). Data on modification of the disability effect by patient age with respect to mortality was lacking, which meant that the authors had to apply the same mortality HR across all patient ages. Similarly, a 2014 study examined the cost-effectiveness of rtPA using data from a meta-analysis of rtPA trials,[201] a QALY metric, and mortality data from the Riks-Stroke study, and reported a gain of 0.39 QALYs per patient with a lifetime cost-saving of $25,000 in their model.[202] Their limitations notwithstanding, these studies illustrate how disability-stratified QALY metrics can be meaningfully applied to clinical trials in acute stroke. In Chapter 6, I will also examine the relationship between 3-month mRS and 5-year quality-adjusted life expectancy after ischaemic stroke.

1.8 SUMMARY OF THESIS OBJECTIVES

In this introductory chapter, I have highlighted uncertainties regarding late functional recovery beyond 3-months after ischaemic stroke, as well as specific uncertainties regarding differences in outcome between men and women, and between lacunar and non-lacunar strokes. I have also highlighted the paucity of high-quality, population-based data regarding how short-term post-stroke disability outcomes, as captured in stroke trials using the 3-month mRS, translates into long-term outcomes of interest. Such disability-stratified data are crucial to guide clinical prognostication and cost-effectiveness analyses as well as the design, analysis, and interpretation of acute stroke trials. Such data is also essential to demonstrate the predictive validity of the mRS as an outcome measure for ischaemic stroke.

As noted previously, I will seek to clarify some of these uncertainties through the work presented in this thesis, using data from the Oxford Vascular Study (OXVASC) – an ongoing population-based, prospective cohort study of the incidence and outcome of all acute vascular events in a population of 92,728 individuals, irrespective of age, registered with 100 general practitioners in 9 general practices in Oxfordshire, UK. The specific objectives of this thesis, introduced throughout Chapter 1, are summarized below:

1. To examine the time-course of functional disability and cause-specific mortality in ischaemic stroke, relating 3-month mRS to 5-year disability and mortality (Chapter 2)
2. To assess potential differences in the severity and prognosis of ischaemic stroke/TIA between men and women, whilst carefully taking age and pre-morbid functional status into account (Chapter 3)

3. To compare rates of functional recovery beyond 3-months in lacunar versus non-lacunar ischaemic strokes, hypothesizing that lacunar strokes are more likely to demonstrate late recovery (Chapter 4)
4. To compare the predictive power of the ordinal mRS versus its dichotomized forms (0-1/2-6, 0-2/3-6) for 5-year disability, survival, and health/social-care costs after ischaemic stroke, and examine the proportion of patients with pre-morbid mRS>1 or >2 who would risk exclusion with dichotomous approaches (Chapter 5)
5. To derive probability weights for 5-year death, institutionalization, and dementia outcomes, as well as 5-year cost and QALE weights, for the various 3-month mRS scores to inform trial analyses and clinical prognostication (Chapter 6)

Population-based cohort studies like OXVASC are the gold standard when evaluating outcomes after stroke.[203] The core methodology of the OXVASC study will be first presented in Chapter 2, and additional details regarding specific outcome assessments will be presented in subsequent Chapters of the thesis as indicated.

I decided to focus on ischemic stroke, the most common form of stroke, rather than haemorrhagic stroke, in this thesis. Given the differences in pathophysiology between ischemic and haemorrhagic stroke, it is quite possible that the relationship between the different levels of the 3-month mRS and various long-term outcomes differ for ischemic versus haemorrhagic stroke. Haemorrhagic strokes are generally more severe than ischaemic strokes, with higher 3-month mortality,[204] though survivors have been found to have greater improvements in functional status than ischemic stroke patients of the same severity over the course of inpatient rehabilitation.[205,206] Whereas few studies have examined longer-term outcomes in haemorrhagic strokes, these strokes have been found to have higher 2-year healthcare costs than ischemic strokes for a given level of functional disability.[207] In light of these potential differences, the long-term clinical and health economic outcomes of haemorrhagic strokes merit further dedicated analyses.

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1.10 TABLES

Table 1. Categories of the modified Rankin Scale (mRS)[208]

mRS score/category	Description
0	No symptoms at all
1	Able to carry out all usual duties and activities, despite symptoms
2	Unable to carry out all previous activities, but able to look after own affairs without assistance (Slight Disability)
3	Requiring some help, but able to walk without assistance (Moderate Disability)
4	Unable to walk without assistance and unable to attend to own bodily needs without assistance (Moderately Severe Disability)
5	Bedridden, incontinent, and requiring constant nursing care and attention (Severe Disability)
6	Dead

CHAPTER 2

Time-course of evolution of disability and cause-specific mortality after ischaemic stroke

2.1 CHAPTER ABSTRACT

Outcome in stroke trials is often based on 3-month modified-Rankin-scale (mRS). How 3-month mRS relates to longer-term outcomes will depend on late recovery, delayed stroke-related deaths, recurrent strokes, and non-stroke deaths. In this chapter, I evaluated 3-month mRS and death/disability at 1-year and 5-years in the OXVASC study.

In 3-month survivors of ischaemic stroke (2002-2014), I related 3-month mRS to disability (defined as mRS>2) at 1-year and 5-years, and/or death rates, using logistic and Cox regressions adjusted for age and sex. Accrual of disability and index-stroke-related and non-stroke deaths in each post-stroke year was categorized according to 3-month mRS. Analyses were replicated in the clinically relevant subgroups of treatable major strokes, atrial fibrillation-related strokes, and lacunar strokes.

Among 1,606 patients with acute ischaemic stroke, 181 died within 3-months but 126 index-stroke-related deaths and 320 other deaths occurred during the subsequent 4,866 patient-years of follow-up up to 5-years. Although 69/126 (54.8%) post-3-month index-stroke-related deaths occurred after 1-year, mRS>2 at 1-year strongly predicted these deaths (adjusted hazard-ratio: 21.94, 95% confidence interval [95%CI] 7.88-61.09, p<0.0001). Consequently, 3-month mRS>2 was a strong independent predictor of death at both 1-year (aHR: 6.67, 4.16-10.69, p<0.0001) and 5-years (2.93, 2.38-3.60, p<0.0001). Although mRS improved by ≥1 point from 3-months to 1-year in 317/1,266 (25.0%) patients with 3-month mRS≥1, improvement in mRS after 1-year was limited (improvement by ≥1 point: 114/970 [11.8%]; improvement to mRS≤2: 17/332 [5.1%]).

These findings reaffirm use of the 3-month mRS outcome in stroke trials. Although later recovery does occur, extending follow-up to 1-year would capture most long-term stroke-related disability. However, administrative mortality follow-up beyond 1-year has potential to demonstrate translation of early disability gains into additional reductions in long-term mortality, without much erosion by non-stroke-related deaths. These findings also imply that treatments that reduce acute stroke severity (e.g. thrombolysis and thrombectomy) or that prevent disabling strokes (e.g. anticoagulation for atrial fibrillation) are likely to promote sustained independence and long-term survival.

2.2 INTRODUCTION

Acute stroke treatments sometimes involve a trade-off between a reduction in 3-month post-stroke disability and an increase in 7-day mortality.[1,2] The extent to which the increase in early mortality is further offset by recovery from disability or reductions in mortality after 3-months remains uncertain.[3] There may be magnification of treatment-associated differences in mortality from stroke-related causes beyond the acute period, but there may also be erosion from non-stroke-related deaths. Post-stroke disability will be similarly affected by late recovery versus subsequent accrual of non-stroke-related disability. Longer-term follow-up of IST-3 showed that the reduction in 6-month disability seen with thrombolysis was still present at 18-months follow-up,[3] and that thrombolysis reduced mortality from 3-12 months follow-up, which difference was maintained at 3-years,[4] suggesting that follow-up beyond 3-6 months could be informative in other acute stroke trials. However, recommendations for stroke trial design have been inconsistent regarding the appropriate duration of follow-up. The second Stroke Treatment Academic Industry Roundtable (STAIR) encouraged follow-up beyond 3-months to evaluate late treatment effects,[5] as did the National Institute of Neurological Disorders and Stroke (NINDS),[6,7] but the most recent STAIR even proposed that a 7-day assessment might be preferable as a primary outcome measure given the risk of 'contamination' by non-stroke-related morbidity.[8]

Prior cohort studies have suggested an association between post-stroke functional status and long-term mortality, but some were limited by retrospective design,[9] and others by possible selection bias,[10-13] absence of a consistently-timed interview-based disability assessment, and missing data.[10,12,13] Moreover, these studies did not establish how many deaths beyond 3-months or 1-year were related to the index stroke and might thus be preventable by an intervention that reduced severity.

As discussed in Chapter 1, the most commonly used primary outcome measure in acute stroke trials is the modified Rankin Scale (mRS),[14,15] at least partly because it is simple to administer, has good reproducibility and avoids major floor or ceiling effects.[16] Although most functional recovery post-stroke happens in the first few months,[17] recovery beyond 6-months does occur,[18] but there are few published data on the relationship between early mRS and long-term disability. Clarifying the time-course of evolution of disability and mortality, relative to 3-month mRS, should inform the optimal durations of both clinical follow-up in acute stroke trials and data collection on service use, care costs and utilities

for cost- effectiveness analyses. I therefore determined the associations between 3-month mRS in ischaemic stroke patients and long-term disability and survival, both overall and in clinically relevant subgroups, and examined the evolution of disability and cause-specific mortality to 5-years follow-up in the Oxford Vascular Study (OXVASC).

2.3 METHODS

Study Population

The OXVASC population comprises of 92,728 patients registered under about 100 primary-care physicians in 9 general practices across Oxfordshire, United Kingdom. Study methods have been previously published.[19] Recruitment began on April 2002 and is ongoing. Patients in whom stroke was suspected were ascertained using multiple overlapping methods of "hot" and "cold" pursuit to achieve near complete ascertainment of all individuals with transient ischaemic attack (TIA) or stroke. These include: 1) a daily, rapid access "TIA/stroke clinic" to which participating general practitioners and the local accident and emergency department refer all individuals with suspected, but not hospitalized TIA or stroke; 2) daily searches of admissions to the medical, cardiology, stroke, neurology , and other relevant wards; 3) daily searches of the local accident and emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner's reports for out of hospital deaths; 6) monthly searches of general practitioner diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals. Direct assessment of rates of ascertainment has shown that it is near-complete.[20]

Stroke Diagnosis

Patients were assessed urgently by study clinicians and considered for inclusion. Stroke was diagnosed according to the World Health Organization definition.[21] Briefly, a stroke is defined as rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and/or with subarachnoid haemorrhage), loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. Presentations that met these critera but lasted less than 24 hours were classified as TIAs. Assessments of neurological impairment, presentation, medical and social history, and risk factors were made. Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS), as soon as possible after the event. All case information was subsequently reviewed by a senior neurologist (Professor Peter M. Rothwell) on a daily basis and imaging results were assessed by the

study neuroradiologist. The presumed aetiology of stroke was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[22] The ascertainment forms for the OXVASC study are presented at the end of the thesis (see pages 233-254).

Patient Follow-up and mRS Assessment

Patients were followed up face-to-face by a study nurse or physician either in a hospital clinic or at home at 1-month, 3-months, 6-months, 1-year, and 5-years after their event. These follow-up assessment forms for OXVASC are also presented at the end of this thesis (see pages 255-309). Recurrent vascular events and functional status (mRS) were recorded at each follow-up. Raters were all trained in the use of the mRS using an instructional DVD with accompanying written materials produced by the University of Glasgow that has been previously used in large-scale clinical trials.[23]

Pre-morbid disability was assessed using the mRS at the time of ascertainment, based on interviews with the patients and/or carers. Since my analyses sought to predict death based on 3-month mRS, patients with a 3-month mRS of 6 were excluded. Disability at 3-months, 1-year, or 5-years was defined as mRS>2 (score of 3, 4, or 5, excluding 6 i.e. death), as is often the case in acute stroke trials,[16] at the respective follow-up assessment.

Patients who moved out of study area were followed-up by telephone. Additional information was obtained from a carer in patients with significant impairment of cognition or speech. Recurrent events were also identified by daily OXVASC ascertainment and by review of administrative diagnostic codes from hospital and primary care records.

Ascertainment of Deaths and Causes of Death

Deaths and causes of death were ascertained through monthly visits to the coroner's office, review of all death certificates in the study's general practices, practice-specific listings of all ICD-10 (International Classification of Diseases) death codes registered centrally, and daily identification via bereavement officers of patients who were dead on arrival at the hospital or who died soon after. If a patient died before assessment, an eyewitness account of the clinical event was obtained whenever possible and any relevant records were reviewed. If death took place outside the hospital or before investigation, the autopsy result was reviewed. Clinical details were sought from primary-care physicians or other clinicians on all deaths occurring in this cohort of ischaemic stroke survivors.

A list of all deaths occurring in Oxfordshire with a vascular ICD-10 code in any position on the death certificate was generated by the local Department of Public Health. These anonymised

data were provided on a three-monthly basis. After a patient died their GP notes were sent to central storage at the Thames Valley Health Authority headquarters. These notes were used to collect further past medical history, supplement missing data, and ensure accurate diagnosis of cause of death.

Deaths were coded as related to the index stroke if they were deemed to either be directly related to the stroke, or were hastened by complications of the stroke. I took recorded specific post-stroke impairments into account to decide whether a death was potentially index-stroke-related when associated with another direct cause of death. In order to follow a systematic approach, I developed the following criteria based on discussions with Professor Peter Rothwell regarding both their reasonableness and feasibility for application within OXVASC:
1) Aspiration pneumonia - this was coded as index-stroke-related if the patient was documented to be at risk of aspiration owing to new dysphagia as a result of their index stroke.
2) Pulmonary embolism (PE) – this was coded as index-stroke-related if the patient was documented to be newly bed-ridden or have markedly restricted mobility following their stroke, and the PE was not clearly associated with another convincing aetiology like cancer or a recent operation.
3) Sepsis from a urinary source (urosepsis) – this was coded as index-stroke-related if the patient was documented to have new urinary incontinence or bladder dysfunction after their stroke, and/or markedly restricted mobility, and their attending physician suspected that this contributed to their infection.
4) Vascular dementia – this was coded as index-stroke-related if the patient was documented to have new cognitive decline following their index stroke, and no other cause of dementia was identified, and dementia was recorded as one of the causes of death by their attending physician.
5) Fall – this was coded as index-stroke-related if the patient was documented to have new impairments in mobility and balance as a result of the index stroke, and their death was the result of a post-fall injury (such as a fatal traumatic hemorrhage or fracture).

I further coded deaths deemed unrelated to the index stroke, as being related to: (1) a recurrent ischaemic or haemorrhagic stroke, either acutely (<30 days) or non-acutely as a result of further stroke-related disability (ICD I607, I609, I610, I619, I620, I634, I635, I639, I64X, I678, I679, I694, I698); (2) a cardiac cause if the primary cause of death was deemed to be related to heart disease, including acute coronary syndromes (ICD I219, I251) and congestive heart failure; (3) pneumonia or other chest infection; (4) sepsis or other severe infection including meningitis and endocarditis; (5) dementia; (6) PE; (7) peripheral vascular disease (ICD I709,

I710, I711, I713, I714, I718, I719 , I728, I739); (8) cancer; (9) renal failure from acute or chronic kidney disease; (10) gastro-intestinal bleeding; (11) fall or similar trauma, including traumatic subdural haematoma or traumatic subarachnoid haemorrhage; (12) chronic obstructive pulmonary disease or other chronic lung disease; or (13) other cause, if the death did not fall into any of the aforementioned categories.

If the patient had suffered a recurrent stroke before their death, then the death was not coded as being index-stroke-related owing to the added uncertainty of whether stroke-related impairments directly causing or hastening death stemmed from the index stroke or the recurrent one.

Ethical Approval

The study was approved by the Oxfordshire Research Ethics Committee. All strokes were recorded but only patients consenting to follow-up, or with assent through a carer if unable to provide informed consent themselves, were included in the analysis.

Statistical Analyses

Consenting patients recruited from April 2002 to March 2014 and surviving for 3-months after their first stroke in the study period ('index' stroke) were included in the analysis, to focus on the period beyond 90-days post-stroke that is not conventionally captured in stroke trials. Analyses were censored at 15-May-2017.

The proportions of patients who were (a) disabled, (b) dead/disabled, (c) dead from all causes, and (d) dead from index-stroke-related causes at 1, 2, 3, 4, and 5-years were calculated and categorized according to the 3-month mRS (or the mRS between 1 and 3-months if the 3-month mRS was missing). Logistic regression was used to adjust the associations of 3-month mRS and long-term outcomes for age and sex. Survival to 5-years after index stroke was assessed using Kaplan-Meier techniques categorized according to 3-month mRS. Differences in survival in relation to 3-month mRS scores were assessed using age- and sex-adjusted Cox's proportional hazards models.[24]

The above analyses were repeated for the subgroups defined below:

1) **Treatable major strokes** or **Non-hyperacute/minor strokes** – The former were defined as patients seeking medical attention within 6 hours of symptom-onset, presenting either to hospital or emergency services with NIHSS≥5. These were "minimal criteria" to capture the subset that have been the focus of hyperacute stroke trials and would potentially be eligible for

thrombolysis/thrombectomy.[25,26] The remaining patients were classified as non-hyperacute/minor strokes, to facilitate direct comparison.

2) **AF-related** or **non-AF-related strokes**: The former were defined as patients with a pre-stroke diagnosis of AF or AF at presentation, meeting criteria for cardioembolic aetiology per the TOAST classification system.[22]

3) **Lacunar** or **non-lacunar strokes**: Classified by TOAST criteria for small-vessel occlusion.[22]

I was specifically interested in examining the long-term death and/or disability outcomes of AF-related and Lacunar strokes as they have been the focus of several recent stroke trials, particularly of secondary prevention strategies.[27,28]

I also plotted changes in mRS between 3-months and 1-year, and between 1-year and 5-years after the index stroke for all patients, categorized according to 3-month mRS.

Statistical analyses were performed using STATA 13.1.

2.4 RESULTS

Of 1,606 patients with an index acute ischaemic stroke, 181 (11.3%) died within 3-months (Figure 1). Baseline characteristics of all 3-month survivors are shown in Table 1 (subgroups in Table I, Appendix). Complete baseline and follow-up data were available for 1,403 (98.5%) of the 1,425 3-month survivors. Of the 22 survivors who were excluded, 18 refused follow-up and 4 did not have mRS assessed before 3-months follow-up.

Deaths and causes of death

At 5 years, 465 (32.6%) 3-month survivors were dead and 214 (27.3%) of those alive were disabled. 173 (12.1%) patients had not yet reached 5-year follow-up, but 1-year follow-up data were available for 169, including everyone with a 3-month mRS. Ascertainment of causes of death was complete for 446 (95.9%) 3-month survivors. There were 126 post-3-month index-stroke- related deaths and 320 other deaths during 4,866 patient-years of follow-up from 3-months to 5-years. The leading causes of death not related to the index stroke were cancer and cardiac causes (Table 2), accounting for 78 (17.5%) and 71 (15.9%) deaths respectively, followed by pneumonia (52, 11.7%) and recurrent stroke (44, 9.9%). Aspiration pneumonia was the most common associated cause of post-3-month deaths deemed to be related to the index stroke (69, 54.8%).

With each subsequent year, index-stroke-related deaths accounted for a decreasing proportion of new deaths: 57 (41.3%) deaths from 3-months to 1-year post-stroke were deemed to be index-stroke- related, versus only 5 (7.4%) in the fifth year. Although 69/126 (54.8%) post-3-month index-stroke-related deaths occurred after 1-year, the mRS at 1-year strongly predicted these subsequent stroke-related deaths (age- and sex-adjusted HR for mRS>2 vs 0-2: 21.94, 95%CI 7.88-61.09, p<0.0001).

The 3-month mRS scores also predicted 1-year and 5-year mortality (Figure 2 A-B). Kaplan-Meier analyses showed clear early separation of survival curves for 3-month mRS>2 versus 0-2, which persisted at 5-years (Figure 3). By 5-years, the probability of survival was similar for patients with 3-month mRS scores of 3 and 4, with an additional drop observed for mRS 5.

On examining the time-course of 1-5 year deaths, categorized according to 3-month mRS, the cumulative death rate during each year remained higher for mRS>2 versus 0-2, with a step-change from mRS 2 to 3 (Figure 4A). However, mortality differences between mRS 0-2 and >2 – and among mRS categories 3, 4, and 5 – were most pronounced in year-1. Non-stroke deaths occurred less frequently in year-1 in the lower mRS categories, but were less clearly distributed in subsequent years (Figure 4B-C). The rising burden of non-stroke deaths in the lower disability categories accounted for some erosion of mortality differences among mRS categories over time.

On age- and sex-adjusted Cox regressions, 3-month mRS>2 strongly predicted 1-year, 2-year, 3-year, 4-year, and 5-year mortality (Tables II and III, Appendix), although the adjusted hazard ratio for mRS>2 vs 0-2 from 3-months to 1-year (6.67,95%CI 4.16-10.69) was greater than 3-months to 5-years (2.93,2.38-3.60,p<0.0001). Upon using the full range of the mRS in the age- and sex-adjusted Cox models for 1-year and 5-year mortality, the mRS gained predictive value with each increment of the scale (Table IV, Appendix).

Disability and combined disability/death outcomes

Among 5-year survivors, 3-month mRS also predicted disability at 5-years (Figure 2C). In particular, there was a step-change between mRS 2 and 3, with 88/125 (70.4%) of those with 3-month mRS of 3 remaining disabled at 5-years versus 29/231 (12.6%) of those with 3-month mRS of 2(p<0.0001). However, the mRS did often change between 3-months and 1-year (Table 3), with recovery by one or more grades observed in 317/1266 (25.0%) patients with 3-month mRS≥1. Recovery to functional independence (i.e. an improvement to mRS 0-2) by 1-year occurred in 58 (23.1%) patients with 3-month mRS of 3 versus 7 (3.9%)

of those with 3-month mRS of 4. Although all survivors with a 3-month mRS of 5 remained disabled at 1-year, 16 (15.5%) showed an improvement by 1 or 2 grades. Accrual of new disability (mRS>2) at 1-year occurred in 75 (8.6%) patients who had a 3-month mRS≤2. Recurrent strokes or other vascular events accounted for 38 (50.7%) of these deteriorations.

Change in mRS was less frequent between 1 and 5-years (Table 4). While 114/970 (11.8%) patients with 1-year mRS≥1 still showed an improvement in the mRS by one or more grades, indicating some late recovery, only 17/332 (5.1%) survivors with 1-year mRS of 3 or 4 were independent at 5-years. New disability at 5-years occurred in 32/674 (4.7%) patients with 1-year mRS of 0-2, with recurrent vascular events accounting for 13 (40.6%) of these deteriorations.

A step-change from mRS 2 to 3 was also evident on grouping the composite outcome of 5-year disability/death by 3-month mRS (Figure 2D; overall mRS changes between 3-months and 5-years shown in Table V, Appendix). 3-month mRS>2 strongly predicted 5-year disability/death in age- and sex- adjusted logistic regressions (Table II, Appendix). 723 (83.2%) patients in the overall cohort with 3-month mRS of 0-2 were alive (or censored) at 5-years, of whom 47 (6.5%) were disabled, whereas 246 (46.1%) of those with 3-month mRS>2 were alive/censored at 5-years, of whom 202 (82.1%) remained disabled (adjusted odds ratio for 5-year disability/death for mRS>2 versus 0-2: 34.15, 95%CI 23.57-49.48, p<0.0001). The models were all strong (c-statistic≥0.80). Similar findings were observed after excluding patients with pre-morbid disability (Table VI, Appendix).

Subgroup analyses

In addition to having more severe strokes (higher NIHSS) by definition, patients in the treatable major stroke group were generally older and more likely to have pre-morbid disability and comorbidities than the non-hyperacute/minor stroke group (Table I, Appendix). Similar differences were seen on comparing AF-related and non-lacunar stroke patients versus non-AF-related and lacunar stroke patients, respectively. Upon adjusting comparisons for age and sex, most of these differences remained significant.

The lacunar stroke subgroup had fewer patients with 3-month mRS>2, and lower rates of 5-year mortality or dependency (76/234 [32.5%] dead/disabled at 5-years versus 639/1,184 [54.0%] of non-lacunar strokes, p<0.001) including when stratified by 3-month mRS (43/56 [76.8%] of those with 3-month mRS>2 dead/disabled at 5-years versus 450/478 [94.1%] of non-lacunar strokes, p<0.001; see Table V, Figures V-VI). That being said, similar trends

were generally observed across the subgroups as in the overall cohort, with 3-month mRS strongly predicting 1-year and 5-year mortality (Figure IA-B; 1-year and 5-year mortality outcomes for subgroups displayed individually in Figures II and III, Tables II and III, Appendix). Kaplan-Meier analyses in the subgroups also showed clear early separation of survival curves for 3-month mRS>2 versus 0-2, persisting at 5-years (Figure 3B-D and Figure IV, Appendix). A step-change from mRS 2 to 3 was also evident on grouping the composite outcome of 5-year disability and disability/death by 3-month mRS (Figures IC-D; also see Figures V and VI, Table VI, Appendix)

2.5 DISCUSSION

The time course of disability and cause-specific mortality in the first year after stroke in this cohort demonstrates both late recovery from stroke-related disability and magnification of mortality differences among mRS categories, driven by index-stroke-related deaths. Disability and mortality differences persist at 5-years, despite some erosion by recurrent events and non-stroke-related deaths, with 3-month mRS being a strong independent predictor of long-term disability and mortality. After adjustment for age and sex, and on excluding patients with pre-morbid disability, I observed similar trajectories in long-term death and disability in various clinical subgroups once categorized according to 3- month mRS. These findings have implications for the follow-up and interpretation of stroke trials.

Firstly, these results reaffirm the use of the 3-month mRS as a pragmatic outcome measure in acute stroke trials. My finding that 3-month mRS score predicts 5-year mortality, suggesting that reduction of early disability might reduce long-term mortality, is in agreement with four prior studies that examined early stroke disability and long-term mortality,[9-11,13] as well as a 2015 registry study that examined five-year outcomes specifically in thrombolysis recipients.[29] The latter study found that excellent 3-month mRS (0-1) independently predicted 5-year mRS of 0-1 and was the only independent predictor of 5-year mortality other than age.[29] Our study adds a robust population-based design, high rates of ascertainment of all incident strokes, assessment of causes of late post-stroke death, completeness of follow-up (1.5% missing), and replication of findings in important subgroups. Despite an elderly study population (mean age 73-years), I have further demonstrated that patients attaining low levels of post-stroke disability (mRS 0-2) can generally be expected to not only survive longer, but also sustain their independence up to 5-years. These findings also highlight the importance of measuring post-stroke functional outcome even in trials in stroke prevention.

Secondly, my long-term disability results demonstrate that extending acute stroke trial follow-up to 1-year would almost completely capture long-term stroke-related disability. Whereas late recovery appears to occur in about 1 in 4 patients between 3-months and 1-year post-stroke – notwithstanding potential inter-/intra-rater variability in mRS assessment – rates of further recovery or worsening decrease between 1-year and 5-years. However, if disability assessment is done beyond 1-year follow-up, earlier treatment effects appear unlikely to be significantly eroded by non-stroke-related factors. Nevertheless, my results indicate that studies of stroke treatments beyond the acute phase, such as later rehabilitation or stem-cell therapies,[30] should control for the late recovery that can be expected from a substantial proportion of patients in the first year.

Thirdly, my assessment of the causes of post-stroke death demonstrates that whilst over half of post-3-month index-stroke-related deaths occurred after 1-year, the 1-year mRS did strongly predict these later deaths. This helps reassure us that those subsequent deaths were indeed likely related to enduring disability from the index-stroke. Mortality associations with early stroke-related disability are still evident at 5-years, despite some erosion from non-stroke-related deaths. Consequently, whilst some might question the necessity of extending mortality follow-up beyond 1-year, my findings support the conclusions from follow-up of the IST-3 trial that there is significant potential to demonstrate translation of early disability gains into additional reductions in long-term mortality.[4] Trials might limit face-to-face or telephone follow-up of disability to 1-year, but using administrative methods to obtain mortality follow-up to 2-years or beyond appears to be justified.

These findings also have implications for health-economic analyses. Cost-effectiveness analyses of stroke therapies have either assumed a static post-3-month outcome for dependent patients without any added mortality from their disability,[31] or used hazard ratios generated from expert panels rather than real-world data,[32] which may have underestimated the long-term mortality risk of stroke-related disability.[33] Accounting for the potential for a state-change from disabled to non-disabled, particularly in the first year post-stroke as seen in this study, could also add to the robustness of cost- effectiveness models. Longer-term costing and utility data would allow more accurate modelling of expected healthcare cost savings and quality-adjusted-life-year gains from shifts in 3-month mRS.

Athough my analysis has several strengths, including generalisability, with similar 5-year mortality and disability to the 1- and 5-year results reported by prior population-based studies,[34-36] there are some potential shortcomings. Firstly, a randomized controlled trial would be

required to prove a causal association between lowering early disability and reducing mortality. However, my findings imply that treatments promoting an early shift towards lower mRS scores could reduce both long-term disability and mortality. Secondly, my analysis of the causes of post-stroke death is limited by the practical difficulty of establishing reliably in all cases whether an observed death is causally related to disability from the index stroke, particularly beyond 1-year, and especially in relation to a more direct cause of death like pneumonia or PE. Whilst I sought to minimize this limitation by using overlapping sources to ascertain as much information as possible about the circumstances of deaths, I did not formally assess inter- or intra-rater reliability in the designation of index-stroke-related deaths. I also likely underestimated the number of index-stroke-related deaths by coding deaths from recurrent strokes as being unrelated to the index-stroke. Thirdly, it could also be argued that since I defined long-term disability as mRS>2, this made it more likely for me to find a step-change from 3-month mRS 2 to 3 for the 5-year disability outcome. However, I found the same step-change for 5-year mortality. Fourthly, my results may not be entirely generalizable to a clinical trial population owing to differences between patients in my population-based cohort and those who meet enrolment criteria for trials.

In conclusion, this chapter highlights the predictive value of the short-term mRS for long-term clinical outcomes after stroke, with implications for trial follow-up and outcome assessment more generally, including cost-effectiveness analyses. However, further work is required to document the time-course of long-term quality-adjusted life expectancy and healthcare costs in relation to early mRS scores, which I will address in Chapters 5 and 6.

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2.7 TABLES

Table 1. Patient sample and characteristics for all 3-month survivors of ischaemic stroke

	All stroke patients n=1,425
Age, mean (S.D.)	73.2 (12.7)
Sex – male (%)	753 (52.8)
Ethnicity – White (%)	1,362 (95.6)
Previous history(%):	
MI	177 (12.4)
Angina	239 (16.8)
Atrial Fibrillation	260 (18.2)
Hypertension	889 (62.4)
Dyslipidemia	469 (32.9)
Diabetes	205 (14.4)
PVD	108 (7.6)
Stroke	158 (11.1)
TIA	205 (14.4)
Smoking	836 (58.7)
Cancer	22 (15.5)
Prior disability (mRS >2)	244 (17.2)
NIHSS, median (IQR)	2 (1-4)

Abbreviations: AF – Atrial Fibrillation, S.D. – Standard deviation, MI – Myocardial Infarction, PVD – Peripheral Vascular Disease, TIA – Transient Ischaemic Attack, mRS – modified Rankin scale, NIHSS – National Institutes of Health Stroke Scale, IQR – Inter-quartile range.

Table 2. Primary causes of index-stroke-related and non-stroke-related death beyond 90-days in 3-month survivors of ischaemic stroke, for years 1 to 5 post-stroke, expressed as raw numbers and as percentages of all deaths occurring in that year, listed in descending order of proportion of overall deaths.

Cause of Death(%)	**Year 1** (138 deaths)	**Year 2** (85 deaths)	**Year 3** (80 deaths)	**Year 4** (75 deaths)	**Year 5** (68 deaths)	**Overall** (446)
Index stroke-related deaths*						
Aspiration pneumonia	32(56.1)	11(44.0)	13(59.1)	11(64.7)	2(40.0)	69(54.8)
Vascular dementia	2(3.5)	2(8.0)	2(9.1)	0	1(20.0)	7(5.6)
Pulmonary Embolism	3(5.3)	2(8.0)	0	0	0	5(4.0)
Urosepsis	2(3.5)	0	0	0	0	2(1.6)
Fall	1(1.8)	0	1(4.5)	0	0	2(1.6)
Total stroke-related deaths	**57(41.3)**	**25(29.4)**	**22(27.5)**	**17(22.7)**	**5(7.4)**	**126(28.3)**
Non-stroke-related deaths						
Cancer	22(15.9)	13(15.3)	8(10.0)	16(21.3)	19(27.9)	78(17.5)
Cardiac cause	19(13.8)	14(16.5)	17(21.3)	11(14.7)	10(14.7)	71(15.9)
Pneumonia	10(7.2)	10(11.8)	8(10.0)	13(17.3)	11(16.2)	52(11.7)
Recurrent stroke	15(10.9)	11(12.9)	8(10.0)	3(4.0)	7(10.3)	44(9.9)
Sepsis/infection	4(2.9)	3(3.5)	4(5.0)	2(2.7)	2(2.9)	15(3.4)
Dementia	1(0.7)	0	4(5.0)	4(5.3)	4(5.9)	13(2.9)
Peripheral Vascular Disease	1(0.7)	2(2.4)	2(2.5)	0	1(1.5)	6(1.3)
Pulmonary Embolism	1(1.2)	0	0	3(4.0)	1(1.5)	5(1.1)
Chronic lung disease	1(0.7)	1(1.2)	1(1.3)	0	2(2.9)	5(1.1)
Renal Failure	2(1.4)	2(2.4)	1(1.3)	0	0	5(1.1)
Gastro-intestinal bleeding	2(1.4)	0	0	1(1.3)	0	3(0.7)
Fall	0	0	0	1(1.3)	0	1(0.2)
Other	3(2.2)	4(4.7)	5(6.3)	4(5.3)	6(8.8)	22(4.9)
Total nonstroke-related deaths	**81(58.7)**	**60(70.6)**	**58(72.5)**	**58(77.3)**	**63(92.6)**	**320(71.7)**

*****This refers to deaths deemed to be directly related to, or hastened by, the **index** stroke or its complications (such as immobility), which were not better explained by a recurrent vascular event. Under the index-related stroke section, percentages in bold are in relation to all deaths that year; the off-set percentages are in relation to just index-stroke-related deaths that year. Bolded percentages in each column (total stroke-related and non-stroke-related deaths) add up to 100%; the various sub-sections under index-stroke-related deaths do not add up to 100% as there were deaths in each year that were deemed to be index-stroke-related but did not fall under these specific sub-sections.

Table 3. mRS changes between 3 months and 1 year for all 3-month stroke survivors

	mRS 1 year after index stroke								
	0	**1**	**2**	**3**	**4**	**5**	**Death (%)**	**Improvement in mRS* (%)**	**Total**
3-month mRS									
0	63	61	9	2	0	0	2 (1.5)	N/A	137
1	66	252	76	18	4	0	11 (2.6)	66 (15.5)	427
2	22	104	119	42	9	0	9 (3.0)	126 (41.3)	305
3	0	13	45	128	33	4	28 (11.2)	58 (23.1)	251
4	0	0	7	44	77	11	41 (22.8)	51 (28.3)	180
5	0	0	0	1	15	45	42 (40.8)	16 (15.5)	103
Total	151	430	256	235	138	60	133 (9.5)	317 (25.0)	1403

* Improvement refers to the 1-year mRS score being one or more grades lower than the 3-month mRS. 3-month mRS missing in 22 cases. p<0.0001. The denominator in each case is the row total, except for "317 (25.0)" where the denominator was 1266 (excluding the 137 patients with 3-month mRS 0 who could not improve any further).

Table 4. mRS changes between 1 year and 5 years for 3-month stroke survivors with full 5 years of follow-up

	mRS 5 years after index stroke								
	0	**1**	**2**	**3**	**4**	**5**	**Death (%)**	**Improvement in mRS (%)**	**Total**
1-year mRS									
0	42	38	5	1	0	0	11 (11.3)	N/A	97
1	45	189	46	8	9	0	54 (15.4)	45 (12.8)	351
2	1	43	102	8	4	2	66 (39.2)	44 (19.5)	226
3	0	6	10	70	33	10	87 (40.3)	16 (7.4)	216
4	0	0	1	7	33	8	67 (57.8)	8 (6.9)	116
5	0	0	0	0	1	15	36 (69.2)	1 (1.9)	52
Total	88	276	164	94	80	35	321 (30.3)	114 (11.8)	1058

p<0.0001. This table excludes 138 patients who died in post-stroke year 1 and 173 patients who had not yet attained 5 years of follow-up (censored cases). It includes 3 patients not included in Tables V and VI, for whom 1-year and 5-year mRS scores were available but I had been unable to assess their mRS at or before 3 months.

2.8 FIGURES

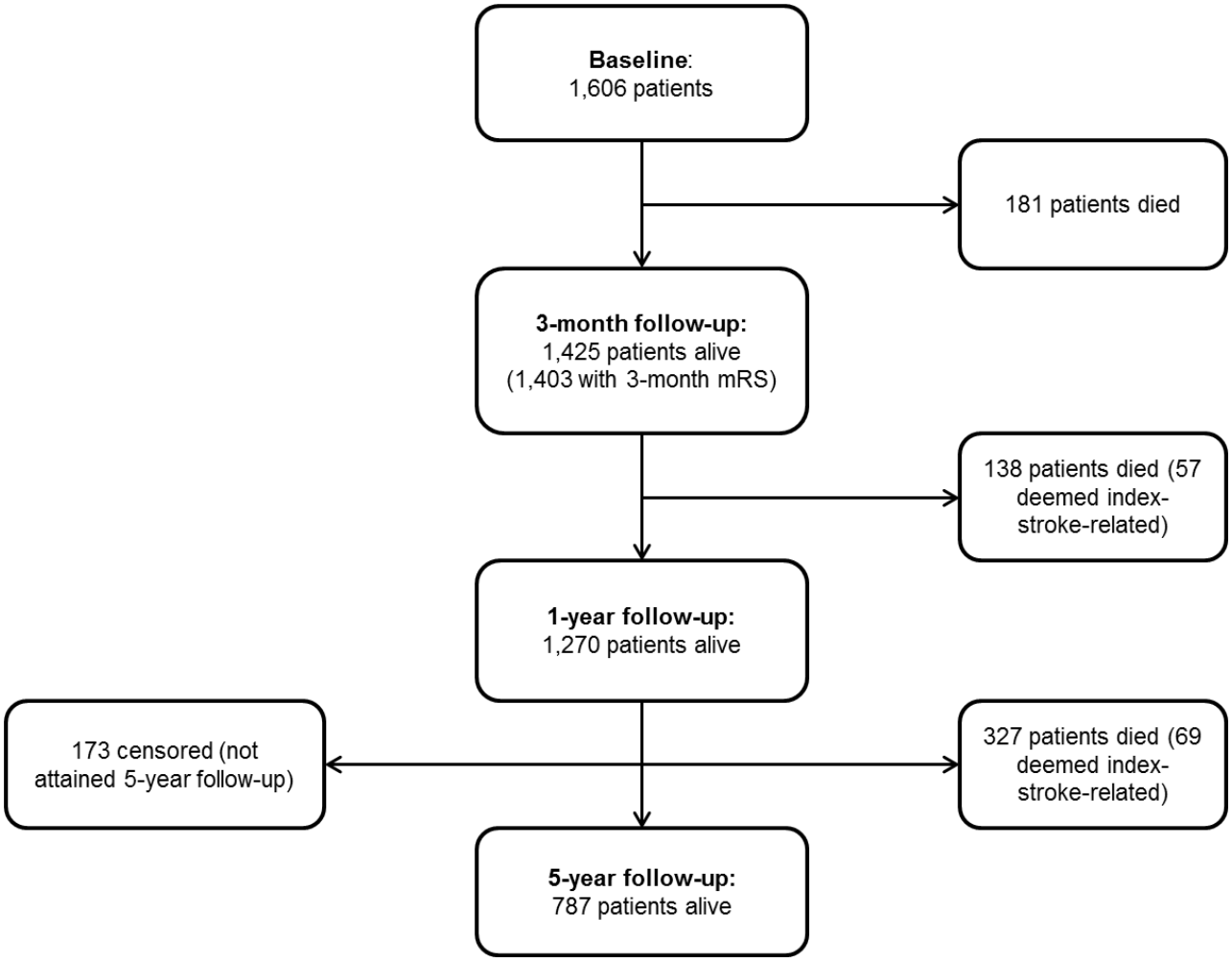

Figure 1. Flowchart illustrating the ischaemic stroke patients who were alive at baseline and at 3-month, 1-year, and 5-year follow-up assessments.

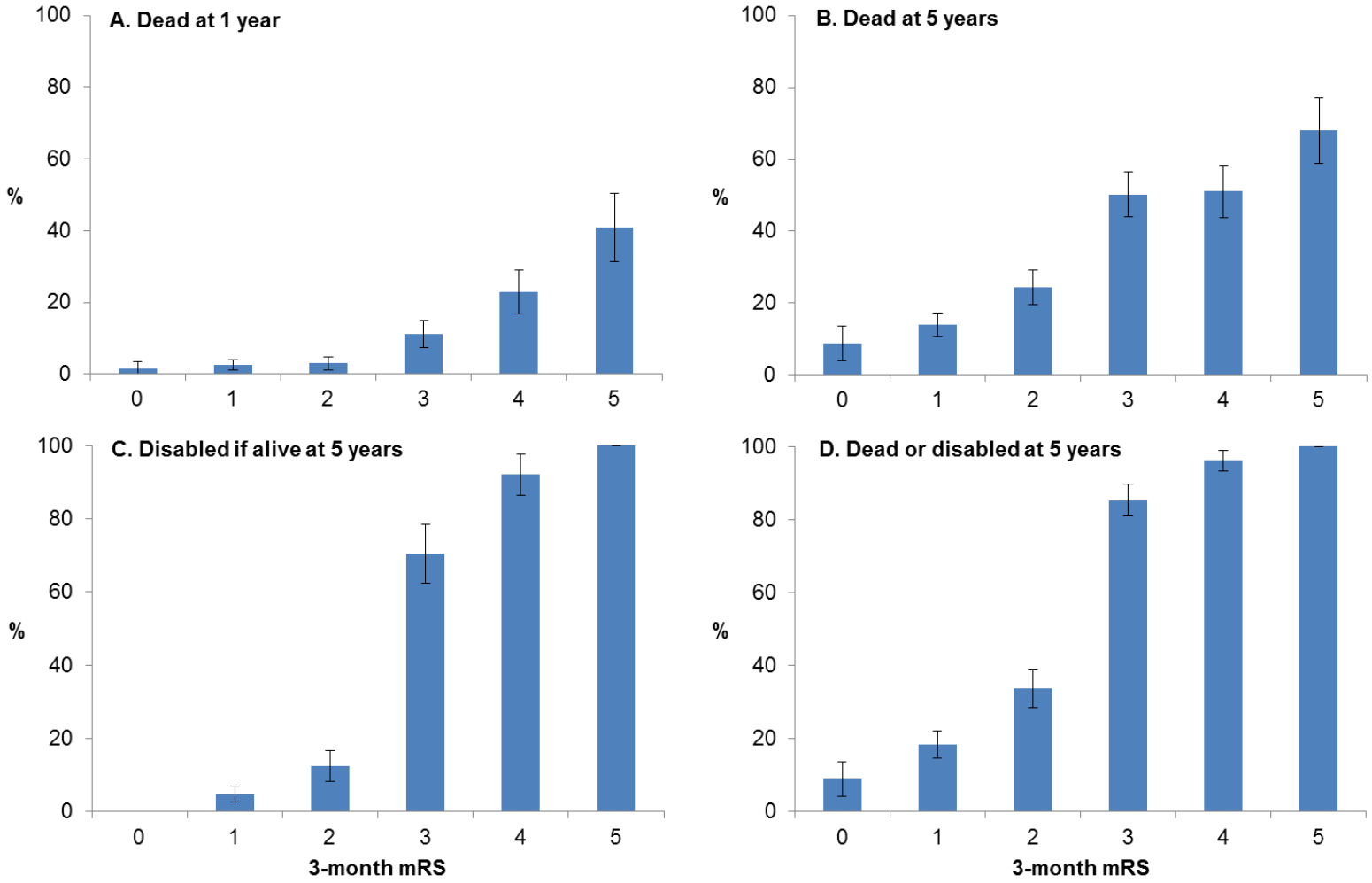

Figure 2. Proportions of 3-month survivors of ischaemic stroke, categorized according to 3-month mRS, who were: (A) dead at 1-year; (B) dead at 5-years; (C) disabled (mRS>2) at 5- years, only including those alive at 5-years in the total; and (D) dead/disabled at 5- years. Bars represent 95% confidence intervals.

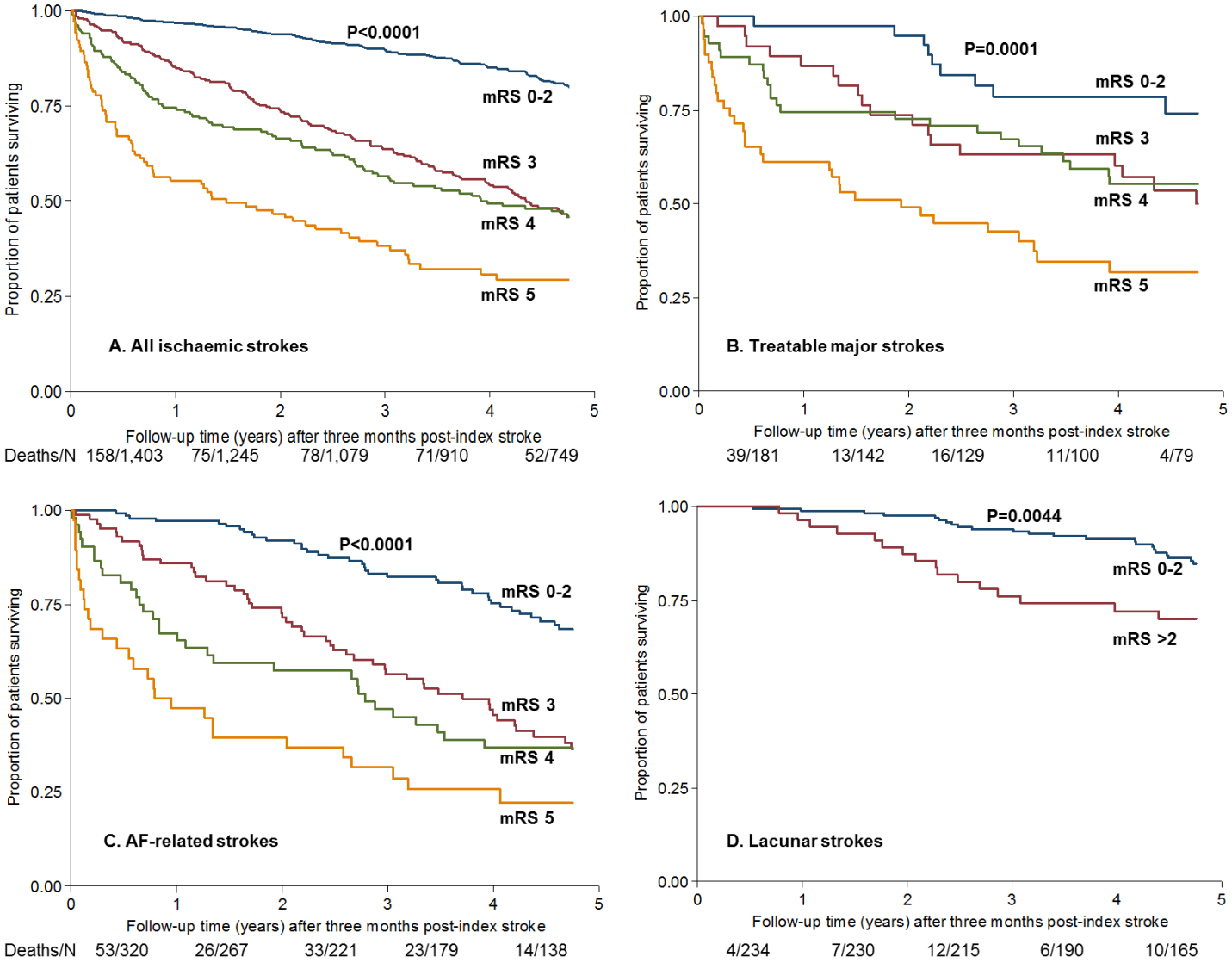

Figure 3. Kaplan-Meier survival curves after index stroke for 3-month survivors (3- month mRS 0-2 versus 3, 4, 5), for (A) all ischaemic strokes, (B) treatable major strokes potentially eligible for thrombolysis/thrombectomy, (C) AF-related strokes, and (D) lacunar strokes. Owing to few patients with 3-month mRS>2 for the lacunar group, I compared mRS 0-2 versus >2. P-values from log-rank test for each group are shown. The numbers shown below each panel are all deaths in each time period (Year 0 to 1, 1 to 2, and so on), over the total number of individuals at risk for that period.

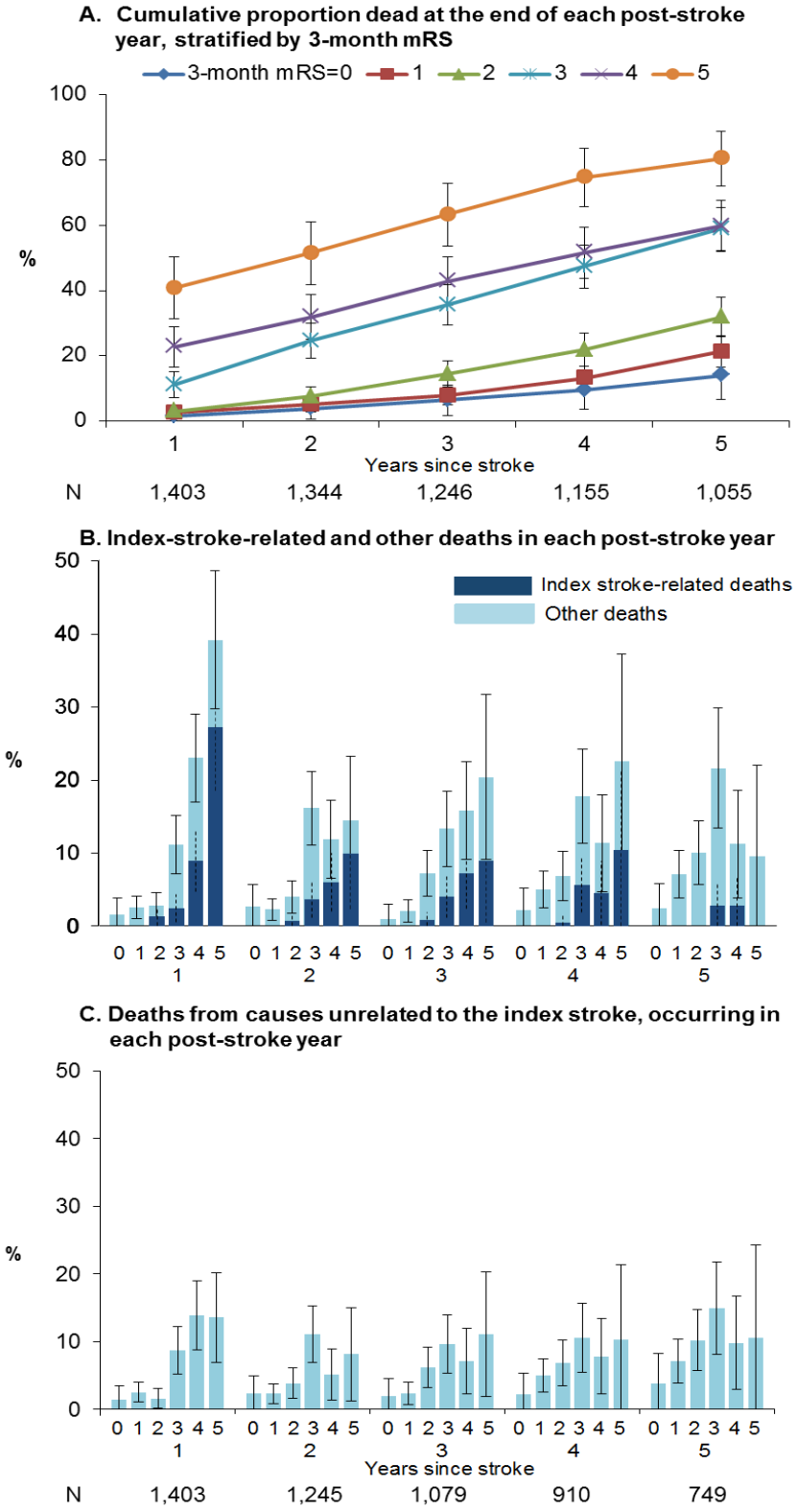

Figure 4. Proportions of 3-month ischaemic stroke survivors, categorized by 3- month mRS, representing: (A) cumulative deaths at the end of each post-stroke year, (B) new deaths at the end of each post-stroke year from causes related and unrelated to the index stroke, and (C) only from non-stroke related causes, for post-stroke years 1 through 5. Only patients with known follow-up status (dead/alive) for a given year are included in the denominator for that year in panel A; panels B and C further restrict the denominator to those who were alive at the start of each year. These numbers are shown below panels A and C respectively. Bars (solid for all-cause, dashed for stroke-related deaths) represent 95% confidence intervals.

2.9 APPENDIX
Supplementary Tables and Figures for Chapter 2

Supplemental Tables

Table I. Patient sample and characteristics for all 3-month survivors of ischaemic stroke and subgroups of interest

	Treatable major stroke patients (n=183)	**Non-hyperacute/ minor stroke patients** (n=1,243)	Age- and sex-adjusted P	**AF-related stroke patients** (n=329)	**Non-AF-related stroke patients** (n=1,096)	Age- and sex-adjusted P	**Lacunar stroke patients** (n=234)	**Non-lacunar stroke patients** (n=1,191)	Age- and sex-adjusted P
Age, mean (S.D.)	75.3 (11.9)	72.9 (12.8)		78.3 (9.8)	71.7 (13.1)		69.9 (12.0)	73.8 (12.8)	
Sex – male (%)	90 (49.2)	663 (53.3)		168 (51.1)	585 (53.4)		143 (61.1)	610 (51.2)	
Previous history(%):									
MI	31 (16.9)	146 (11.8)	**0.060***	61 (18.5)	116 (10.6)	**0.001***	13 (5.6)	164 (13.8)	**0.002***
Angina	30 (16.4)	209 (16.8)	0.71	79 (24.0)	160 (14.6)	**0.007***	32 (13.7)	207 (17.4)	0.46
Atrial Fibrillation	54 (29.5)	206 (16.6)	**<0.001***	257 (78.1)	3 (0.3)	**<0.001***	2 (0.9)	258 (21.7)	**<0.001***
Hypertension	120 (65.6)	769 (61.9)	0.63	231 (70.2)	658 (60.0)	0.10	145 (62.0)	744 (62.5)	0.87
Dyslipidemia	60 (32.8)	409 (32.9)	0.98	118 (35.9)	351 (32.0)	0.11	72 (30.8)	397 (33.3)	0.45
Diabetes	23 (12.6)	183 (14.7)	0.48	50 (15.2)	155 (14.1)	0.64	42 (17.9)	163 (13.7)	0.10
PVD	15 (8.2)	93 (7.5)	0.75	31 (9.4)	77 (7.0)	0.21	13 (5.6)	95 (8.0)	0.31
Stroke	19 (10.4)	139 (11.2)	0.54	53 (16.1)	105 (9.6)	**0.03***	22 (9.4)	136 (11.4)	0.66
TIA	26 (14.2)	179 (14.4)	0.74	67 (20.4)	138 (12.6)	**0.02***	29 (12.4)	176 (13.8)	0.75
Smoking	108 (59.0)	729 (58.7)	0.57	186 (56.5)	650 (59.3)	0.98	147 (62.8)	689 (57.9)	0.70
Cancer	37 (20.2)	184 (14.8)	0.15	61 (18.5)	160 (14.6)	0.90	32 (13.7)	189 (15.9)	0.61
Prior disability (mRS ≥3)	38 (20.8)	206 (16.6)	0.62	76 (23.2)	168 (15.4)	0.45	17 (7.3)	227 (19.1)	**0.003***
NIHSS, median (IQR)	10 (7-15)	2 (0-3)	**<0.001***	3 (1-8)	2 (0-4)	**<0.001***	2 (1-3)	2 (1-5)	**<0.001***

Significant differences (p<0.05) between groups are indicated by an asterisk (*). For each subgroup pair (Treatable major strokes versus non-hyperacute/minor strokes, AF-related versus non-AF-related strokes, and lacunar versus non-lacunar strokes), age was compared using an independent samples T-test, while median and distribution of NIHSS were compared using independent-samples Median and Mann-Whitney U Tests respectively. The remaining dichotomous variables were compared using the Chi-squared test. Abbreviations: AF – Atrial Fibrillation, S.D. – Standard deviation, MI – Myocardial Infarction, PVD – Peripheral Vascular Disease, TIA – Transient Ischaemic Attack, mRS – modified Rankin scale, NIHSS – National Institutes of Health Stroke Scale, IQR – Inter-quartile range.

Table II. Impact of 3-month mRS (>2 versus 0-2) on disability/death at 5-years (logistic regression) and 5-year mortality (Cox regression) for all 3-month ischaemic stroke survivors and subgroups, adjusted for age and sex

	mRS >2 versus 0-2		Age		Male		N	c-statistic
	aOR/HR(95%CI)	p>|z|	aOR/HR	p>|z|	aOR/HR	p>|z|		
All stroke patients								
aOR (death/ disability)	34.15 (23.57-49.48)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	0.81 (0.60-1.10)	0.180	1403	0.90
aHR(death)	2.93 (2.38-3.60)	<0.0001*	1.08 (1.07-1.09)	<0.0001*	1.25 (1.03-1.52)	0.022*		
Treatable major strokes								
aOR	41.65 (13.31-130.36)	<0.0001*	1.08 (1.03-1.12)	<0.0001*	2.08 (0.68-6.37)	0.198	181	0.91
aHR	2.40 (1.19-4.86)	0.015*	1.10 (1.07-1.14)	<0.0001*	1.83 (1.13-2.95)	0.015*		
Non-hyperacute/minor strokes								
aOR	29.00 (19.37-43.42)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	0.74 (0.54-1.02)	0.068	1222	0.89
aHR	2.92 (2.33-3.66)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.19 (0.96-1.47)	0.119		
AF-related strokes								
aOR	27.64 (13.09-58.35)	<0.0001*	1.08 (1.04-1.12)	<0.0001*	1.01 (0.53-1.90)	0.988	320	0.89
aHR	2.65 (1.81-3.87)	<0.0001*	1.07 (1.05-1.10)	<0.0001*	1.44 (1.04-1.99)	0.030*		
Non-AF-related strokes								
aOR	35.19 (22.94-53.99)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	0.76 (0.54-1.07)	0.117	1083	0.90
aHR	2.92 (2.28-3.75)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	1.15 (0.90-1.47)	0.255		
Lacunar strokes								
aOR	8.97 (4.13-19.49)	<0.0001*	1.09 (1.04-1.13)	<0.0001*	0.72 (0.35-1.47)	0.369	234	0.85
aHR	1.18 (0.59-2.35)	0.633	1.11 (1.06-1.16)	<0.0001*	1.32 (0.68-2.56)	0.417		
Non-lacunar strokes								
aOR	45.89 (29.54-71.30)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	0.86 (0.61-1.20)	0.377	1169	0.91
aHR	3.16 (2.53-3.94)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.27 (1.04-1.56)	0.021*		

$p>|X^2|$ was <0.0001 for all the models. Significant p-values (<0.05) are indicated by an asterisk(*).

Abbreviations: aOR – adjusted odds ratio from logistic regression for 5-year disability/death, aHR – adjusted hazard ratio from Cox regression for 5-year mortality

Table III. Impact of dichotomized 3-month mRS (>2 vs 0-2) on mortality for post-stroke years 1 to 4 for 3-month stroke survivors – controlling for age and sex – including treatable major strokes and related subgroups.

	mRS >2 versus 0-2		Age		Male		Total (n)
	Adj. HR (95% CI)	p>|z|	Adj. HR (95% CI)	p>|z|	Adj. HR (95% CI)	p>|z|	
All stroke patients							
Year 1	6.67 (4.16-10.69)	<0.0001*	1.06 (1.04-1.08)	<0.0001*	1.55 (1.09-2.20)	0.014*	1403
Year 2	4.80 (3.43-6.71)	<0.0001*	1.07 (1.05-1.08)	<0.0001*	1.32 (1.01-1.74)	0.046*	
Year 3	3.86 (2.94-5.08)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.17 (0.93-1.49)	0.186	
Year 4	3.34 (2.64-4.22)	<0.0001*	1.08 (1.07-1.09)	<0.0001*	1.26 (1.02-1.56)	0.032*	
Treatable major strokes							
Year 1	9.61 (1.31-70.43)	0.026*	1.09 (1.04-1.14)	<0.0001*	1.75 (0.86-3.53)	0.120	181
Year 2	14.2 (1.95-103.2)	0.009*	1.10 (1.05-1.14)	<0.0001*	2.06 (1.12-3.78)	0.020*	
Year 3	2.51 (1.14-5.55)	0.023*	1.11 (1.07-1.15)	<0.0001*	1.83 (1.07-3.12)	0.027*	
Year 4	2.42 (1.15-5.09)	0.020*	1.11 (1.07-1.15)	<0.0001*	1.70 (1.02-2.81)	0.040*	
Non-hyperacute/minor strokes							
Year 1	5.97 (3.59-9.93)	<0.0001*	1.05 (1.03-1.08)	<0.0001*	1.59 (1.06-2.40)	0.027*	1222
Year 2	4.34 (3.03-6.21)	<0.0001*	1.06 (1.04-1.08)	<0.0001*	1.22 (0.89-1.67)	0.210	
Year 3	3.87 (2.87-5.23)	<0.0001*	1.07 (1.05-1.09)	<0.0001*	1.09 (0.83-1.42)	0.544	
Year 4	3.35 (2.60-4.32)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	1.21 (0.96-1.54)	0.107	
AF-related strokes							
Year 1	10.48 (3.20-34.3)	<0.0001*	1.06 (1.02-1.10)	0.006*	1.55 (0.86-2.81)	0.148	320
Year 2	5.20 (2.64-10.25)	<0.0001*	1.07 (1.04-1.11)	<0.0001*	1.56 (0.99-2.47)	0.056	
Year 3	3.85 (2.29-6.49)	<0.0001*	1.07 (1.04-1.10)	<0.0001*	1.37 (0.92-2.03)	0.117	
Year 4	3.21 (2.08-4.96)	<0.0001*	1.07 (1.05-1.10)	<0.0001*	1.40 (0.98-2.00)	0.061	
Non-AF-related strokes							
Year 1	5.94 (3.51-10.07)	<0.0001*	1.06 (1.03-1.08)	<0.0001*	1.54 (1.00-2.38)	0.051	1083
Year 2	4.55 (3.07-6.73)	<0.0001*	1.06 (1.04-1.08)	<0.0001*	1.19 (0.84-1.68)	0.333	
Year 3	3.74 (2.70-5.16)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.06 (0.79-1.44)	0.681	
Year 4	3.27 (2.47-4.32)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	1.18 (0.90-1.53)	0.227	
Lacunar strokes							
Year 1	Only 1 death, so N/A						234
Year 2	1.99 (0.52-9.55)	0.389	1.15 (1.03-1.28)	0.011*	2.31(0.52-10.21)	0.269	
Year 3	1.68 (0.68-4.19)	0.262	1.12 (1.06-1.20)	<0.0001*	1.00 (0.41-2.43)	0.996	
Year 4	1.50 (0.67-3.34)	0.324	1.12 (1.06-1.19)	<0.0001*	1.14 (0.52-2.49)	0.739	
Non-lacunar strokes							
Year 1	6.66 (4.13-10.75)	<0.0001*	1.05 (1.03-1.08)	<0.0001*	1.57 (1.11-2.23)	0.011*	1169
Year 2	4.78 (3.39-6.74)	<0.0001*	1.06 (1.04-1.08)	<0.0001*	1.33 (1.01-1.76)	0.046*	
Year 3	4.06 (3.04-5.41)	<0.0001*	1.07 (1.05-1.09)	<0.0001*	1.21 (0.95-1.55)	0.126	
Year 4	3.51 (2.74-4.48)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.29 (1.04-1.61)	0.021*	

$p>|X^2|$ was <0.0001 for each regression presented, except for Lacunar Strokes in Year 2, for which it was 0.0027.

Table IV –Impact of the 3-month mRS (using the full range of scores from 0 to 5) on 1-year and 5-year mortality for 3-month stroke survivors – controlling for age and sex.

		1-year Mortality		5-year Mortality	
		aHR(95%CI)	**p>|z|**	**aHR(95%CI)**	**p>|z|**
3-month mRS		0=Reference		0=Reference	
	1	1.57 (0.35-7.08)	0.560	1.36 (0.73-2.52)	0.337
	2	1.53 (0.33-7.12)	0.587	1.89 (1.02-3.49)	0.042*
	3	4.62 (1.09-19.67)	0.038*	3.53 (1.93-6.43)	<0.0001*
	4	11.15 (2.66-46.73)	0.001*	4.58 (2.49-8.43)	<0.0001*
	5	26.24 (6.27-109.76)	<0.0001*	9.00 (4.84-16.74)	<0.0001*
Age		1.07 (1.04-1.09)	<0.0001*	1.08 (1.07-1.09)	<0.0001*
Male		1.95 (1.36-2.80)	<0.0001*	1.39 (1.14-1.69)	0.001*
		$p>\|X^2\|$	<0.0001*	$p>\|X^2\|$	<0.0001*
		n	1403	n	1403

Table V. mRS changes between 3 months and 5 years (or 1 year if censored) for 3-month stroke survivors

All stroke patients

	mRS 5 years after index stroke							
	0	**1**	**2**	**3**	**4**	**5**	**Death (%)**	**Total**
3-month mRS								
0	54	59	9	1	0	0	14 (10.2)	137
1	65	213	63	11	8	1	66 (15.5)	427
2	24	81	92	20	10	2	76 (24.9)	305
3	0	6	27	55	27	8	128 (51.0)	251
4	0	0	8	21	42	12	97 (53.9)	180
5	0	0	0	3	10	19	71 (68.9)	103
Total	143	359	199	111	97	42	452 (32.2)	1403

3-month mRS missing in 22 cases; 5-year mRS missing in 47, censored in 168; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Treatable major stroke patients

	mRS 5 years after index stroke							
	0	**1**	**2**	**3**	**4**	**5**	**Death (%)**	**Total**
3-month mRS								
0	2	1	0	0	0	0	0	3
1	2	7	0	2	1	0	2 (14.3)	14
2	1	6	6	2	0	0	7 (31.8)	22
3	0	0	4	12	2	1	19 (50.0)	38
4	0	0	3	6	17	5	24 (43.6)	55
5	0	0	0	1	7	9	32 (65.3)	49
Total	5	14	13	23	27	15	84 (46.4)	181

3-month mRS missing in 2 cases; 5-year mRS missing in 8, censored in 13; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Non-hyperacute/minor stroke patients

	mRS 5 years after index stroke							
	0	**1**	**2**	**3**	**4**	**5**	**Death (%)**	**Total**
3-month mRS								
0	52	58	9	1	0	0	14 (10.5)	134
1	63	206	63	9	7	1	64 (15.5)	413
2	23	75	86	18	10	2	69 (24.4)	283
3	0	6	23	43	25	7	109 (51.2)	213
4	0	0	5	15	25	7	73 (58.4)	125
5	0	0	0	2	3	10	39 (72.2)	54
Total	138	345	186	88	70	27	368 (30.1)	1222

3-month mRS missing in 21 cases; 5-year mRS missing in 39, censored in n=155 censored; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

AF-related stroke patients

	mRS 5 years after index stroke							
	0	**1**	**2**	**3**	**4**	**5**	**Death (%)**	**Total**
3-month mRS								
0	8	5	0	0	0	0	4 (23.5)	17
1	7	33	9	3	0	0	17 (24.6)	69
2	2	16	14	2	4	1	20 (33.9)	59
3	0	1	7	13	10	3	51 (60.0)	85
4	0	0	1	4	11	4	32 (61.5)	52
5	0	0	0	0	4	5	29 (76.3)	38
Total	17	55	31	22	29	13	153 (47.8)	320

3-month mRS missing in 9 cases; 5-year mRS missing in 5, censored in 27; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Non-AF-related stroke patients

	mRS 5 years after index stroke							
	0	**1**	**2**	**3**	**4**	**5**	**Death (%)**	**Total**
3-month mRS								
0	46	54	9	1	0	0	10 (8.3)	120
1	58	180	54	8	8	1	49 (13.7)	358
2	22	65	78	18	6	1	56 (22.8)	246
3	0	5	20	42	17	5	77 (46.4)	166
4	0	0	7	17	31	8	65 (50.8)	128
5	0	0	0	3	6	14	42 (64.6)	65
Total	126	304	168	89	68	29	299	1083

3-month mRS missing in 13 cases; 5-year mRS missing in 42, censored in 141; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Lacunar stroke patients

	mRS 5 years after index stroke							
	0	**1**	**2**	**3**	**4**	**5**	**Death (%)**	**Total**
3-month mRS								
0	12	7	0	0	0	0	1 (5.0)	20
1	21	43	15	2	3	1	11 (11.5)	96
2	7	17	23	2	1	0	12 (19.4)	62
3	0	2	11	11	0	1	12 (32.4)	37
4	0	0	0	5	5	1	4 (26.7)	15
5	0	0	0	1	0	2	1 (25.0)	4
Total	40	69	49	21	9	5	41 (17.5)	234

3-month mRS available for all cases; 5-year mRS missing in 11, censored in 19; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Non-lacunar stroke patients

	mRS 5 years after index stroke							
	0	**1**	**2**	**3**	**4**	**5**	**Death (%)**	**Total**
3-month mRS								
0	42	52	9	1	0	0	13 (11.1)	117
1	44	170	48	9	5	0	55 (16.6)	331
2	17	64	69	18	9	2	64 (26.3)	243
3	0	4	16	44	27	7	116 (54.2)	214
4	0	0	8	16	37	11	93 (56.4)	165
5	0	0	0	2	10	17	70 (70.7)	99
Total	103	290	150	90	88	37	411 (35.1)	1169

3-month mRS missing in 22 cases; 5-year mRS missing in 36, censored in 149; for all of them, mRS at 1 year was available and this was used instead. p<0.0001.

Table VI. Impact of dichotomized 3-month mRS (0-2 versus >2) on disability or death at 5 years for 3-month stroke survivors , for the overall cohort and relevant subgroups – controlling for age and sex, and excluding patients with premorbid disability

	mRS >2		Age		Male		Total (n)	c-statistic
	Adj. OR (95% CI)	p>|z|	Adj. OR (95% CI)	p>|z|	Adj. OR (95% CI)	p>|z|		
All stroke patients	25.22 (16.85-37.74)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	0.80 (0.59-1.10)	0.172	1171	0.87
Treatable major strokes	31.49 (10.02-98.93)	<0.0001*	1.07 (1.03-1.12)	0.001*	1.96 (0.54-6.00)	0.237	145	0.90
Non-hyperacute/ minor strokes	19.80 (12.65-30.99)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	0.74 (0.53-1.03)	0.074	1026	0.85
AF-related strokes	31.86 (12.71-79.90)	<0.0001*	1.08 (1.03-1.12)	<0.0001*	1.00 (0.51-1.97)	0.997	249	0.87
Non-AF-related strokes	22.52 (14.31-35.42)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	0.74 (0.52-1.06)	0.101	922	0.86
Lacunar strokes	6.42 (2.79-14.81)	<0.0001*	1.09 (1.04-1.13)	<0.0001*	0.64 (0.30-1.33)	0.230	217	0.83
Non-lacunar strokes	35.52 (21.83-57.78)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	0.87 (0.61-1.23)	0.429	954	0.88

$p>|X^2|$ was <0.0001 for each regression presented. Significant differences ($p<0.05$) between groups are indicated by an asterisk (*).

Supplemental Figures

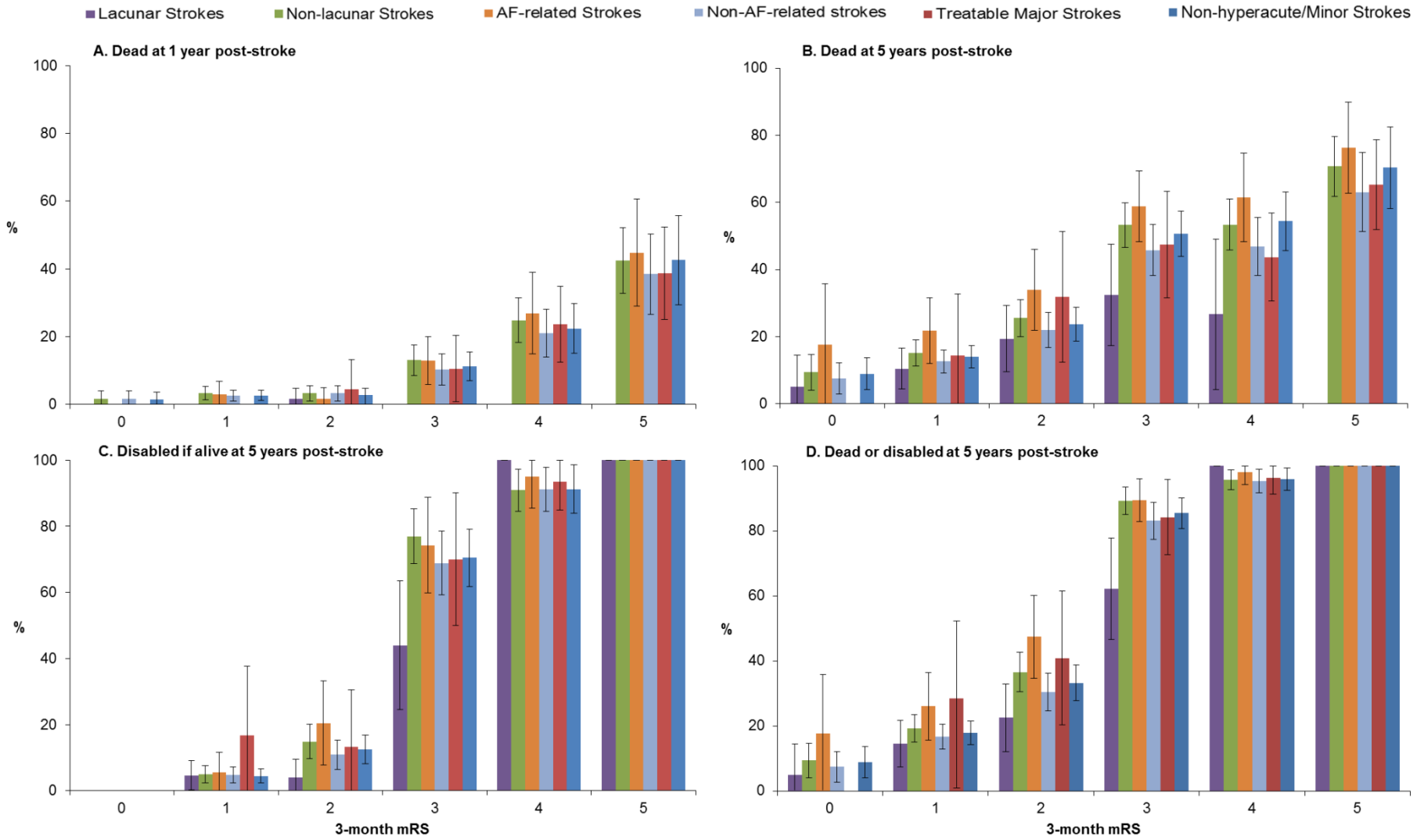

Figure I. Proportions of 3-month ischaemic stroke survivors in subgroups, stratified by 3-month mRS, who were: (A) dead at 1-year; (B) dead at 5-years; (C) disabled (mRS>2) at 5-years, only including those alive at 5-years; and (D) dead/disabled at 5-years.

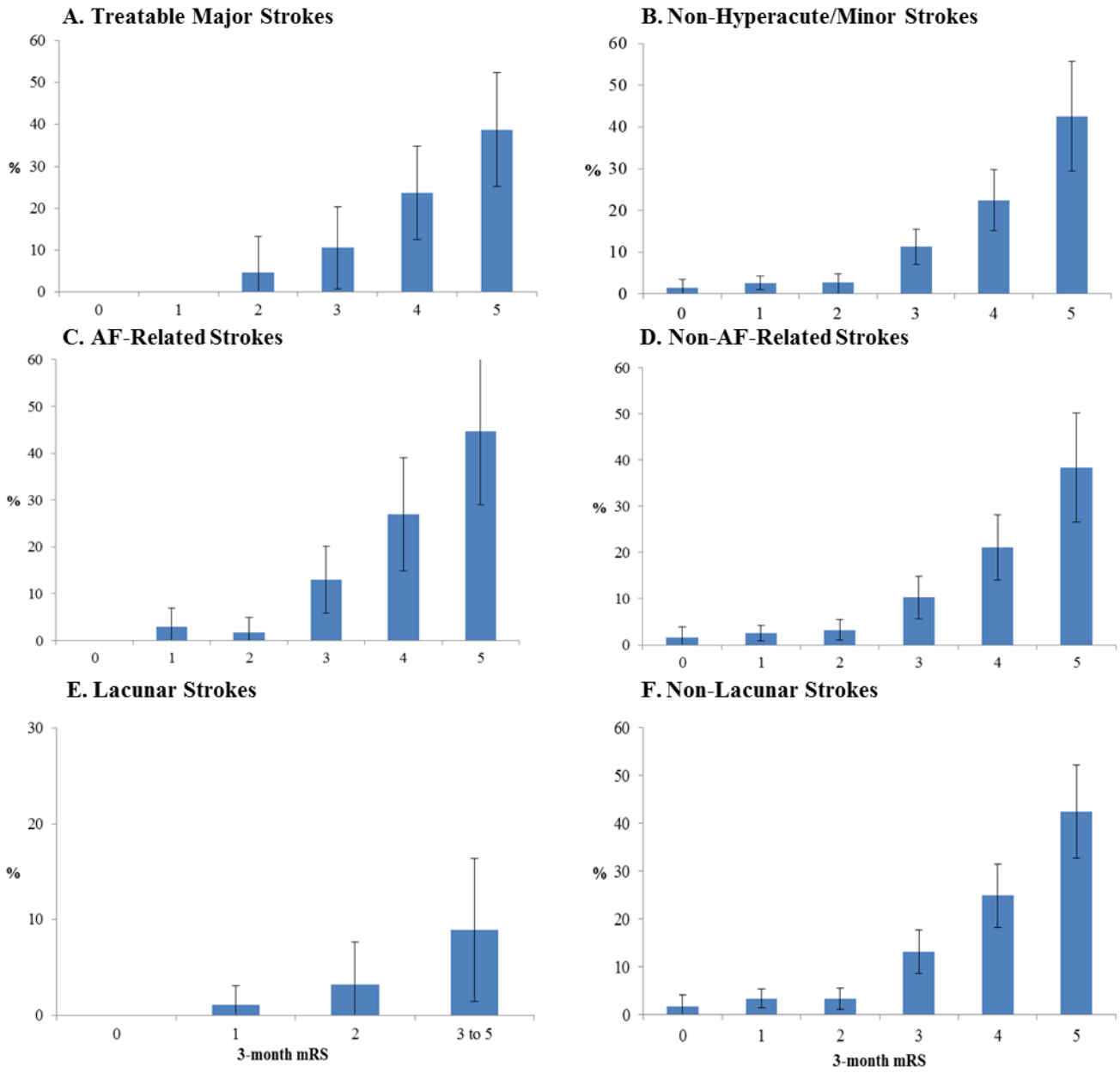

Figure II – Proportions of 3-month survivors of ischaemic stroke for key subgroups, stratified by 3-month mRS, who were dead at 1 year (2 years for the lacunar subgroup, as there was only 1 death in the first year). Bars represent 95% confidence intervals.

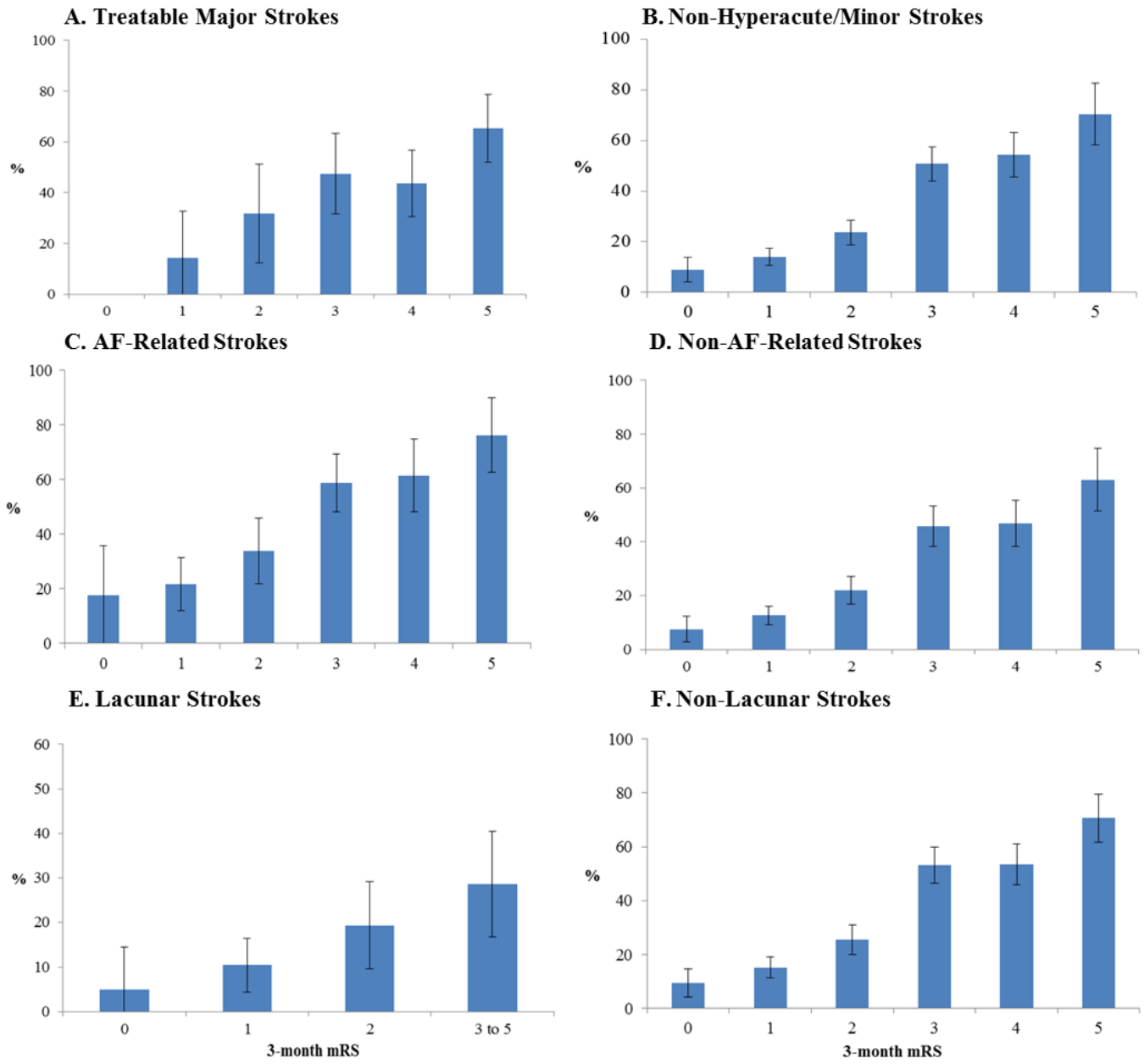

Figure III - Proportions of 3-month survivors of ischaemic stroke for key subgroups, stratified by 3-month mRS, who were dead at 5 years. Bars represent 95% confidence intervals.

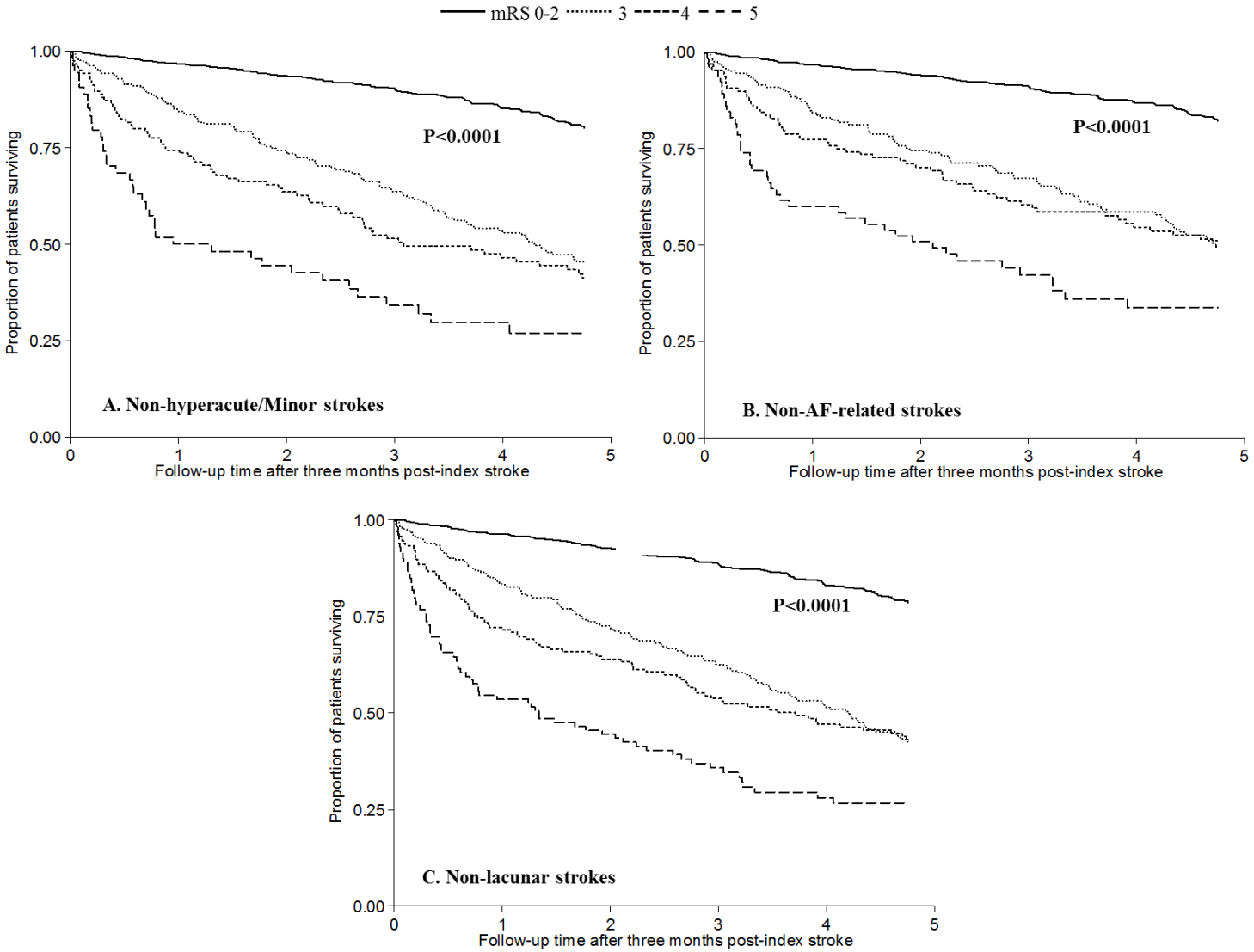

Figure IV – Kaplan-Meier survival curves after index stroke for 3-month survivors (mRS 0-2 versus 3, 4, 5), for (A) non-hyperacute/minor strokes, (B) non-AF-related strokes, and (C) non-lacunar stroke subgroups. P values obtained from the log-rank test for each group are displayed.

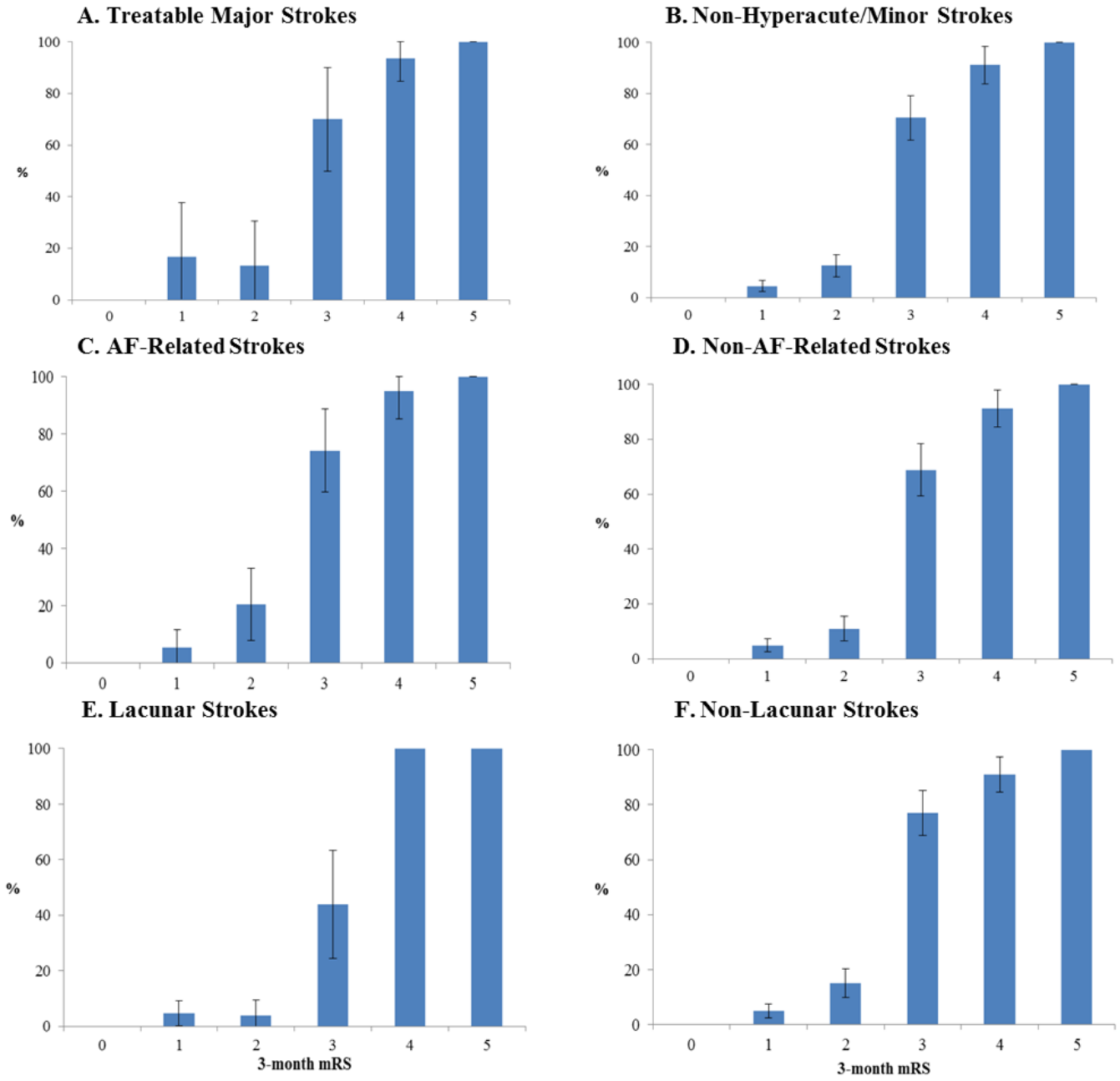

Figure V – Proportions of 3-month survivors of ischaemic stroke for key subgroups, stratified by 3-month mRS, who were disabled (mRS >2) at 5 years, only including those alive at 5 years in the total. Bars represent 95% confidence intervals.

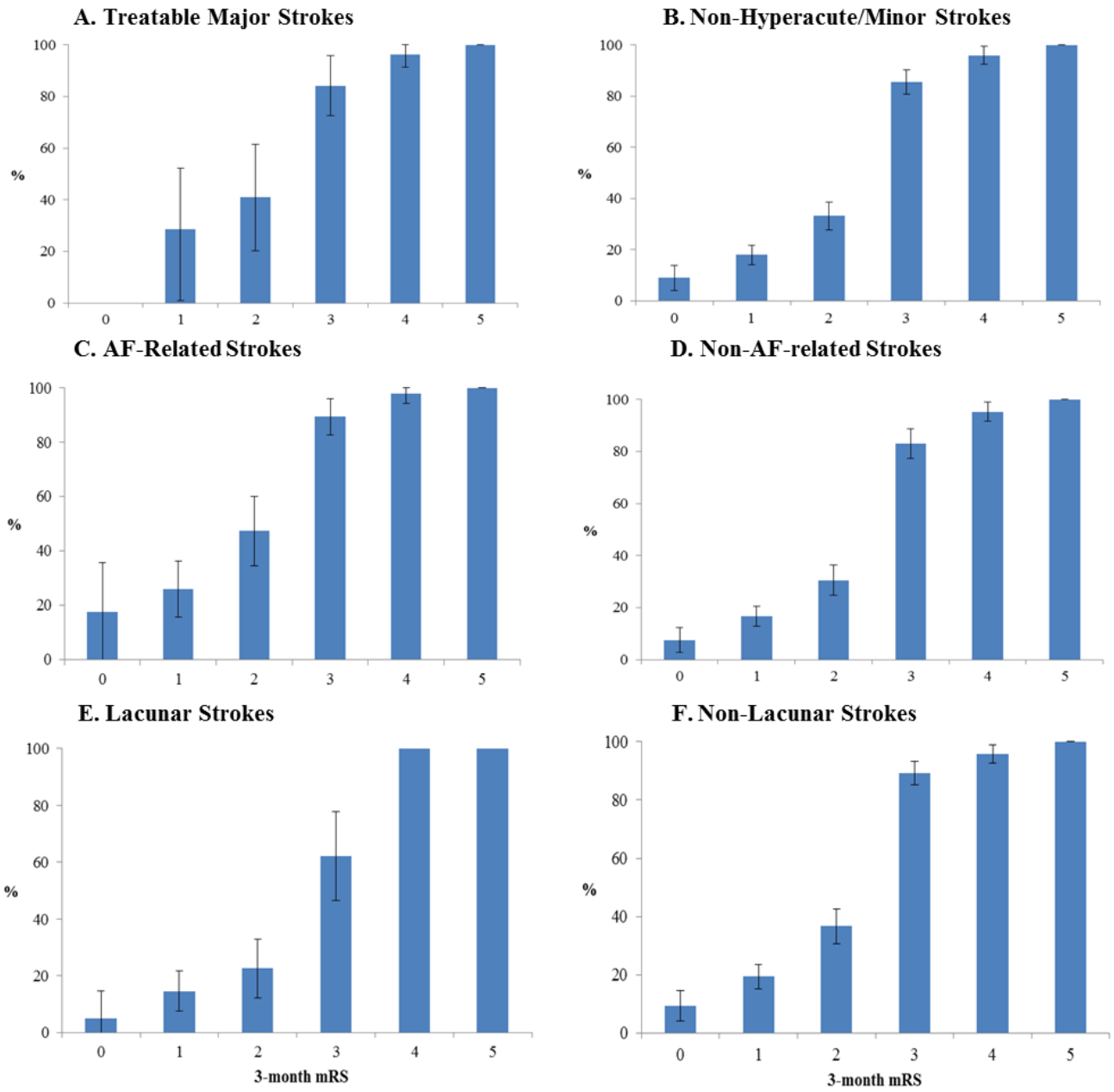

Figure VI – Proportions of 3-month survivors of ischaemic stroke for key subgroups, stratified by 3-month mRS, who were dead or disabled at 5 years. Bars represent 95% confidence intervals.

CHAPTER 3

Pre-morbid functional status and apparent sex differences in stroke severity and outcome

3.1 CHAPTER ABSTRACT

Several studies have reported unexplained worse outcomes after ischaemic stroke in women but none have included the full spectrum of symptomatic ischaemic cerebrovascular events while adjusting for prior handicap.

Using prospective population-based incident cohort data of all TIAs and ischaemic strokes in OXVASC recruited between April 2002 and March 2014, I compared pre-morbid and post-event mRS in women and men, and change in mRS score at 1-month, 6-months, 1-year, and 5-years after stroke. Baseline stroke-related neurological impairment was measured using the NIHSS.

Among 2,553 patients (50.6% women) with a first TIA/ischemic stroke, women had a worse handicap 1-month after ischaemic stroke (age-adjusted odds ratio [aOR] for mRS score 1.35, 95%CI 1.12-1.63). However, women also had a higher pre-morbid mRS score compared with men (aOR 1.58, 1.36-1.84). There was no difference in stroke severity when adjusting for age and pre-morbid mRS (aOR 1.10; 0.90-1.35), and no difference in the pre/post-stroke change in mRS at 1-month (aOR 1.00, 0.82-1.21), 6-months, 1-year, and 5-years. Women had a lower mortality rate and there was no sex-difference in the risk of recurrent stroke.

There was no evidence of a worse outcome of ischaemic stroke in women when adjusting for age and pre-morbid mRS. Failure to account for sex differences in pre-morbid handicap may explain the contradictory findings in previous studies. Properties of the mRS may also contribute to these inconsistencies.

3.2 INTRODUCTION

Many studies have reported greater stroke severity and worse outcome in women, albeit with some conflicting results.[1-3] Potential explanations for these inconsistencies include different source populations, lack of statistical power, and methodological limitations. Firstly, age difference at the time of stroke, if not properly accounted for, may lead to the spurious finding of a worse outcome in women.[4, 5] Secondly, functional status prior to the index stroke is another potential confounding factor, often overlooked, that may influence stroke severity and prognosis even after adjustment for age. Disentangling the respective effect of sex, age, and prior handicap is important as it could shift the focus from sex differences to age-related differences in outcomes. In this respect, the properties of the mRS, the most commonly used measure of post-stroke handicap, may especially impact the observed sex-differences. As I demonstrated in Chapter 2, the mRS is a strong predictor of long-term death/disability outcomes after ischaemic stroke, but being a global disability measure it also captures non-stroke-related or pre-morbid disability and could therefore result in a conflation of differences in pre-morbid functional status with differences in post-stroke outcomes.

Thirdly, most previous studies did not include the full spectrum of symptomatic ischemic cerebrovascular events, particularly TIA and minor stroke and also pre-hospital deaths and severe strokes in community institutions. Only by including the full range of event severity can analyses reliably address sex differences in severity outcomes. To my knowledge, no published study has met these three conditions.

Therefore, I sought to assess potential sex differences in the severity and prognosis of ischaemic stroke/TIA between men and women in OXVASC, whilst carefully taking age and pre-morbid functional status into account.

3.3 METHODS

Study population

OXVASC methodology was previously described in Chapter 2. For this chapter, I included all consecutive patients aged 18 years or older with a first TIA or ischaemic stroke between April 1, 2002 and March 31, 2014. Cohort entry was taken as the date of the first recorded TIA or stroke occurring during the study period. Follow-up data was included until death, 5-year follow-up, or the end of the study period (May 15, 2017), whichever occurred first.

Statistical analyses

Descriptive statistics were used to summarize the baseline characteristics of the cohort stratified by sex. Ordinal logistic regression analysis was used to compare the handicap (pre-morbid mRS) between men and women before the occurrence of the cerebrovascular event, adjusting for age, history of stroke or dementia, and other variables listed in Table 1. Similarly, I compared stroke severity (using NIHSS divided into 7 categories) between men and women while adjusting for the same variables as well as for pre-morbid mRS.

Handicap after stroke was evaluated in several ways. I first compared mRS scores at 1-month, 6-months, 1-year, and 5-years after ischaemic stroke between women and men using ordinal regression. Then, to account for pre-morbid handicap in the assessment of post-stroke mRS, I assessed change in mRS score between pre-morbid score and 1-month, 6-months, 1-year, and 5-years after stroke using ordinal regression analysis adjusted for age.

Change in mRS score was classified into the following 3 categories: no increase, increase by 1 point, or increase by ≥2 points. In a subsequent analysis, I also assessed changes in mRS as a binary outcome (increase, yes/no) using logistic regression. Finally, among patients with a pre-morbid mRS score of ≤2, I compared the percentage of women and men reaching an mRS score of ≥3 at 1-month. Crude and age-adjusted rates of recurrent stroke and all-cause mortality along with 95% confidence intervals (CIs) were estimated, stratified by sex, based on the Poisson distribution. Cox proportional hazards models were used to estimate separately the hazard ratio (HR) of recurrent stroke and all-cause mortality in women compared with men, adjusting for baseline characteristics listed in Table 1 as well as for stroke severity. When studying recurrent stroke, the analysis was repeated using Cox proportional hazards models modified for competing risks of death.[6] Potential confounders were measured at cohort entry.

To assess the robustness of my results, all analyses were repeated among patients with a first in life-time cerebrovascular event only and with censoring at the time of any recurrent stroke. Confidence intervals were calculated and statistical significance was set at $p<0.050$.

3.4 RESULTS

Of 2,553 patients with a first TIA or ischaemic stroke in the study period, 1,293 (50.6%) were women and 1,260 (49.4%) were men, with a mean follow-up of 4.2 years (standard deviation 3.4). The baseline characteristics of women and men at the time of the event are shown in Table 1. Women were older and had a lower prevalence of coronary artery disease, peripheral vascular disease and hyperlipidemia compared with men, after taking age into account. The

same trend was found when the analysis was confined to the elderly (>85, predominantly women, Table 2). However, despite a lesser burden of vascular comorbidities overall, women had a higher pre-morbid mRS score compared with men (ordinal regression OR 2.01, 95%CI 1.74-2.33, Figure 1). This difference persisted after adjusting for age (OR 1.58, 1.36-1.84), for age, prior stroke and dementia (OR 1.62, 1.37-1.92) or for all variables listed in Table 1 (OR 1.77, 1.48-2.13). Among 2,194 patients with a known marital status, 44.2% of women and 73.2% of men were married or living with a partner (age-adjusted OR 0.34, 0.28-0.41).

A total of 949 (37.2%) patients had a TIA and 1,604 (62.8%) had an ischaemic stroke with no difference in proportion between women and men (age-adjusted p=0.13) (Figure 2). The event was incident in 86.4% of patients and recurrent in 13.6%, with very similar figures in both sexes (age-adjusted p=0.97). Women had slightly more events originating from the carotid territory than men (74% and 69.7%, respectively, age-adjusted p=0.17) (Figure 3). The aetiology was most frequently undetermined in both women and men (31.6% and 31.9%, respectively, age-adjusted p=0.04) followed by cardioembolic (Figure 4). The frequency of cardioembolic strokes in women (28.1%) versus men (24.3%) did not differ significantly upon adjusting for age (p=0.97).

Regarding the distribution of cerebrovascular event severity measured by NIHSS, women had more severe events than men (OR 1.49, 1.23-1.80). However, this difference was halved when adjusted for age (OR 1.23, 1.01-1.50) and was no longer apparent when adjusting for age and pre-morbid mRS (OR 1.10, 0.90-1.35), or age, pre-morbid mRS, and other variables listed in Table 1 (OR 1.19, 0.94-1.52). The apparent effect of female sex on severity did not vary with age (p=0.85 for interaction). Interestingly, adjusting for all baseline comorbidities listed in Table 1 but omitting pre-morbid mRS in the model still resulted in an apparently higher severity in women (OR 1.27, 1.00-1.62). In a subgroup analysis restricted to patients with ischaemic stroke (i.e. excluding TIA), women had more severe stroke than men (age/mRS-adjusted OR 1.26, 1.02-1.56) (Figure 5). This increased severity was not statistically significant when also adjusting for ischemic stroke subtype (OR 1.22, 0.98-1.53). Only 21 (1.3%) ischaemic stroke patients received thrombolysis, with no significant difference between men and women (8/802, 1.0% versus 13/798, 1.6%, p=0.28). Importantly, post-stroke inpatient rehabilitation admission rates were similar for women (43.9%) and men (41.2%), including after adjustment for age and NIHSS (adjusted OR 0.91, 0.73-1.13). Post-stroke depression was just as frequent in women (23.8%) and men (21.4%).

Women had a worse 1-month mRS score compared with men following ischaemic stroke (crude OR 1.87; 95%CI 1.56-2.24 and age-adjusted OR 1.35, 1.12-1.63, Figure 1). However, female sex was not associated with a higher risk of increased mRS score either in the whole cohort (age-adjusted OR 1.00, 0.82-1.21), or in the subgroup of patients aged 65 or older (age-adjusted OR 0.95, 0.76-1.18). Changes in mRS score from pre-morbid state to 1-month post-stroke, stratified by age and sex, are shown in Figure 6. Results were unchanged when assessing mRS change as a binary outcome (age-adjusted OR 0.91, 0.73-1.14; and 0.86, 0.67-1.10, respectively). Similarly, among patients who were functionally independent pre-stroke (pre-morbid mRS 0-2), women were no more likely than men to have a 1-month mRS≥3 (age-adjusted OR 1.15, 0.90-1.48).

Women also had a worse 6-month post-stroke mRS compared with men (crude OR 1.92, 1.60-2.30; age-adjusted OR 1.35, 1.12-1.62). Results were very similar considering only individuals alive at 6-months (crude OR 1.84, 1.50-2.27; age-adjusted OR 1.47, 1.19-1.81). However, again female sex was not associated with a higher risk of increased mRS score following stroke either in the whole cohort (age-adjusted OR 1.04, 0.85 -1.27), or in the subgroup of patients aged 65 or older (age-adjusted OR 1.01, 0.81-1.26). Results were unchanged when assessing mRS change as a binary outcome (age-adjusted OR 1.00, 0.80-1.26; and 0.93, 0.73-1.20, respectively). Among pre-morbidly functionally independent patients, women were only slightly more likely than men to have a 6-month mRS ≥3 (age-adjusted OR 1.29, 1.002-1.67). Results were similar at 1-year and 5-years, showing no higher risk of increased mRS score in women.

During 10,670 person years of follow-up, 219 (16.9%) women and 199 (15.8%) men had a recurrent ischaemic stroke with similar age-adjusted rates: 4.60 (4.01-5.27) per 100 persons/year in women and 4.64 (4.03-5.33) per 100 persons/year in men, respectively. In Cox multivariable analysis, female sex was not associated with a higher risk of recurrent ischaemic stroke (HR 0.97; 95% CI 0.79-1.20), with similar results when controlling for competing risks.

Death occurred in 620 (48%) women and 482 (38%) men during follow-up. Mortality rates increased with age and were similar in women and men when stratified by age, whether during the first year or during the entire study period (Figure 7). In Cox univariate analysis, women had a 32% higher risk of death compared with men (HR 1.32, 1.17-1.48). However, this apparent higher mortality was no longer seen when controlling for age (HR 0.95, 0.84 -1.07) and for baseline comorbidities and severity of stroke (HR 0.82, 0.72-0.94). All results were virtually the same in sensitivity analyses restricting the cohort to incident cerebrovascular events only.

3.5 DISCUSSION

In this chapter, I have shown the impact of potential confounders on the apparent sex differences in severity and outcome of stroke/TIA. Overall, about one third of women and men presented with a TIA, they had a similar proportion of events originating from the anterior circulation, and cardioembolic aetiology was equally represented in men and women when taking age into account. However, women had a higher pre-morbid mRS score compared with men, even when adjusting for age and comorbidities, such that the apparently higher severity of cerebrovascular events in women did not remain after adjustment for age and pre-morbid mRS. When ignoring pre-morbid mRS score, women appeared to have a worse functional status than men after ischaemic stroke. However, change in mRS score 1-month after ischaemic stroke was similar between women and men, including among those with pre-morbid functional independence. Finally, women were not at higher risk of recurrent ischaemic stroke and had, in fact, a significantly lower mortality rate than men after adjusting for age and comorbidities.

For this chapter, I included TIAs along with ischaemic strokes in order to cover the whole spectrum of ischaemic cerebrovascular events as opposed to most previous studies.[2] If there was a sex difference in cerebral susceptibility to ischaemia, as some have argued, then the proportion of TIA versus stroke might differ in men and women. However, the proportion of strokes was very similar in both sexes even though women were on average older than men. Moreover, the apparent higher severity of stroke in women was mostly explained by an older age and a worse handicap prior to the event rather than by sex. Interestingly, the pre-morbid mRS score was still worse in women compared with men after adjusting for age and several comorbidities at baseline. Frailty may still play a role in the sex-difference in pre-morbid mRS due to unmeasured confounders. Other factors related to the properties of the mRS scale might also contribute to this difference. Prior studies on stroke severity yielded inconsistent results [2, 7-16] but they did not account for both age and some measure of handicap before stroke or specifically assess ischaemic stroke/TIA while taking both factors into account. Therefore, future studies on sex differences, including clinical trials planning sex-stratified analyses, should properly account for age and collect information on handicap prior to the event of interest.

Moreover, in many instances, it may be more relevant to examine effectiveness based on pre-morbid functional status rather than sex as I observed no clinically substantial differences between sexes. In the subgroup of patients with ischaemic stroke only, however, women had slightly higher NIHSS scores than men even after accounting for age and pre-morbid mRS because of the greater proportion of cardioembolic strokes in women, given their older age. Of

note, as previously reported, the proportion of cardioembolic stroke was not more frequent in women after adjusting for age;[17] previous studies using TOAST criteria and reporting a higher proportion of this subtype in women did not adjust for age.[13, 18]

Importantly, change in mRS score between pre-morbid estimate and at 1-month and 6-months after stroke was similar in women and men. Moreover, rates of recurrence of stroke/TIA were similar and mortality rate was lower in women in accordance with other studies.[7, 19, 20] Conversely, using various scales, some studies found that women had a worse functional status than men following stroke but did not adjust for pre-morbid functional status.[2, 21] This finding can be expected if women have already a worse functional status before stroke, as previously reported.[22-24] One study did not find any difference in post-stroke functional status (6-month Barthel Index) after adjusting for pre-stroke disability and comorbidities,[24] while another still found a worse 3-month functional status in women in multivariable analysis adjusting for pre-morbid mRS but methodological differences may explain this result.[22] A recent study on functional outcome after intracerebral hemorrhage also did not show any sex-difference in adjusted analyses including age and pre-morbid mRS among other factors.[25] Finally, it remains possible that inconsistencies between studies are partly related to the lack of precision of the mRS scale and my conclusions may not apply to other disability or handicap scales.

This study has several strengths. OXVASC is a prospective population-based cohort study with nearly complete ascertainment of vascular events in a well-defined geographic region. Therefore, selection bias towards the exclusion of very old women with severe stroke living in an institution for instance is unlikely to have occurred. Patients with minor events were also included as the study population was not limited to patients seen in emergency department or hospitalised, in contrast to many previous studies. Finally, the prospective and standardised data collection by stroke specialists and access to life-long primary care records ensures completeness and accuracy of data and limits the potential for recall bias. Some potential limitations must, however, be acknowledged. First, the OXVASC population is mostly composed of Caucasian patients, and thrombolysis rates were low, so my results may not be entirely generalizable to non-Caucasian or more hyperacutely treated populations. Second, some residual confounding by unmeasured factors cannot be excluded, but accounting for age and pre-morbid mRS score already corrected fully for apparent sex-differences. Moreover, there was no apparent difference in acute care as measured by t-PA use and admission to inpatient rehabilitation. Third, although pre-morbid and post-event mRS were measured using standardised forms, scoring was of course not done while blinded for sex. However, data in OXVASC were not collected with the intention of testing the hypothesis of sex-differences in

stroke outcomes, so systematic differences in rating are unlikely to entirely explain my results. Similarly, none of the previous studies evaluating stroke outcomes in men and women assessed handicap with assessors blinded for sex.

In conclusion, I found no substantial sex differences in severity, functional recovery (mRS outcome), or recurrence of stroke/TIA. Future studies addressing sex differences in cerebrovascular diseases should take into account functional status prior to the event of interest as most apparent differences between women and men may be due to age and pre-morbid functional status rather than sex per se.

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3.7 TABLES

Table 1. Characteristics of the cohort of 2,553 patients with a first ischaemic stroke or transient ischaemic attack in the study period

	Women (%)	Men (%)	Age-adjusted P*
Cohort size	1293 (50.6)	1260 (49.4)	
Age			
Mean (SD)	76.5 (12.6)	71.4 (12.6)	
Median (range)	79 (22-101)	73 (21-98)	
<45 (%)	29 (2.2)	40 (3.2)	
45-54 (%)	56 (4.3)	99 (7.9)	
55-64 (%)	121 (9.4)	198 (15.7)	
65-74 (%)	261 (20.2)	345 (27.4)	
75-84 (%)	460 (35.6)	412 (32.7)	
≥85 (%)	366 (28.3)	166 (13.2)	
Comorbidities			
Hypertension	855 (66.1)	745 (59.1)	0.1314
Diabetes	172 (13.3)	185 (14.7)	0.3637
Angina pectoris	190 (14.7)	222 (17.6)	**<0.0001**
Myocardial infarction	116 (9.0)	180 (14.3)	**<0.0001**
Peripheral vascular disease	68 (5.3)	122 (9.7)	**<0.0001**
Congestive heart failure	142 (11.0)	119 (9.4)	0.4012
Prior TIA	121 (9.4)	110 (8.7)	0.4301
Prior stroke †	140 (10.8)	123 (9.8)	0.7731
Hyperlipidemia	455 (35.2)	492 (39.1)	**0.0409**
Valvular disease	148 (11.5)	121 (9.6)	0.7703
Atrial fibrillation	270 (20.9)	252 (20.0)	**0.0427**
Cancer	237 (18.3)	212 (16.8)	0.3900
Venous thromboembolism	84 (6.5)	74 (5.9)	0.9027
Dementia ‡	104 (10.1)	59 (6.0)	0.2741
Smoking			
Current	147 (11.4)	214 (17.0)	0.1221
Former	394 (30.7)	659 (52.3)	**<0.0001**
Non-smoker	742 (57.8)	385 (30.6)	**<0.0001**
Migraine	307 (23.7)	204 (16.2)	**<0.0001**
Pre-morbid mRS			
0	417 (32.4)	595 (47.3)	**<0.0001**

	Women (%)	Men (%)	Age-adjusted P*
1	328 (25.5)	368 (29.2)	
2	184 (14.3)	118 (9.4)	
3	221 (17.2)	109 (8.7)	
4	76 (5.9)	43 (3.4)	
5	16 (1.2)	7 (0.6)	
0-2 §	27 (2.1)	10 (0.8)	**0.0057**
>2 ǀ	17 (1.3)	9 (0.7)	0.6567
Medications			
Anticoagulants	60 (4.6)	83 (6.6)	**0.0222**
Antiplatelets	500 (38.7)	465 (36.9)	0.0830
Antihypertensive medications	784 (60.6)	701 (55.6)	0.9269
Statins	313 (24.2)	371 (29.4)	**0.0006**

*Using logistic regression and age as a continuous variable

†ischaemic or haemorrhagic stroke

‡Information was missing for 548 patients

§For these patients the modified Rankin scale score was between 0 and 2 but the exact score was unknown

ǀFor these patients the modified Rankin scale score was greater than 2 but the exact score was unknown

Table 2. Characteristics of the 532 patients aged ≥85 years with an ischaemic stroke or TIA

	Women (%)	Men (%)	Age-adjusted P*
Cohort size	366 (68.8)	166 (31.2)	
Age			
Mean (SD)	89.5 (3.6)	88.1 (2.9)	
Median (range)	89 (85-101)	87 (85-98)	
85-89 (%)	199 (54.37)	123 (74.10)	
≥90 (%)	167 (45.63)	43 (25.90)	
Comorbidities			
Hypertension	252 (68.85)	103 (62.05)	0.0693
Diabetes	34 (9.29)	15 (9.04)	0.7965
Angina pectoris	80 (21.86)	40 (24.10)	0.5005
Myocardial infarction	46 (12.57)	30 (18.07)	0.1662
Peripheral vascular disease	27 (7.38)	15 (9.04)	0.7908
Congestive heart failure	67 (18.31)	31 (18.67)	0.7862
Prior TIA	37 (10.11)	22 (13.25)	0.2693
Prior stroke[†]	40 (10.93)	27 (16.27)	0.1438
Hyperlipidemia	95 (25.96)	46 (27.71)	0.7114
Valvular disease	60 (16.44)	21 (12.80)	0.2428
Atrial fibrillation	122 (33.33)	52 (31.33)	0.8420
Cancer	87 (23.77)	41 (24.70)	0.7985
Venous thromboembolism	26 (7.10)	11 (6.63)	0.9217
Dementia[‡]	51 (17.83)	17 (13.08)	0.2261
Smoking			
Current	10 (2.77)	3 (1.81)	0.4508
Former	106 (29.44)	111 (66.87)	**<0.0001**
Non-smoker	243 (67.50)	52 (31.33)	**<0.0001**
Migraine	57 (15.57)	22 (13.25)	0.3488
Pre-morbid mRS			
0	57 (15.83)	31 (18.79)	
1	62 (17.22)	48 (29.09)	
2	70 (19.44)	32 (19.39)	**0.0316**
3	110 (30.56)	37 (22.42)	

4	40 (11.11)	12 (7.27)	
5	8 (2.22)	0 (0.00)	
0-2 [§]	3 (0.83)	1 (0.61)	0.8413
>2 [|]	10 (2.78)	4 (2.42)	0.9465
Medications			
Anticoagulants	14 (3.83)	11 (6.63)	0.1700
Antiplatelets	178 (48.63)	77 (46.39)	0.4756
Antihypertensive medications	236 (64.48)	101 (60.84)	0.2235
Statins	66 (18.03)	35 (21.08)	0.9459

Abbreviations: SD standard deviation. TIA transient ischemic attack

*Using logistic regression and age as a continuous variable

[†]ischaemic or haemorrhagic stroke

[‡]Information was missing for 7 patients

[§]For these patients the modified Rankin scale score was between 0 and 2 but the exact score was unknown

[|]For these patients the modified Rankin scale score was greater than 2 but the exact score was unknown

3.8 FIGURES

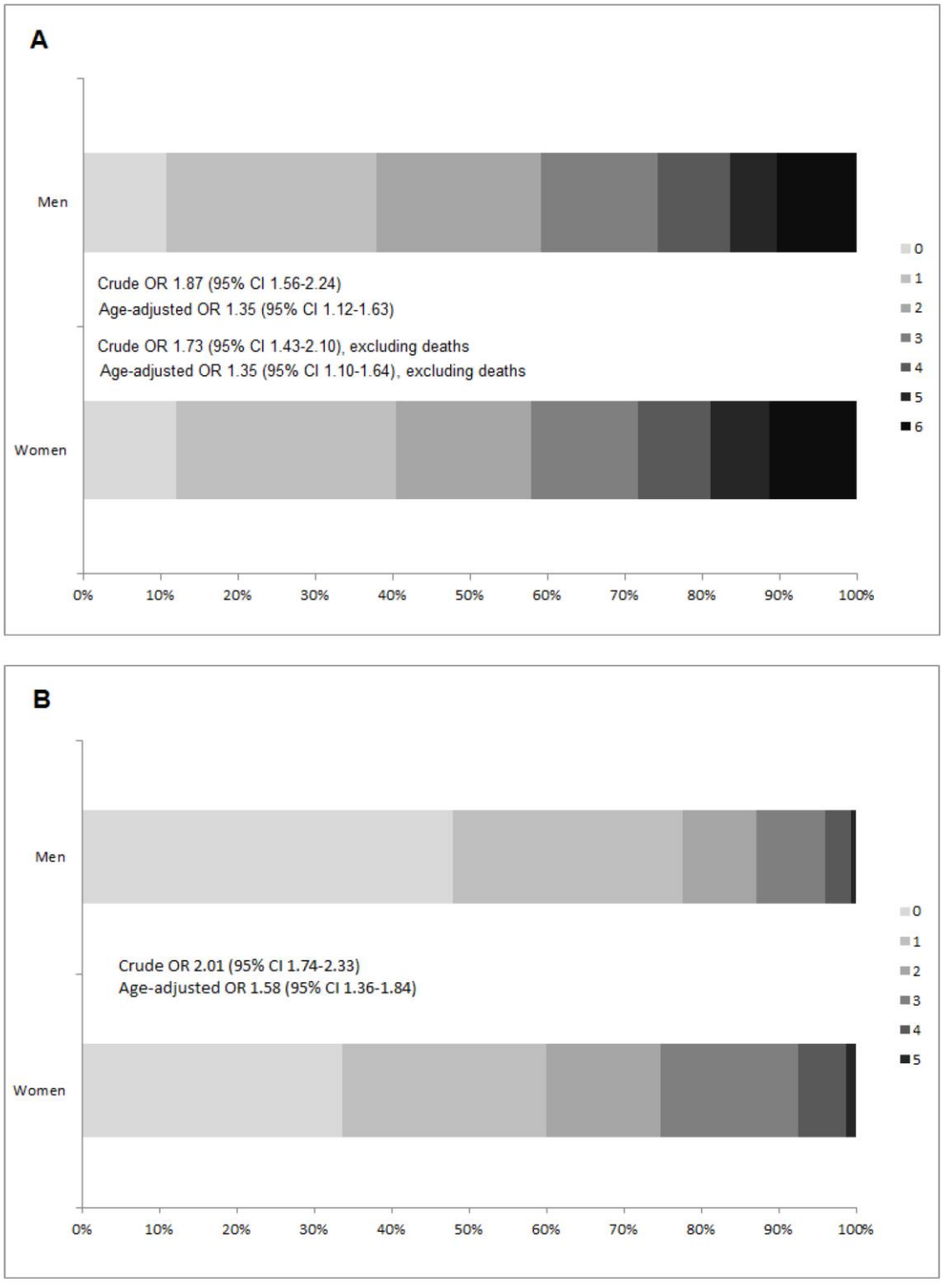

Figure 1. Distribution of modified Rankin Scale (mRS) 1-month after stroke among men and women (A) and mRS prior to stroke (B).

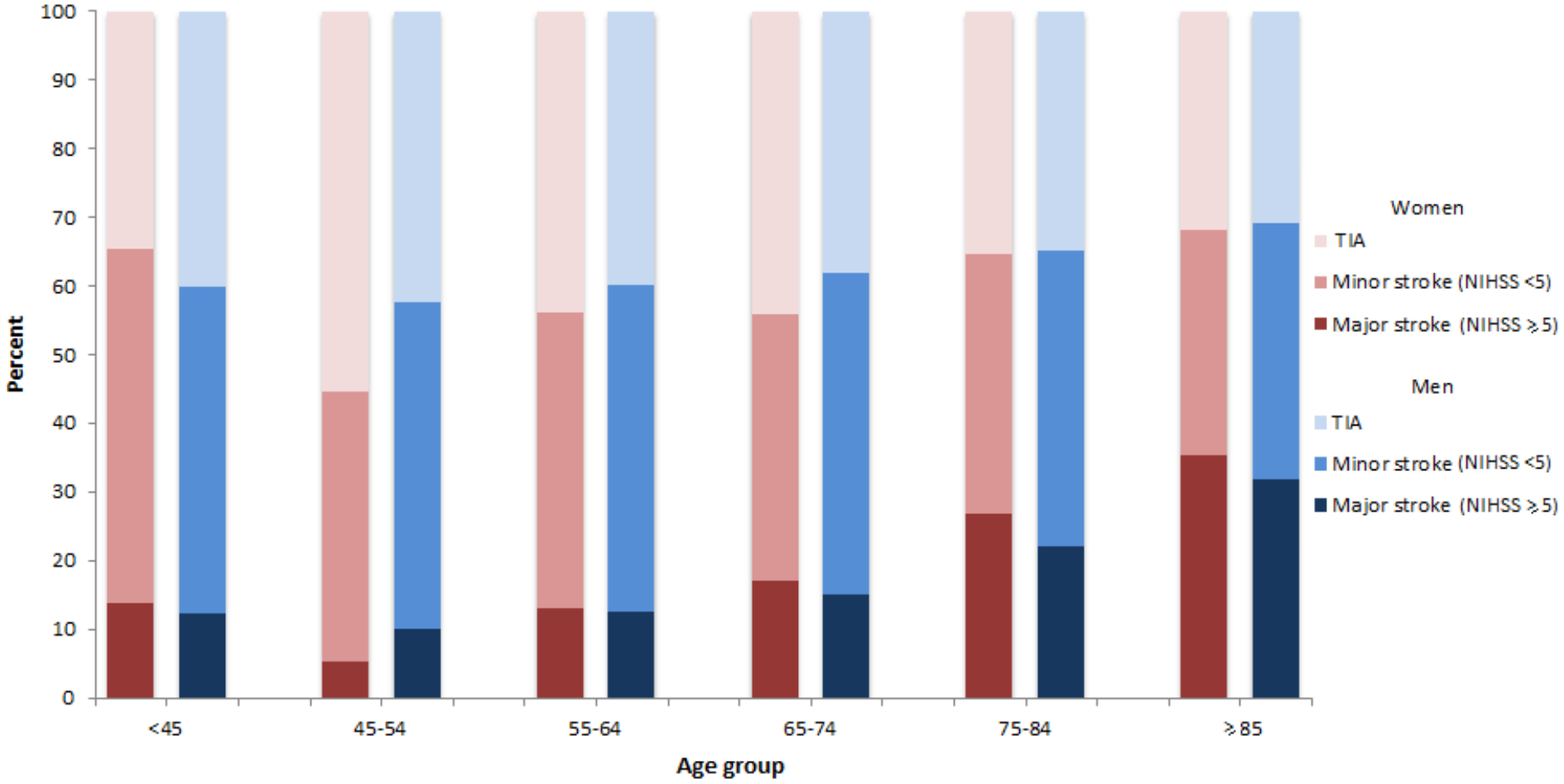

Figure 2. Distribution of stroke/TIA among men and women, by age category.

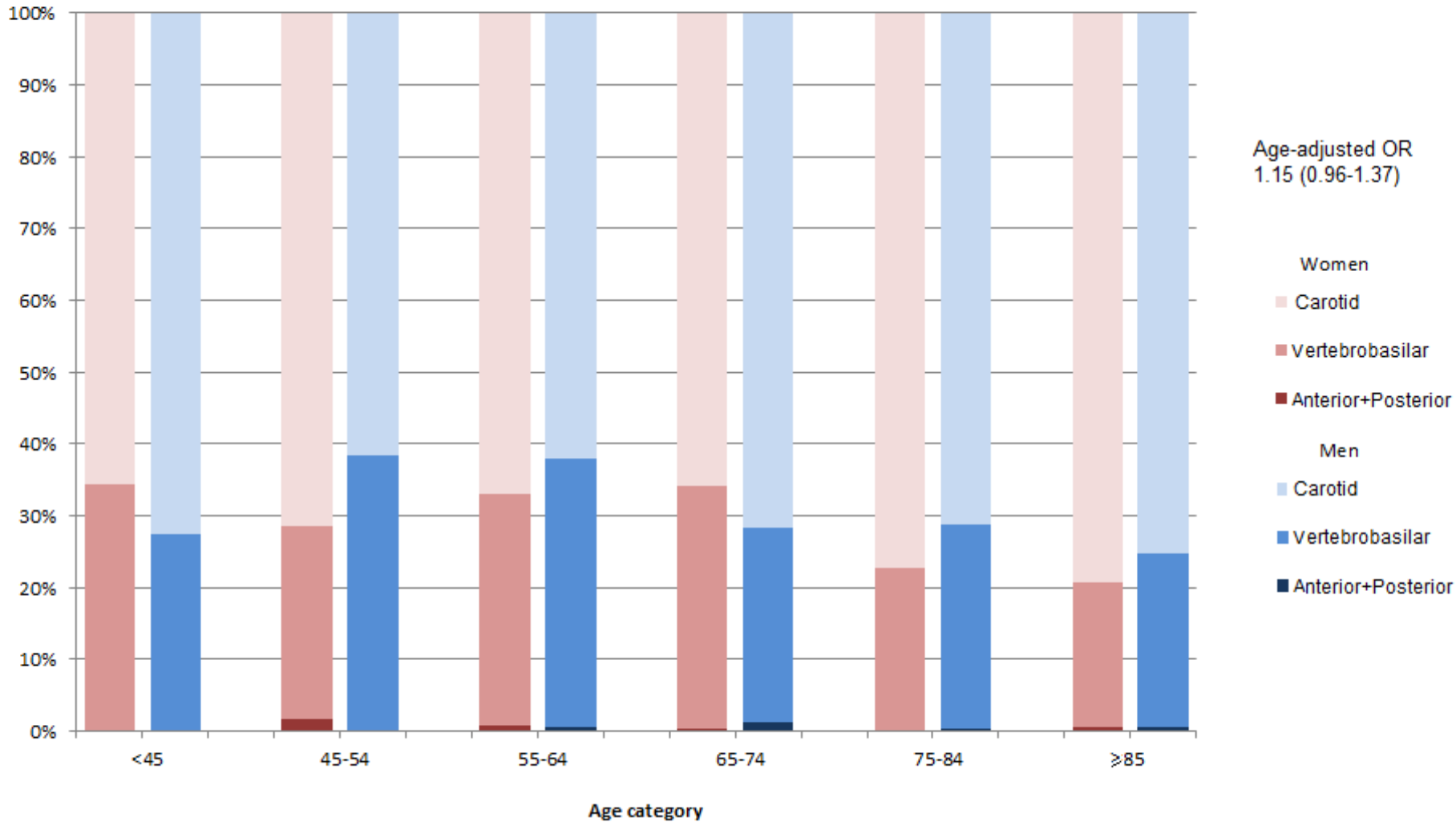

Figure 3. Distribution of vascular territory taking imaging into account, by sex and age category.

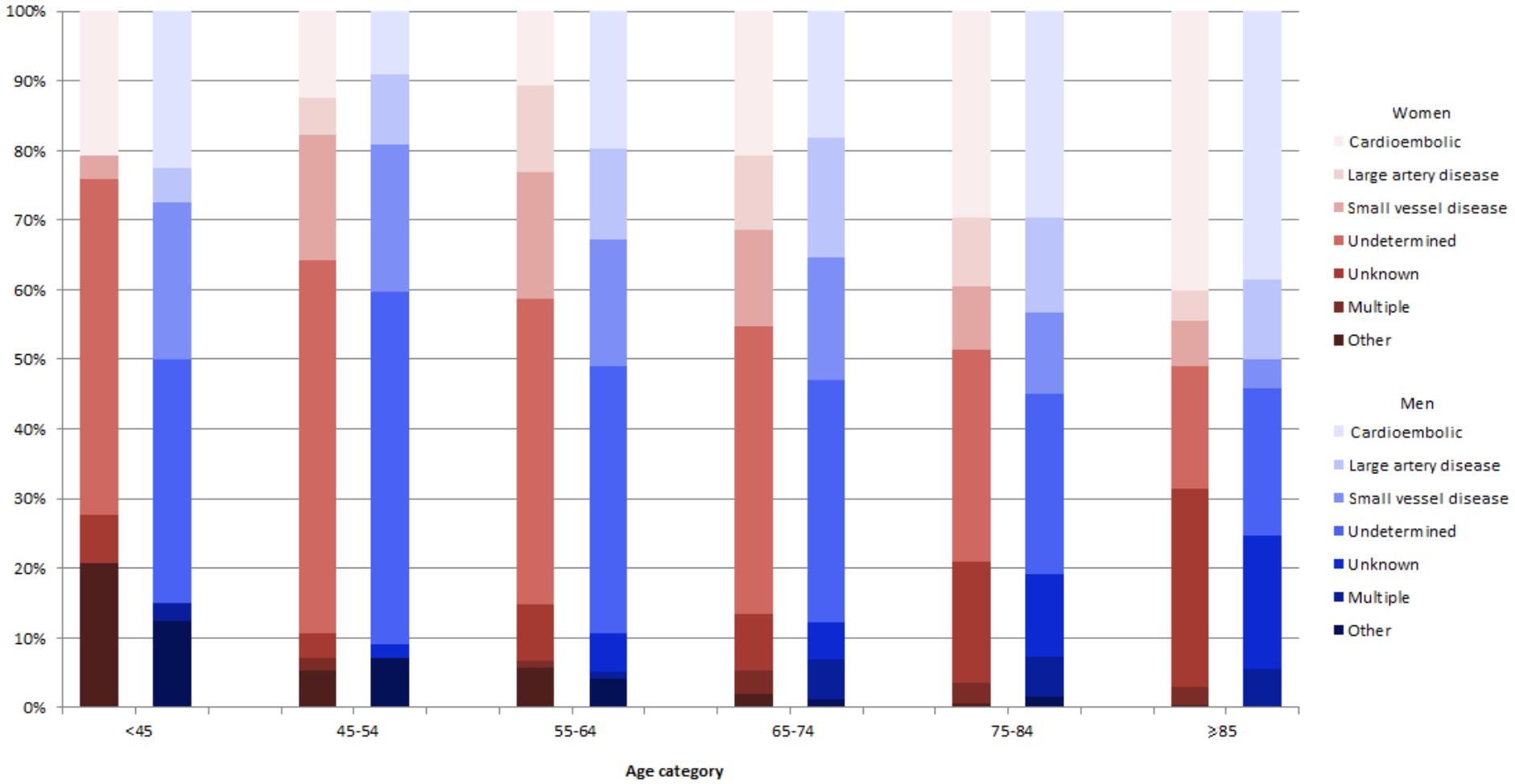

Figure 4. Distribution of TOAST classification by age and sex.

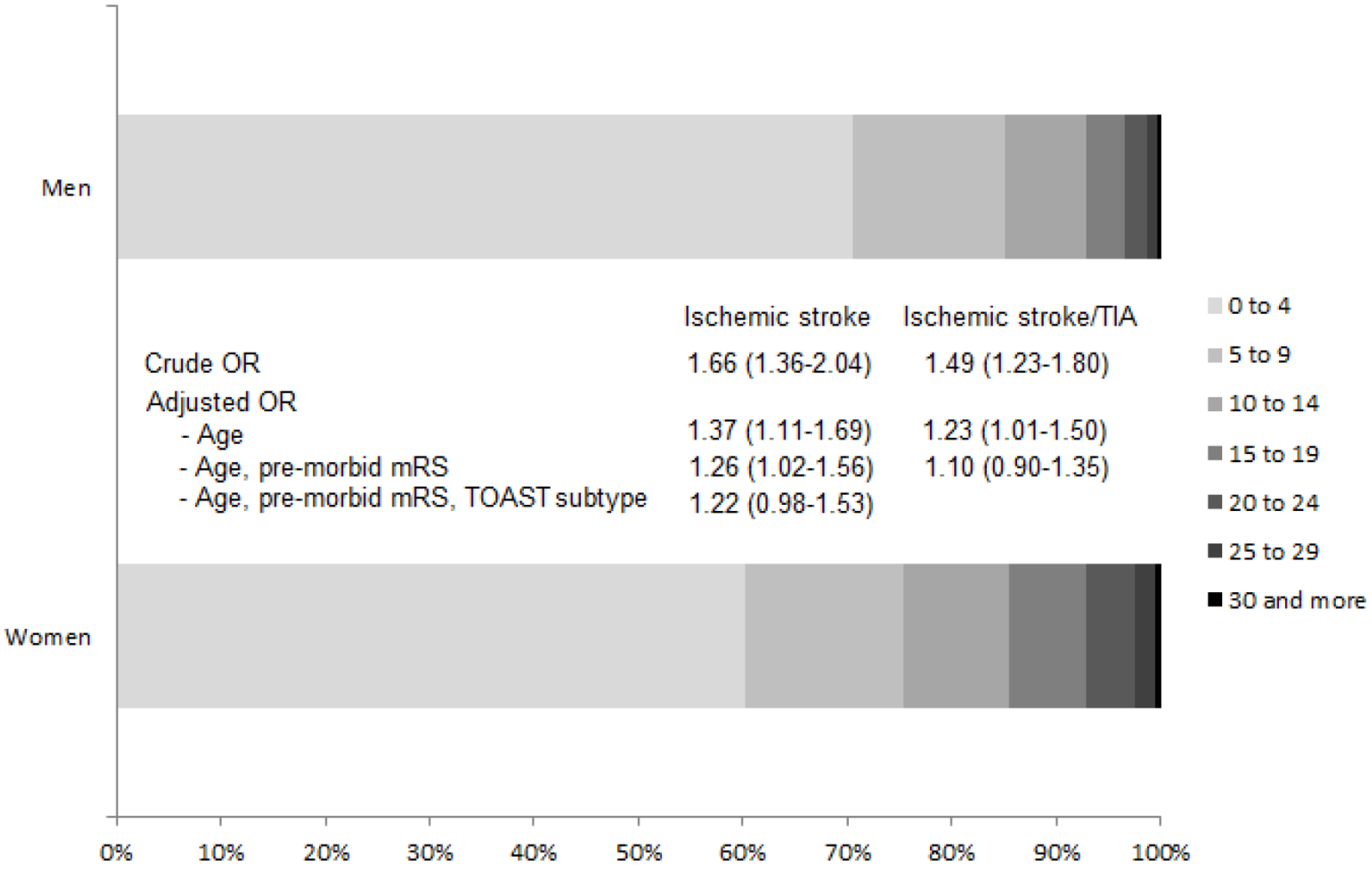

Figure 5. Distribution of NIHSS score among men and women with ischaemic stroke.

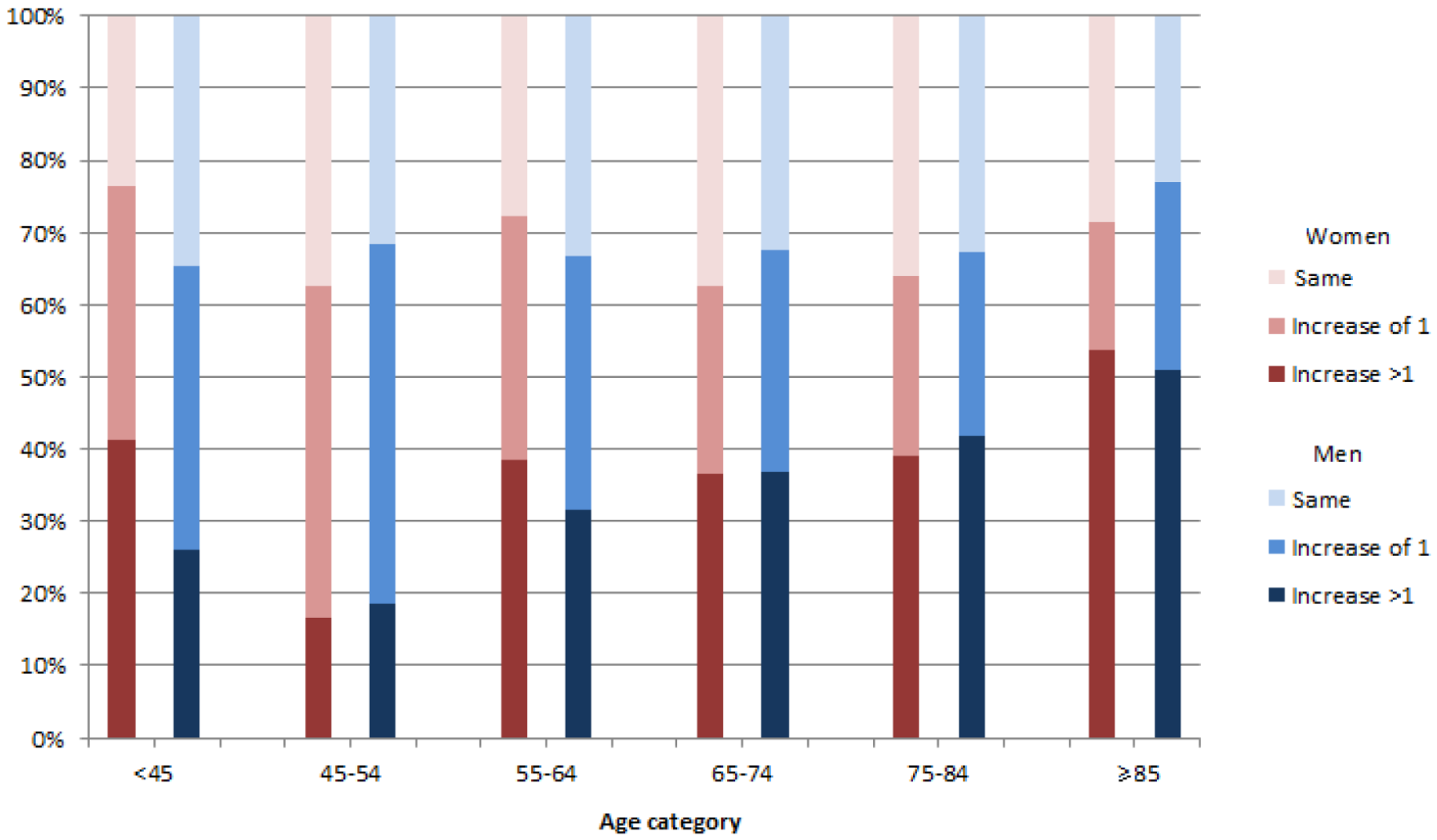

Figure 6. Distribution of the change in mRS score prior to and 1-month after the ischaemic stroke by sex and age category.

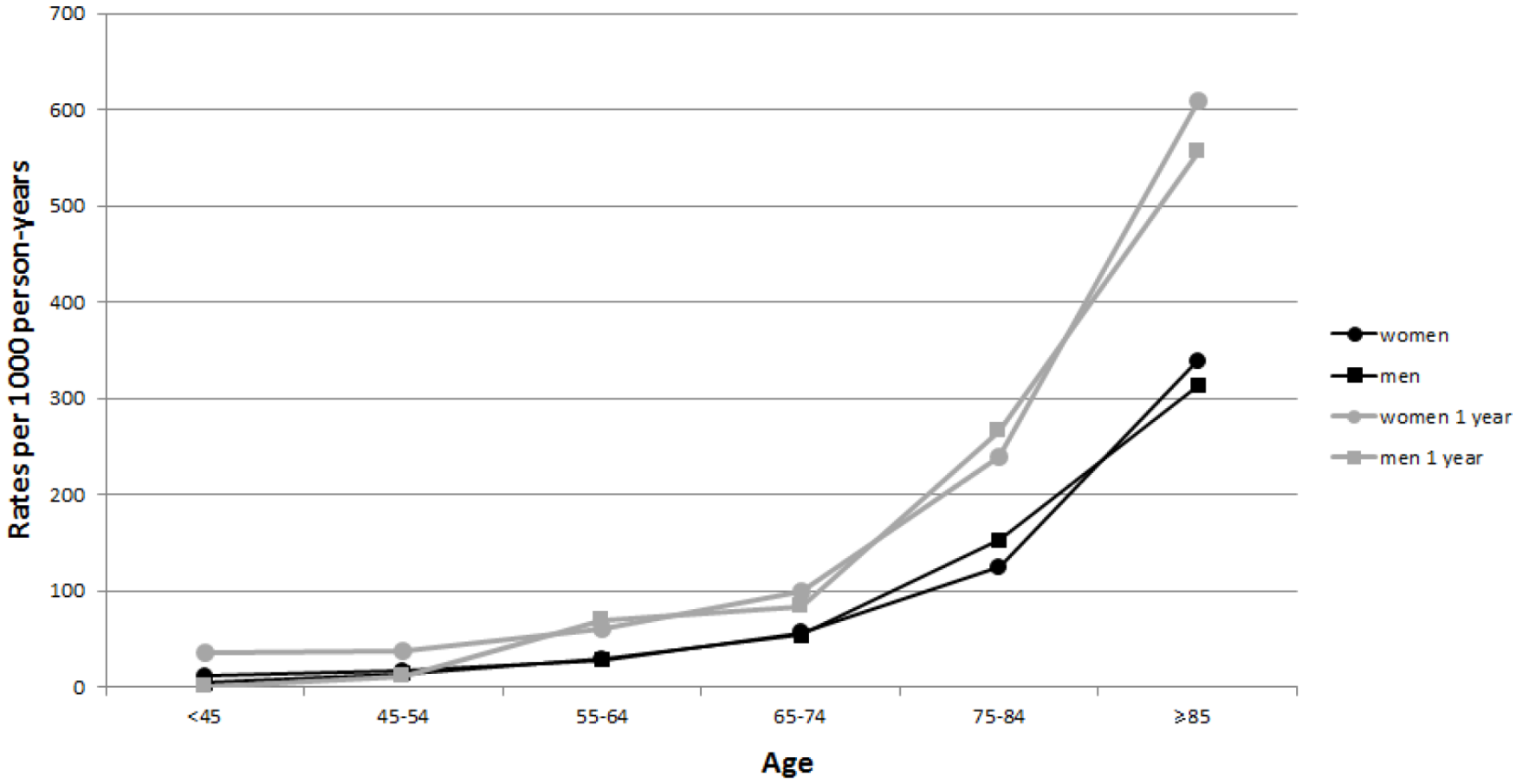

Figure 7. Mortality rates per 1000 person-years during the first year or during the entire study period.

CHAPTER 4

Late functional recovery after lacunar stroke

4.1 CHAPTER ABSTRACT

Non-acute interventions to enhance late stroke recovery are often tested initially in patients with lacunar stroke owing to their low mortality and isolated motor deficits. It is generally assumed that neurological recovery is near complete by 3-months after the stroke, but there have been few studies of the capacity for late recovery beyond 3-months.

In 3-month ischaemic stroke survivors of OXVASC, I examined changes in functional status (mRS, Rivermead Mobility Index [RMI], Barthel Index [BI]) in lacunar versus non-lacunar strokes from 3-60 months post-stroke, stratifying by age. I used logistic regression adjusted for age, sex, and baseline disability to compare recovery (≥1 mRS grades, ≥1 RMI points and/or ≥2 BI points), particularly from 3-12 months.

Among 1,425 3-month survivors, the 234 lacunar stroke patients did not differ from others for outcome at 3-months (aOR for 3-month mRS>2: 1.14, 95%CI 0.75-1.74, p=0.55), but were much more likely to demonstrate further recovery between 3-months and 1-year (aOR: 1.64, 1.17-2.31, p=0.004). Results were similar on restricting the analysis to patients with 3-month mRS 2-4 (the range commonly recruited into recovery studies) and on excluding recurrent events (aOR[mRS] adjusted for age, sex, and 3-month-mRS: 2.28, 1.34-3.86, p=0.002). Similar results were seen with the BI and RMI (aOR[RMI] adjusted for age, sex, and 3-month-RMI: 1.78, 1.20-2.64, p=0.004).

These findings demonstrate that lacunar strokes have greater potential for late functional recovery from 3-12 months post-stroke, supporting the focus of studies of restorative therapies on this group. However, such studies cannot assume that improvements after 3-months are treatment-related, and should therefore be randomized and controlled.

4.2 INTRODUCTION

Functional recovery after stroke is driven partly by structural and functional plasticity within surviving neural elements.[1] Therapies for post-stroke recovery and rehabilitation seek to modify these factors. For example, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) involve applying excitatory stimuli to the ipsilesional cortex to promote the efficacy of remaining cells, or inhibitory stimuli to the contralesional cortex to reduce inhibitory connections to the ipsilesional cortex.[2, 3] The efficacy of such restorative therapies is often evaluated in less-disabled patients, often with small subcortical (lacunar) strokes and isolated motor deficits,[4-6] since enrolling patients with too severe injuries can not only hamper behavioural training and patient retention, but also prevent detection of any treatment effects owing to their limited capacity for neuroplasticity.[7] These early studies sometimes lack a separate control group,[8-10] making the assumption that improvements seen beyond a few months post-stroke are likely to be related to the treatment, based on the conventional axiom that most meaningful recovery post-stroke occurs in the first 3-6 months.[11] However, when randomized trials of initially promising treatments have subsequently been done, they have often been disappointing.[2, 3]

Although the capacity for neuroplasticity is known to be influenced by the nature of the initial injury,[12] the differential implications of lesion location and stroke subtype for recovery remain uncertain. Lacunar infarcts, primarily affecting the subcortical white matter, account for around a quarter of all strokes,[13] but mechanisms of white-matter damage and repair remain relatively understudied. Whilst some studies have suggested that certain lacunar syndromes might have a greater capacity for recovery,[14] others have found no significant differences in recovery at discharge in cortical or subcortical strokes.[15] Of the few studies that have examined recovery beyond the acute phase, some found no differences[16] whilst others suggested that lacunar strokes fare worse,[17] but were limited by small sample size and/or retrospective design. In Chapter 2, I showed that about 1 in 4 patients demonstrate late recovery between 3-months and 1-year after ischaemic stroke, and found that lacunar strokes appeared to have better 5-year death/disability outcomes than non-lacunar strokes when stratified by 3-month mRS, raising the question of whether lacunar and non-lacunar strokes differ in their capacity for late recovery. Clarifying the late recovery trajectories of lacunar versus non-lacunar strokes will help inform the design of restorative treatment trials and test underlying assumptions about treatment effects in uncontrolled studies.

I therefore compared rates of functional recovery beyond 3-months in lacunar strokes versus non-lacunar ischaemic strokes in OXVASC, hypothesizing that lacunar strokes would be more likely to demonstrate late recovery.

4.3 METHODS

Study population and follow-up

OXVASC methodology was previously described in Chapter 2. For this chapter, I included consenting patients with ischaemic stroke recruited from April 2002 to March 2014. Patients did not receive any interventions beyond standard care. As noted previously, these patients were followed up by a study nurse or physician either in a hospital clinic or at home at 1-month, 3-months, 6-months, 1-year, and 5-years post-stroke. At each visit, functional status was assessed using the mRS, Rivermead Mobility Index (RMI), and Barthel Index (BI). The mRS, as noted previously, classifies patients into one of seven categories ranging from 0 (no symptoms) to 6 (death).[18] The RMI assesses functional mobility on 15 tasks and ranges from 0 (cannot perform any) to 15 (can perform all),[19] whereas the 20-point BI scale used in OXVASC assesses activities of daily living and ranges from 0 (dependent for all) to 20 (independent for all).[20] These scales are often used as primary outcome measures in trials of stroke recovery therapies.[3] In addition to being trained in the use of the mRS using an instructional DVD with accompanying written materials produced by the University of Glasgow (previously used in large clinical trials),[18] all raters underwent additional training and observation in the use of the RMI and BI. Pre-stroke mRS and BI were determined at enrollment.

In addition to the collection of data on deaths and recurrent events as described previously, for this chapter I also obtained healthcare resource use data for these patients from the date of the stroke until 1-May-2017, including post-stroke hospital-based rehabilitation admissions (with length of stay [LOS]) and community-based rehabilitation services (physiotherapy, occupational therapy, speech/language therapy).

Statistical Analyses

Only patients surviving for 3-months after their first stroke in the study period ('index' stroke) were included in the analyses, to focus on the period beyond the 90-day endpoint favoured by acute stroke trials. Analyses were censored at 15-May-2017.

I classified the patients as lacunar or non-lacunar strokes using the TOAST (Trial of Org10172 in Acute Stroke Treatment) criteria for small-vessel occlusion.[21] These lacunar strokes represented a relatively phenotypically-pure subset of small subcortical strokes. As a sensitivity analysis, I also examined recovery trends in patients with lacunar stroke syndromes (LACS per Oxfordshire Community Stroke Project [OCSP] classification) who did not necessarily meet strict TOAST criteria for radiological lesion extent and small-vessel aetiology.[13]

I plotted 3-month mRS against initial NIHSS score to examine the potential for early recovery in the first 3-months post-stroke. I then examined recovery beyond 3-months by plotting changes in mRS between 3-months and 6-months, 6-months and 1-year, and between 1-year and 5-years after the index stroke for lacunar versus non-lacunar patients. I further stratified these patients by age (<75 years and >75 years) to account for age-differences between lacunar and non-lacunar strokes.

As demonstrated in Chapter 2, any improvement in mRS scores can be clinically meaningful, as long-term mortality and dependency rise with each increment of the scale,[22] so patients were deemed to show recovery if the score decreased by ≥1 grades. Logistic regression was used to model the association of lacunar versus non-lacunar stroke with recovery on the mRS in each time-period of interest, adjusted for age, sex, and the baseline score for that time-period (e.g. 3-month mRS when examining recovery from 3-months to 1-year; 1-year mRS for recovery from 1-year to 5-years). Patients with mRS=0 at the beginning of each time-period were excluded from the respective regression since they could not show recovery. To minimize bias of the 1-year recovery analysis in favour of lacunar strokes from their lower mortality, whilst avoiding survivorship bias, I used the most recent mRS prior to death (i.e. 6-month mRS) whenever available for those patients who died within 1-year, and otherwise excluded 1-year deaths. To focus on patients with mild-to-moderate disability who might be recruited in recovery trials, I repeated the analysis using only patients with 3-month mRS of 2-4. To verify that findings were not reflecting disability differences unrelated to the index stroke, I repeated these regressions progressively excluding patients who had: recurrent vascular events, pre-stroke mRS>2, and relevant chronic conditions (peripheral vascular disease, heart failure, valvular disease, or cancer).

I sought to validate my findings by repeating these analyses with the RMI and BI. The minimal clinically important difference (MCID) for the RMI is not established, but test/retest studies suggest that increases by ≥1 points are reliable, so this was deemed indicative of recovery on logistic regression.[19] The MCID for the BI is 1.85 points, so increases by ≥2 points were deemed indicative of recovery.[20] Patients with 3-month RMI=15 and BI=20 were excluded from the relevant regressions as they could not show recovery; here I defined pre-morbid disability as pre-stroke BI<20.

Statistical analyses were performed using STATA 13.1. Trends in ordinal data in lacunar and non-lacunar strokes were compared using the non-parametric Wilcoxon rank-sum test corrected for ties.

4.4 RESULTS

Complete baseline and follow-up mRS data were available for 1,403 (98.5%) and RMI/BI data for 1,228 (86.2%) of the 1,425 3-month survivors. There was no difference between lacunar and non-lacunar strokes with missing RMI/BI data (n=197) in the distribution of NIHSS scores (p_{trend}=0.58), 3-month mRS (p_{trend}=0.14), or improvement on mRS from 3-months to 1-year (p_{trend}=0.36). Compared to patients with non-lacunar strokes, lacunar stroke patients were younger (p<0.0001), more often men (p=0.006), had lower initial NIHSS, and were less likely to have a history of myocardial infarction, atrial fibrillation, or pre-morbid disability (Table 1). Importantly, there was no difference between lacunar and non-lacunar strokes in utilization of thrombolysis (NIHSS-adjusted OR: 0.67, 95%CI 0.08-5.44, p=0.71), hospital-based rehabilitation (NIHSS-adjusted OR: 0.77, 0.53-1.12, p=0.18; mean LOS if NIHSS≥5: lacunar=54.9 days, non-lacunar=63.9 days, p=0.57), or community-based rehabilitation services (NIHSS-adjusted OR: 0.97, 0.63-1.49, p=0.88). Over 5-years of follow-up, there were fewer deaths in the lacunar stroke group but no differences in recurrent strokes, other vascular events, or post-stroke depression (Table 1).

Lacunar stroke patients did not differ from other stroke patients with respect to early post-stroke outcome at 3-months (odds of mRS>2 adjusted for age, sex, initial NIHSS score, thrombolysis, and pre-stroke disability=1.14, 95%CI 0.75-1.74, p=0.55, Figures I-II in the Appendix). 3-month RMI and BI scores (Figures III-IV) were also no different after adjusting for age, sex, NIHSS, and prior disability (adjusted coefficent[RMI]: 0.03, -0.48-0.53, p=0.92, acoef[BI]: 0.42, -0.18-1.02, p=0.17), and lacunar patients were no less likely to have 3-month RMI<15 or BI<20 (aOR:1.14,0.80-1.62,p=0.46).

Lacunar strokes were, however, much more likely to show recovery by ≥1 mRS grades between 3-months and 6-months (71/214 [33.2%] versus 242/1,052 [23.0%]; 3-month-mRS 2-4: 49/114 [43.0%] versus 160/621 [25.8%], p<0.001, Figure V), including after adjusting for age, sex, and 3-month mRS (aOR: 1.55, 1.11-2.18, p=0.01, n=1,206). These patients were also more likely to demonstrate recovery between 6-months and 1-year (39/198 [19.7%] versus 139/973 [14.3%]; 3-month-mRS 2-4: 24/96 [25.0%] versus 87/557 [15.6%],p=0.02, Figure VI). Consequently, recovery between 3-months and 1-year was also more common for lacunar strokes (75/214 [35.1%] versus 251/992 [25.3%], aOR: 1.64, 1.17-2.31, p=0.004, n=1206, Figure VII). This difference remained after restricting the analysis to those with 3-month mRS of 2-4 (57/114 [50.0%] versus 182/590 [30.9%], p<0.001, Figure 1), excluding recurrent events (aOR: 2.28, 1.34-3.86, p=0.002, n=488),

adjusting for pre-morbid disability (aOR: 2.11, 1.23-3.61, p=0.007), and further excluding patients with pre-morbid disability or relevant chronic conditions (Figure 2).

Similar trends were observed for recovery per the RMI/BI between 3-months and 1-year (Figure VIII). Of 225 patients with 3-month mRS≥1 and 3-month RMI<15 or 3-month BI<20 whose mRS score improved between 3-months and 1-year, 161 (71.6%) also showed an improvement in the RMI and/or BI (OR for patients with recovery per mRS also showing improvement per RMI/BI: 3.44, 2.46-4.80, p<0.0001; BI: 7.50, 4.81-11.7, p<0.0001). Patients with lacunar strokes were also significantly more likely to show recovery on the RMI and/or BI between 3-months and 1-year post-stroke, adjusted for age, sex, and 3-month RMI/BI (aOR: 1.55, 1.06-2.26, p=0.02, n=799; aOR[RMI]: 1.78, 1.20-2.64, p=0.004, n=752). This difference remained upon adjusting for recurrent events and pre-morbid BI (aOR: 1.59, 1.09-2.33, p=0.02; aOR[RMI]: 1.80, 1.21-2.67, p=0.004) or upon excluding recurrent events and pre-morbidly disabled patients (Figure 3, Figure IX). Patients with lacunar stroke were also significantly more likely to show improvement between 3-months and 1-year on one or more of the 3 scales (mRS, BI, or RMI) adjusted for age, sex, and NIHSS (aOR: 1.70, 1.26-2.28, p=0.001, n=1251), even upon restricting to patients with 3-month mRS of 2-4 and excluding those with recurrent events (aOR: 2.32, 1.34-4.02, p=0.003, n=488).

Beyond 1-year, improvements on the mRS were rarer in both groups (lacunar: 21/179 [11.7%], rest: 93/787 [11.8%], p=0.98, Figure X) and were no more likely with lacunar strokes after adjusting for age, sex, and 1-year-mRS (aOR[mRS]: 0.84, 0.50-1.43, p=0.53, n=961; excluding deaths or recurrent events: 0.92, 0.51-1.69, p=0.80, n=484). Similarly, lacunar stroke patients were no more likely than other 5-year survivors to show further recovery on the RMI/BI beyond 1-year (aOR: 0.83, 0.46-1.47, p=0.51, n=590; excluding deaths/recurrent-events: 0.77, 0.38-1.56, p=0.47, n=242, Figure XI).

Similar results were seen when performing all of these analyses with LACS stroke syndromes versus other syndromes, despite the greater similarity of their baseline characteristics (Table 2, Figure XII in Appendix). LACS strokes were no more likely to show early recovery within 3-months (aOR for 3-month mRS>2: 1.26, 0.89-1.77, p=0.19), but were significantly more likely to show late recovery on the mRS between 3-months and 1-year (aOR[mRS]: 1.37, 1.02-1.84, p=0.03), particularly between 3-months and 6-months (aOR: 1.62, 1.12-2.33, p=0.01 excluding recurrent events and pre-stroke mRS>2). Similarly, 1-year survivors were more likely to show recovery on the RMI/BI between 3-months and 1-year, adjusted for age, sex, 3-month-RMI/BI, and recurrent events (aOR[RMI/BI]: 1.44, 1.03-2.01,

p=0.03; aOR[RMI]: 1.41, 1.01-1.98, p=0.04, n=760). Beyond 1-year, no differences in recovery were seen (aOR[mRS]: 0.90, 0.66-1.24, p=0.53; aOR[RMI/BI]: 0.72, 0.38-1.37, p=0.32).

4.5 DISCUSSION

By prospective assessment of disability using three commonly-used scales in a population-based cohort study, I have shown that lacunar strokes have a greater potential for late recovery in the first year post-stroke, in the absence of interventions beyond standard care. This difference remained significant in multiple sensitivity analyses and was not accounted for by differences in 3-month disability, pre-morbid or non-stroke-related disability, mortality, or recurrent events. Recovery beyond 1-year was rare and no more likely in lacunar strokes. These findings have implications for the design and interpretation of trials of restorative therapies, and for our understanding of functional recovery.

First, these findings validate the practice of piloting and focusing studies of non-acute stroke recovery therapies like rTMS or tDCS in lacunar stroke patients. In addition to the known lower severity and mortality of lacunar strokes,[23] their greater intrinsic potential for late recovery makes them especially appealing for enrollment in trials of new therapies. The selection of such paitents might improve the detection of treatment effects that could be missed in a mixed sample of non-lacunar or cortical strokes lacking the same substrate for recovery. For example, analyses of a robot-based rehabilitation study[24] and a negative trial of epidural motor cortex stimulation[25] found that responders were typically lacunar/sub-cortical strokes who more often had intact motor system physiology, specifically cortical function and connectivity. Leveraging these attributes in lacunar stroke may be a promising therapeutic avenue.

Second, these findings imply that studies of recovery therapies cannot assume that improvements seen in the first year post-stroke are treatment-related, even if undertaken beyond 3-months post-stroke. Studies focusing on lacunar strokes should be randomized and controlled to ensure that improvement exceeds what is expected from their natural history. For instance, uncontrolled rTMS studies have reported that patients with lacunar/subcortical strokes were much more likely to improve, but this difference cannot simply be ascribed to a treatment response.[26] Similarly, if such therapies are then tested in the general stroke population in larger trials, the treatment and control groups should be balanced in their representation of lacunar strokes to prevent confounding by a greater capacity for late-recovery in either group. This baseline characteristic is not always reported

in high-profile recovery trials,[27] and it is worth noting that some recent rehabilitation trials that balanced the proportion of lacunar strokes have been negative.[28, 29] I propose that reporting the proportion of lacunar strokes in each arm should be routine practice for all recovery trials within 1-year post-stroke.

Third, the similarity of recovery beyond 1-year post-stroke in lacunar and non-lacunar strokes suggests that benefits seen with recovery therapies administered after 1-year are likely valid even if there are potential inter-group differences in the proportion of lacunar strokes. However, since about 1 in 10 patients generally show some meaningful functional recovery beyond 1-year, even such studies should include a control/placebo group for comparison.

Fourth, these findings lend credence to the phenomenon of late recovery beyond 3-months post-stroke and underscore the importance of further studying mechanisms of late subcortical or white-matter recovery. Emerging evidence indicates that these mechanisms include time-dependent processes like cortical activation, network modulation,[30] contralesional cortical reorganization,[31] enhanced inter-hemispheric connectivity,[32] and modulation of axo-myelinic synapses to alter myelin properties or recruit companion glia.[33] MRI lesions shrink over 1-year in almost half of lacunar strokes,[34] with axonal remodeling giving rise to poorly-organized, randomly-oriented axons in the initial post-stroke months, followed by gradual organization into single direction-oriented fibers.[35] These mechanisms may explain why the lacunar patients in OXVASC showed no difference in 3-month recovery but improved markedly over the next 9-months. That these differences persisted on adjusting for age is compatible with recent evidence that white-matter neuroplasticity, unlike cortical plasticity, does not diminish with age.[36]

Although my analysis has several strengths, including generalizability, with similar 5-year mortality and disability to prior population-based studies,[37] there are some potential shortcomings. Firstly, I assessed recovery using disability scales and did not serially determine neurological impairments such as using the NIHSS or Fugl-Meyer assessment,[38] which may be more sensitive to small improvements in post-stroke deficits. However, any insensitivity would likely result in similar underestimation of recovery in lacunar and non-lacunar strokes; moreover, improvement by a few points on an impairment-based scale may not translate into meaningful functional recovery,[39] which I sought to study. On the other hand, the use of functional outcome scales means that my analyses are unable to differentiate between improvement in neurological impairment and adaptation to impairment, as either of these

processes can result in an improvement in functional status. For instance, lacunar stroke patients may simply be better able to adapt to enduring impairments given their relatively intact cortices. Additional studies using serial measurements of neurological impairment will therefore be required to further clarify the nature of this observed late functional improvement. Secondly, functional outcome scales like the mRS are vulnerable to confounding by non-stroke-related disability. However, inter-group differences remained significant upon adjusting and/or excluding pre-morbid disability and excluding those with potentially disabling comorbidities. Thirdly, one might argue that apparent improvements on the mRS simply reflected potential inter-rater variability.[18] However, this seems unlikely, as my findings remained consistent after adjusting for the 3-month mRS, and upon examining changes on the BI and RMI, both of which have high inter-rater agreement.[40, 41] Fourthly, I could not adjust for all psycho-social factors that could influence stroke recovery like mood or anxiety issues, caregiver or family supports, occupational or financial considerations. However, I suspect that such inter-individual variability is unlikely to have driven the large and robust between-group differences in this study.

In conclusion, lacunar strokes have greater potential for late recovery in the first year post-stroke, supporting the focus of restorative therapies on this group. However, such studies cannot assume that improvements after 3-months are treatment-related, and should be randomized and controlled.

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4.7 TABLES

Table 1. Patient sample and characteristics of 3-month survivors of ischaemic stroke, classified per TOAST criteria for lacunar strokes (small vessel occlusion)

Characteristic	**All strokes** (n=1,425)	**Lacunar strokes** (n=234)	**Non-lacunar strokes** (n=1,191)	**Age- and sex-adjusted P**
Age, mean (S.D.)	73.2 (12.7)	69.9 (12.0)	73.8 (12.8)	
Sex – male (%)	753 (52.8)	143 (61.1)	610 (51.2)	
Previous history(%):				
MI	177 (12.4)	13 (5.6)	164 (13.8)	**0.002***
Angina	239 (16.8)	32 (13.7)	207 (17.4)	0.46
Atrial Fibrillation	260 (18.2)	2 (0.9)	258 (21.7)	**<0.0001***
Hypertension	889 (62.4)	145 (62.0)	744 (62.5)	0.87
Dyslipidemia	469 (32.9)	72 (30.8)	397 (33.3)	0.45
Diabetes	205 (14.4)	42 (17.9)	163 (13.7)	0.10
PVD	108 (7.6)	13 (5.6)	95 (8.0)	0.31
Stroke	158 (11.1)	22 (9.4)	136 (11.4)	0.66
TIA	205 (14.4)	29 (12.4)	176 (13.8)	0.75
Smoking	836 (58.7)	147 (62.8)	689 (57.9)	0.70
Heart Failure	119 (8.4)	4 (1.7)	115 (9.7)	**0.001***
Valvular Heart Disease	134 (9.4)	14 (6.0)	120 (10.1)	0.13
Cancer	22 (15.5)	32 (13.7)	189 (15.9)	0.61
Pre-stroke mRS>2	244 (17.2)	17 (7.3)	227 (19.1)	**0.003***
Pre-stroke BI<20	318 (22.3)	38 (16.2)	280 (23.5)	0.88
Initial NIHSS, mean (SD)	3.7 (5.0)	2.1 (2.2)	4.1 (5.4)	**<0.001***
Recurrent stroke within 5-years of follow-up (%)	211 (14.8)	33 (14.1)	178 (15.0)	0.92
Any recurrent vascular event within 5-years (%)	360 (25.3)	64 (27.4)	296 (24.9)	0.25
Post-stroke depression (%)	350 (24.6)	60 (25.6)	290 (24.4)	0.67
Deaths (%)				
Within 1-year	138 (9.7)	1 (0.4)	137 (11.5)	**0.002***
Within 5-years	464 (37.1)	41 (19.1)	423 (40.8)	**<0.001***

Significant differences ($p<0.05$) between lacunar and non-lacunar strokes are indicated by an asterisk (*). Age was compared using an independent samples T-test, sex using the Chi-squared test, NIHSS using age/sex-adjusted linear regression, and the rest using age/sex-adjusted logistic regression.

Abbreviations: AF – Atrial Fibrillation, S.D. – Standard deviation, MI – Myocardial Infarction, PVD – Peripheral Vascular Disease, TIA – Transient Ischaemic Attack, mRS – modified Rankin scale, BI – Barthel Index, NIHSS – National Institutes of Health Stroke Scale.

Table 2. Patient sample and characteristics for 3-month survivors of ischaemic stroke, classified per Oxfordshire Community Stroke Project criteria for lacunar stroke syndromes (LACS)

Characteristic	**LACS strokes** (n=362)	**Non-LACS strokes** (n=1,063)	**Age- and sex-adjusted P**
Age, mean (S.D.)	71.5 (12.6)	73.7 (12.6)	
Sex – male (%)	207 (57.2)	541 (50.9)	
Previous history(%):			
MI	35 (9.7)	141 (13.3)	0.07
Angina	58 (16.0)	177 (16.7)	0.33
Atrial Fibrillation	38 (10.5)	214 (20.1)	0.87
Hypertension	225 (62.2)	653 (61.4)	0.65
Dyslipidemia	108 (29.8)	358 (33.7)	0.10
Diabetes	56 (15.5)	146 (13.7)	0.56
PVD	25 (6.9)	83 (7.8)	0.52
Stroke	39 (10.8)	114 (10.7)	0.76
TIA	48 (13.3)	155 (14.6)	0.66
Smoking	224 (61.9)	608 (57.2)	0.60
Heart Failure	24 (6.6)	91 (8.6)	0.36
Valvular Heart Disease	27 (7.5)	104 (9.8)	0.26
Cancer	57 (15.8)	159 (15.0)	0.44
Pre-stroke mRS >2	47 (13.0)	185 (17.4)	0.24
Pre-stroke BI <20	72 (19.9)	233 (21.9)	0.86
Initial NIHSS, mean (SD)	2.6 (2.8)	4.2 (5.6)	**<0.001***
Recurrent stroke within 5-years of follow-up (%)	47 (13.0)	164 (15.4)	0.40
Any recurrent vascular event within 5-years (%)	88 (24.3)	272 (25.6)	0.81
Post-stroke depression (%)	96 (26.5)	254 (23.9)	0.32
Deaths (%)			
Within 1-year	19 (5.3)	119 (11.2)	**0.007***
Within 5-years	91 (28.1)	374 (40.3)	**0.01***

Significant differences ($p<0.05$) between lacunar and non-lacunar strokes are indicated by an asterisk (*). Age was compared using an independent samples T-test, sex using the Chi-squared test, NIHSS using age/sex-adjusted linear regression, and the rest using age/sex-adjusted logistic regression.

Abbreviations: AF – Atrial Fibrillation, S.D. – Standard deviation, MI – Myocardial Infarction, PVD – Peripheral Vascular Disease, TIA – Transient Ischaemic Attack, mRS – modified Rankin scale, BI – Barthel Index, NIHSS – National Institutes of Health Stroke Scale.

4.8 FIGURES

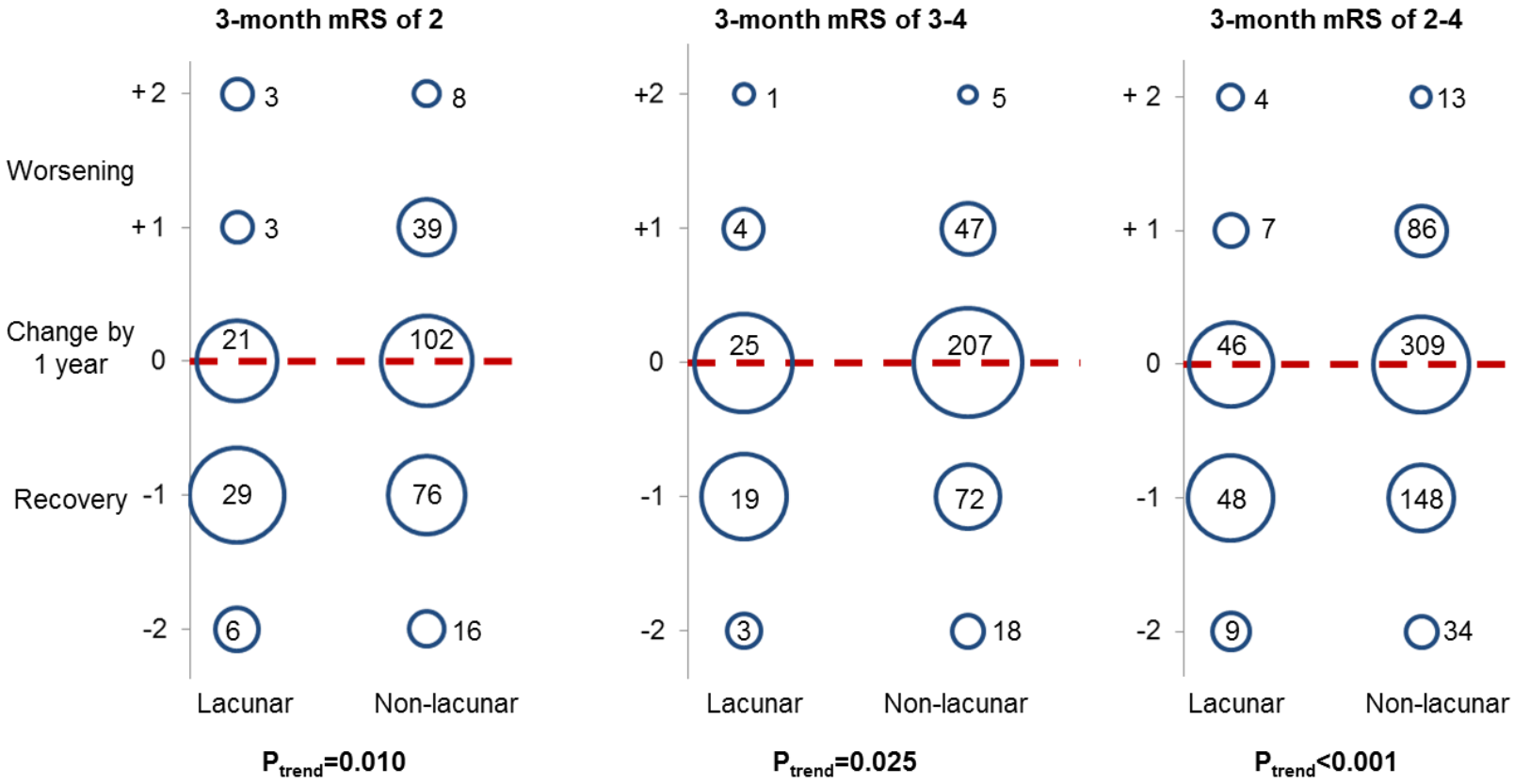

Figure 1. Changes in modified Rankin Scale (mRS) between 3-months and 1-year post-stroke for 3-month survivors of lacunar versus non-lacunar strokes with 3-month mRS of 2, 3-4, and 2-4 (pooled) who could potentially be recruited for trials of stroke recovery therapies. The size of each bubble represents the percentage of patients in the relevant group (lacunar/non-lacunar) at that intersection. Bubbles falling along the dashed line indicate no change in mRS. Bubbles falling above this line indicate a worsening of mRS score in that time period, while those falling below it indicate recovery. Results of non-parametric tests for significance of trend (P_{trend}) are shown below each graph. The results for patients with 3-month mRS of 3 and 4 are displayed together because there were only 15 lacunar stroke patients with 3-month mRS of 4.

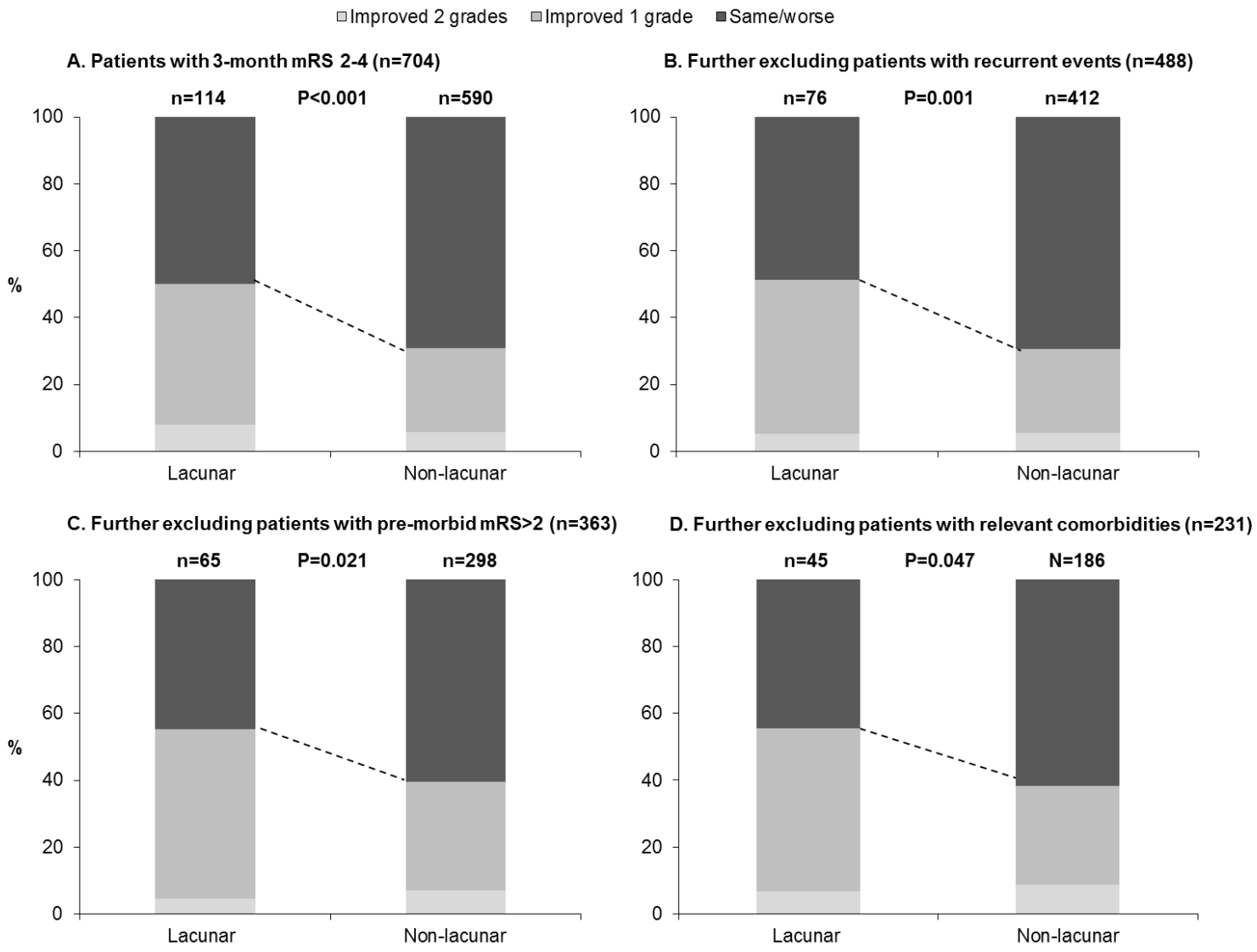

Figure 2. Changes in mRS between 3-months and 1-year post-stroke for 3-month survivors of lacunar versus non-lacunar stroke, (A) including all patients with 3-month mRS of 2 to 4, and then progressively excluding patients with: (B) recurrent vascular events over follow-up, (C) pre-morbid mRS>2, and (D) relevant comorbidities including peripheral vascular disease (PVD), heart failure, valvular heart disease, and/or cancer. P-values shown are from Wilcoxon rank-sum tests for trend.

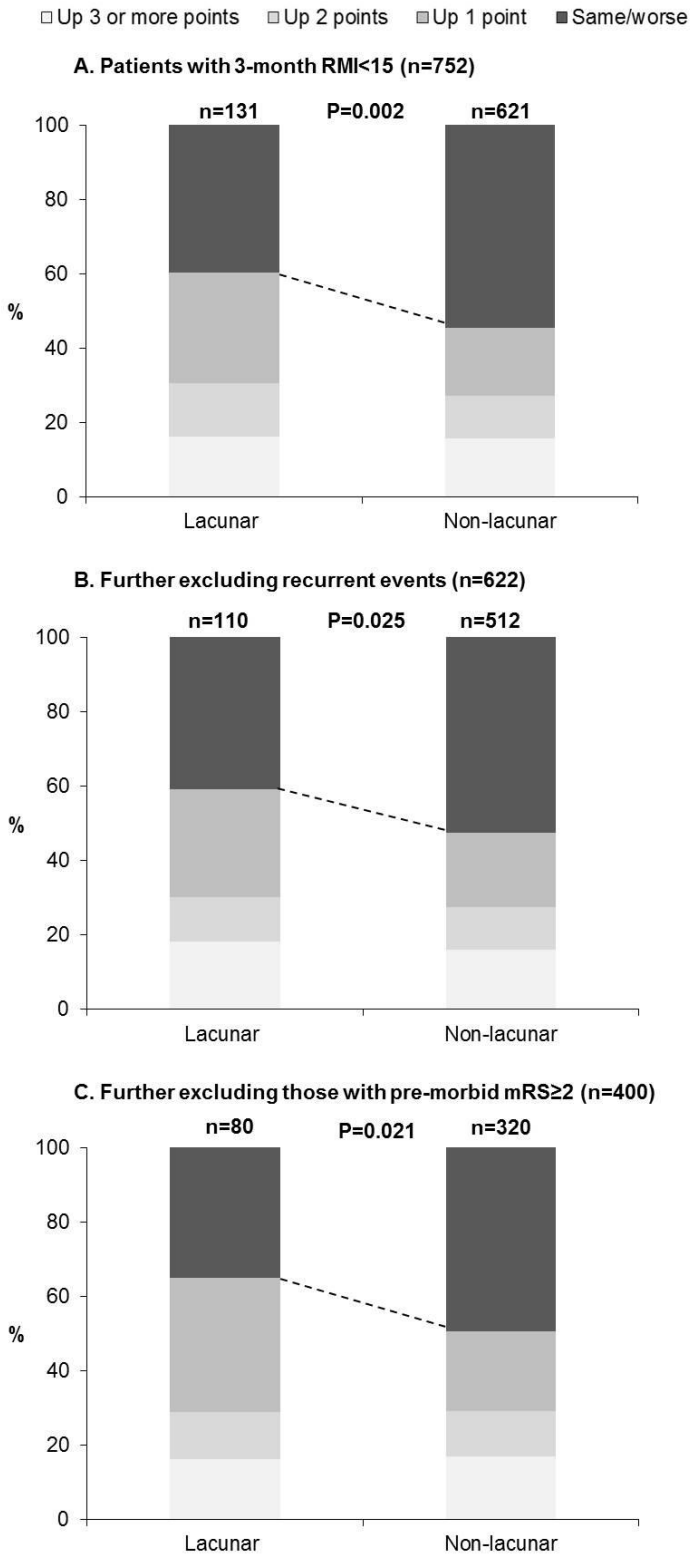

Figure 3. Changes in Rivermead Mobility Index (RMI) between 3-months and 1-year post-stroke for 3-month survivors of lacunar versus non-lacunar stroke, (A) including all patients with 3-month RMI<15, and then progressively excluding (B) those with recurrent strokes over follow-up, and (C) those with pre-morbid mRS≥2. P-values shown are from Wilcoxon rank-sum tests for trend.

4.9 APPENDIX – Supplementary Figures for Chapter 4

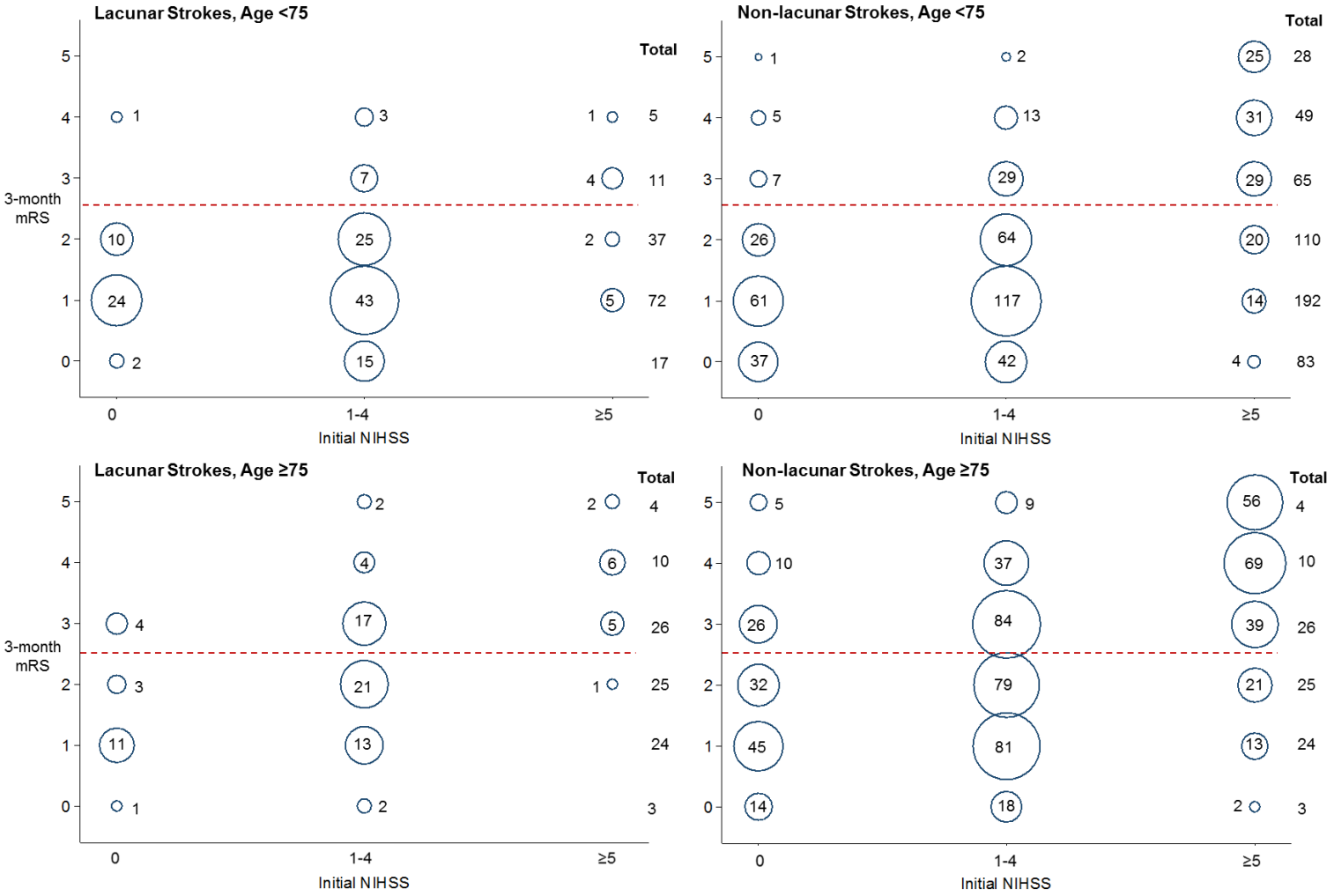

Figure I. 3-month mRS scores by initial NIHSS score, stratified by age<75 and ≥75, for 3-month survivors with lacunar strokes and non-lacunar strokes. The size of each bubble represents the number of patients at that intersection. The dashed line separates patients with moderate or higher disability (mRS 3-5) from those with no or mild disability (mRS 0-2).

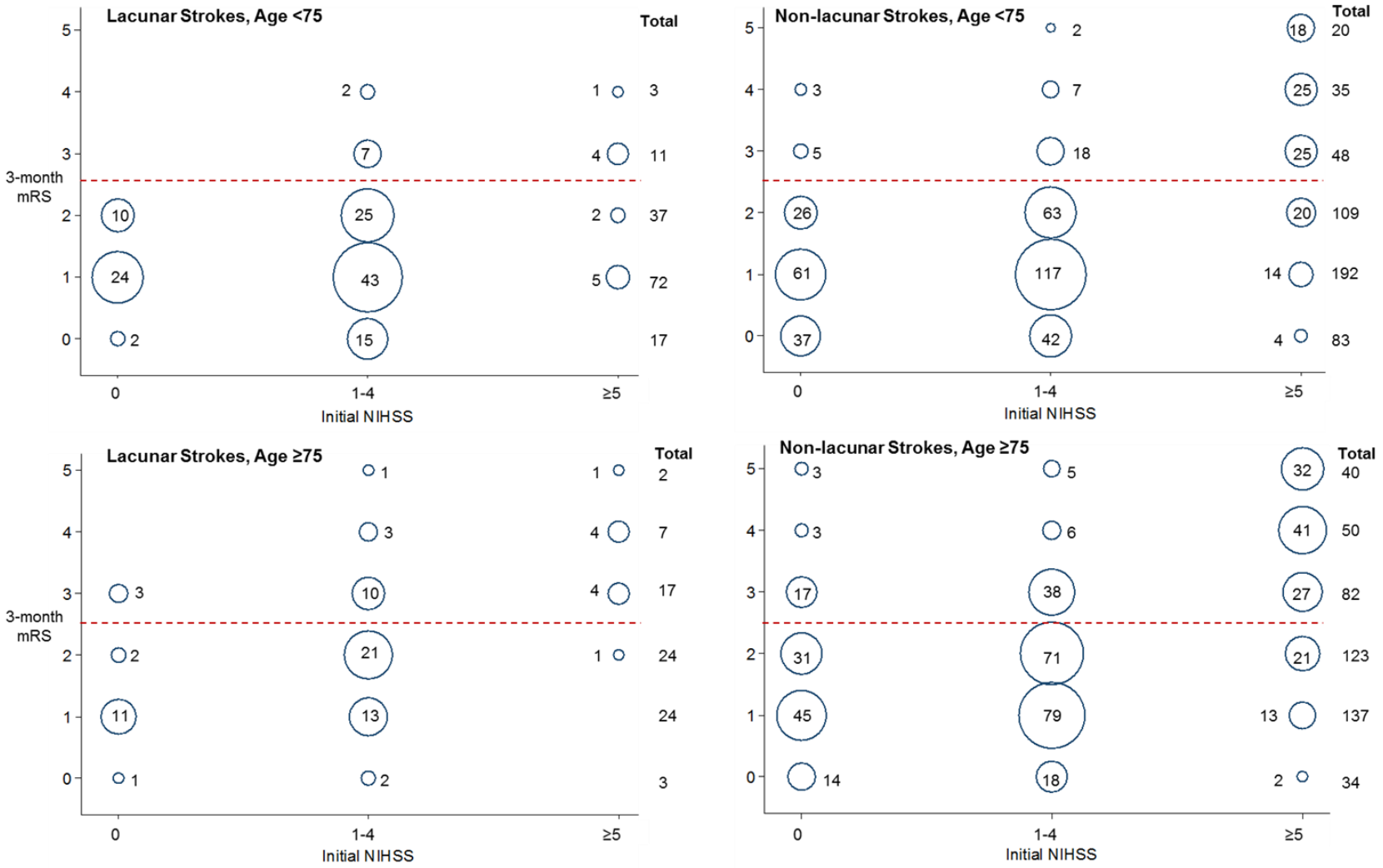

Figure II. 3-month mRS scores by initial NIHSS score, stratified by age<75 and ≥75, for 3-month survivors with lacunar strokes and non-lacunar strokes, excluding those with pre-stroke mRS>2. The size of each bubble represents the number of patients at that intersection. The dashed line separates patients with moderate or higher disability (mRS 3-5) from those with no or mild disability.

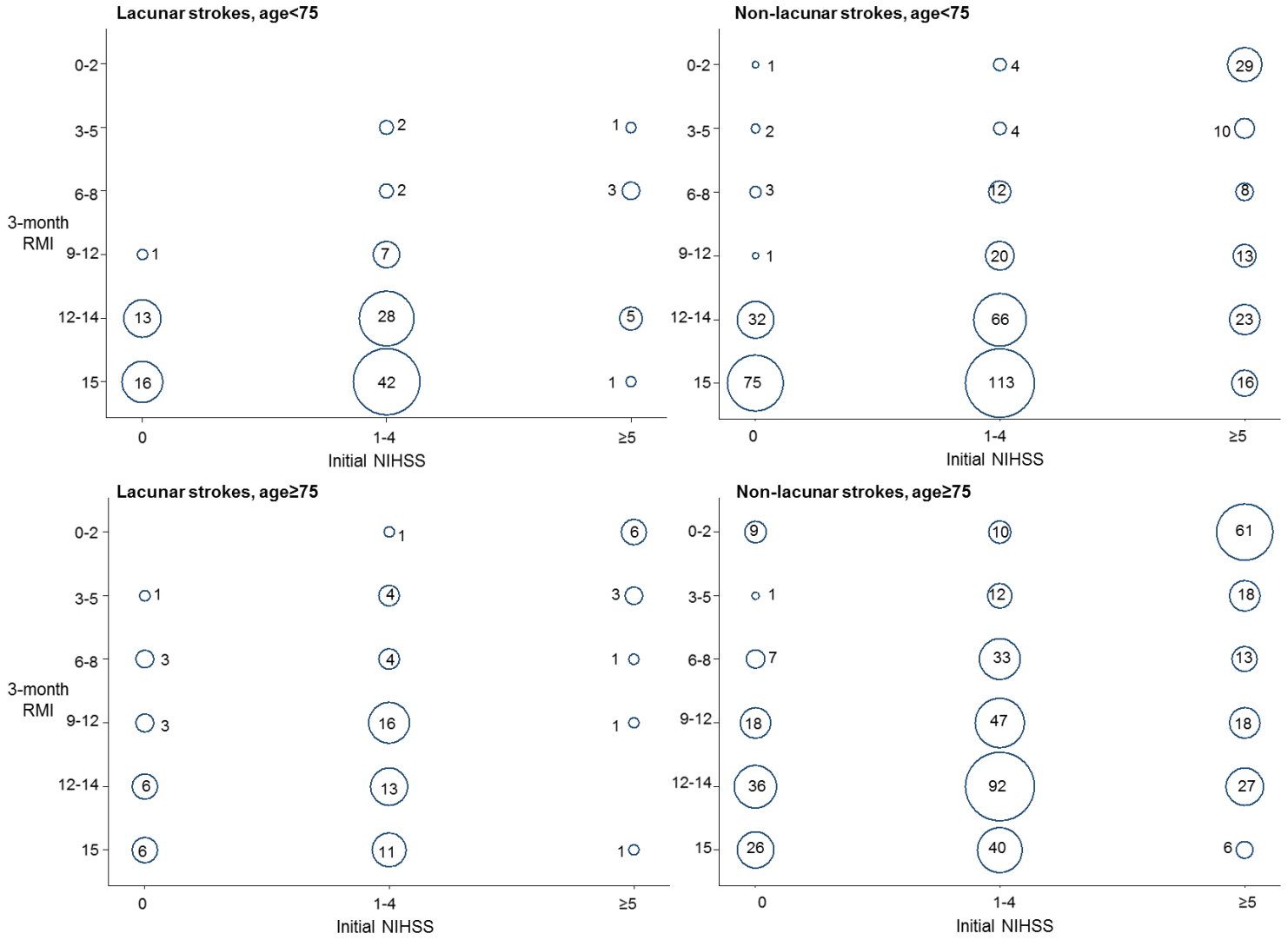

Figure III. 3-month Rivermead Mobility Index (RMI) scores by initial NIHSS score, stratified by age<75 and ≥75, for 3-month survivors with lacunar strokes and non-lacunar strokes.

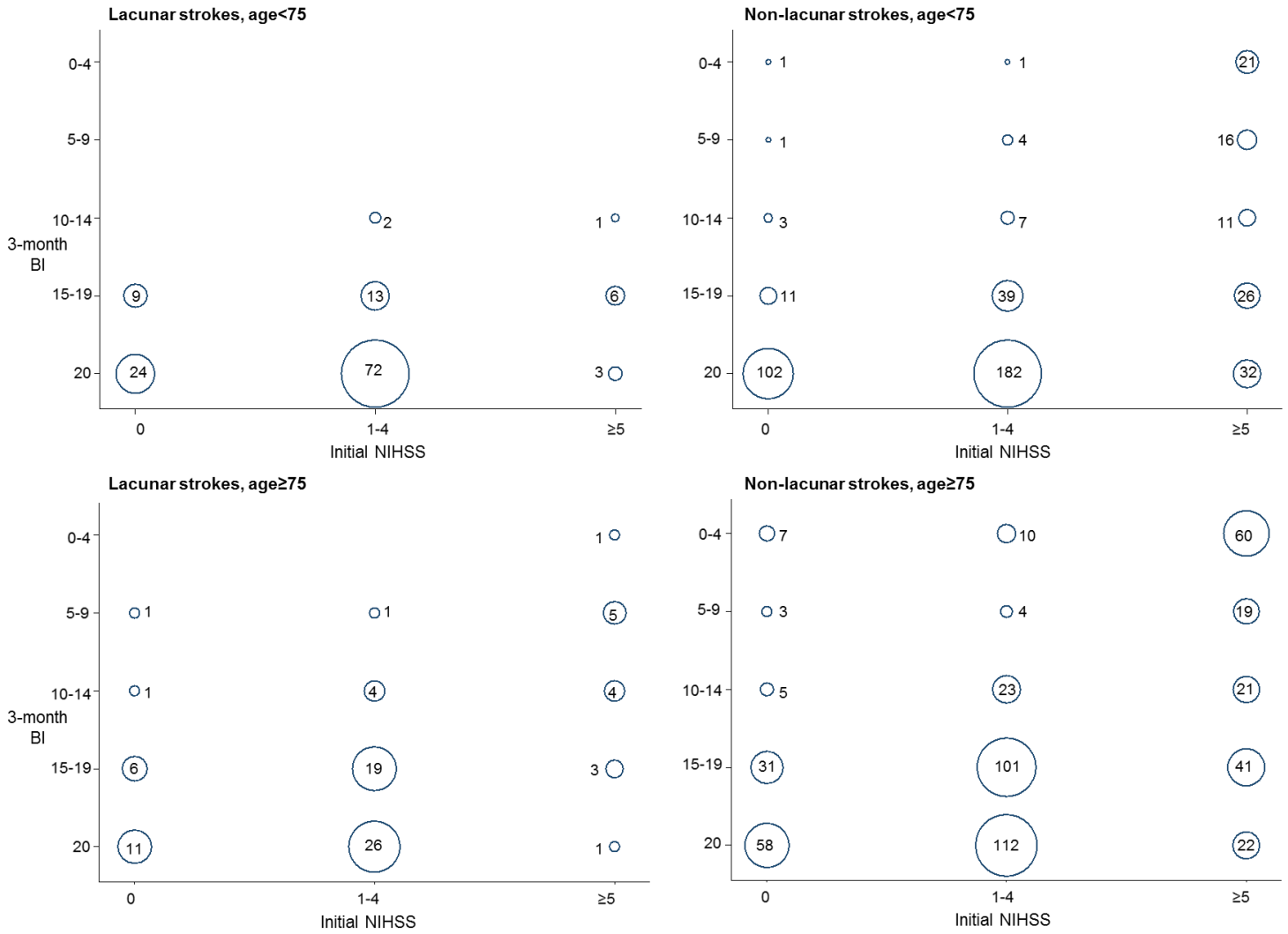

Figure IV. 3-month Barthel Index (BI) scores by initial NIHSS score, stratified by age<75 and ≥75, for 3-month survivors with lacunar strokes and non-lacunar strokes.

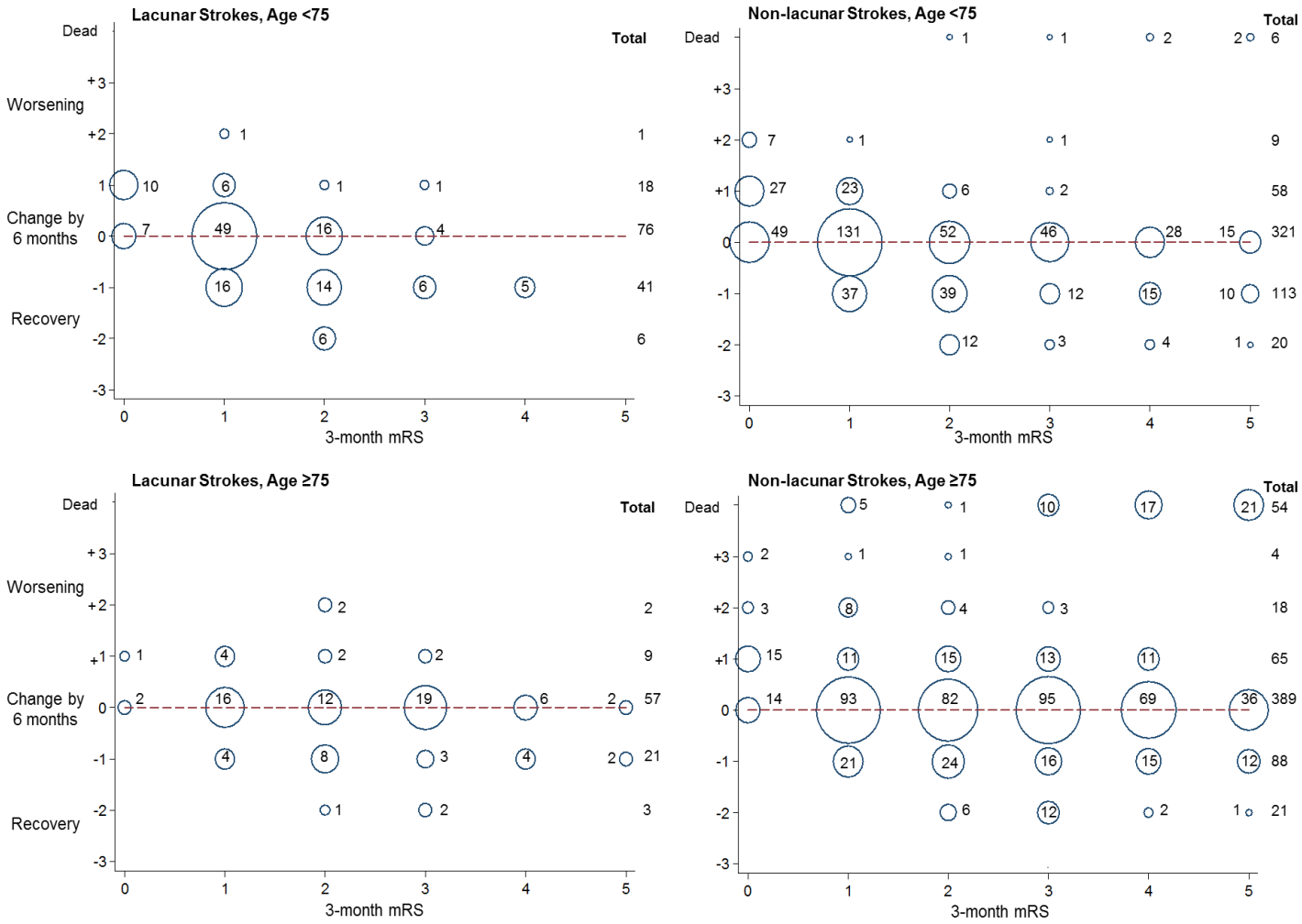

Figure V. Changes in mRS between 3-months and 6-months post-stroke for 3-month survivors with lacunar and non-lacunar stroke, stratified by age<75 and ≥75. The size of each bubble represents the number of patients at that intersection. Bubbles falling along the dashed line indicate no change in mRS. Bubbles falling above this line indicate a worsening of mRS score in that time period, while those falling below it indicate recovery.

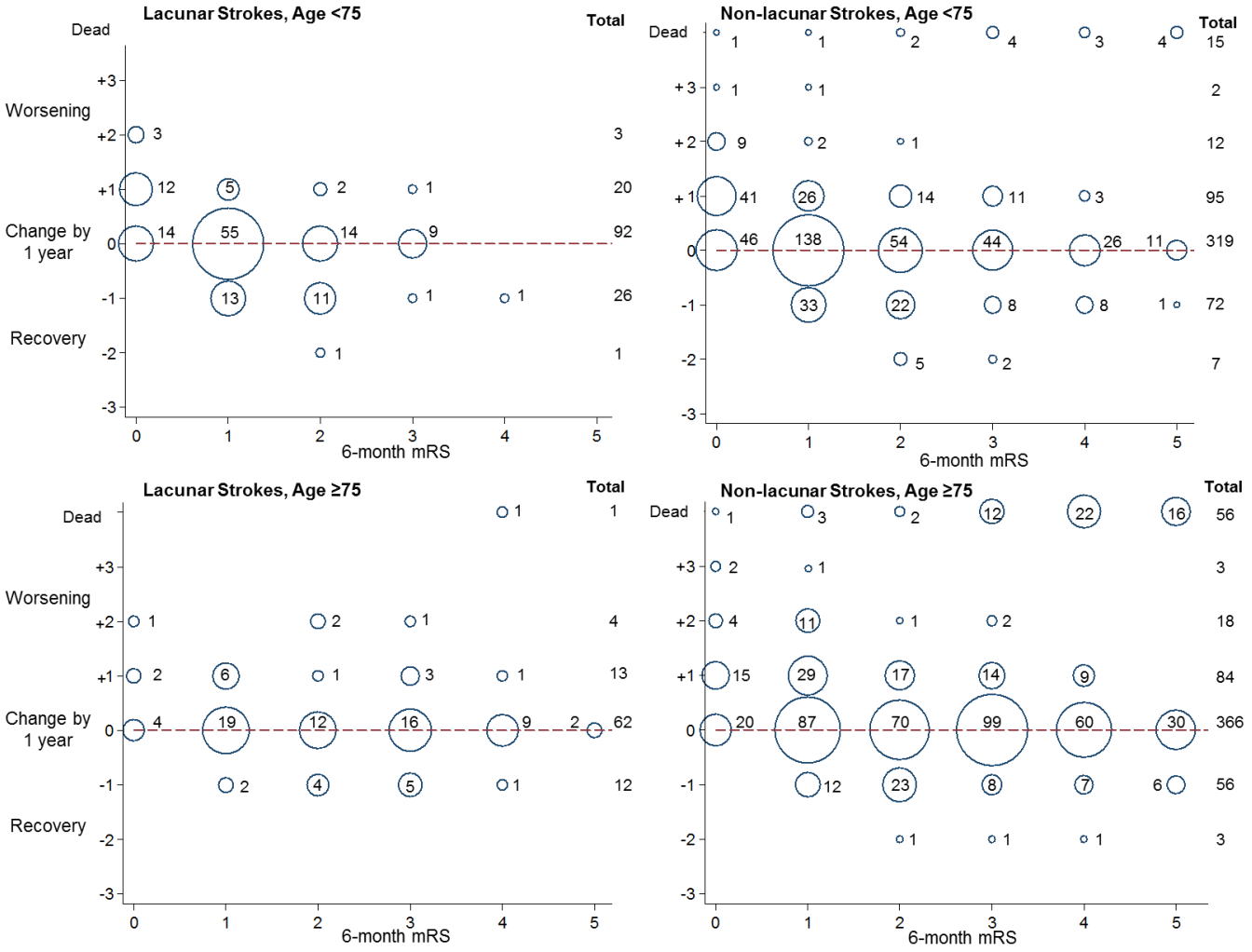

Figure VI. Changes in mRS between 6-months and 1-year post-stroke for 6-month survivors with lacunar and non-lacunar stroke, stratified by age<75 and ≥75. The size of each bubble represents the number of patients at that intersection. Bubbles falling along the dashed line indicate no change in mRS. Bubbles falling above this line indicate a worsening of mRS score in that time period, while those falling below it indicate recovery.

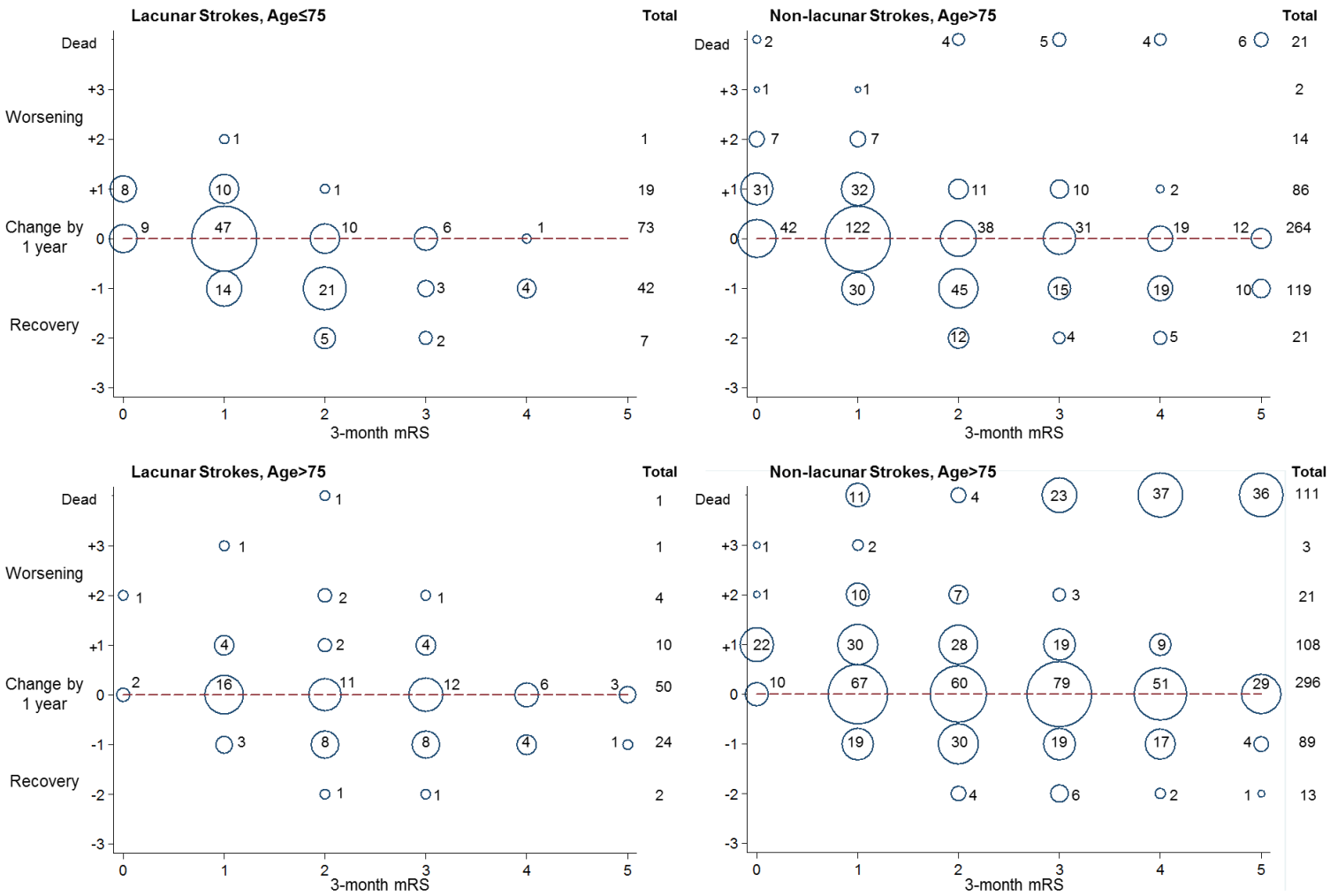

Figure VII. Changes in mRS between 3-months and 1-year post-stroke for 3-month survivors with lacunar and non-lacunar stroke, stratified by age<75 and ≥75. The size of each bubble represents the number of patients at that intersection. Bubbles falling along the dashed line indicate no change in mRS. Bubbles falling above this line indicate a worsening of mRS score in that time period, while those falling below it indicate recovery.

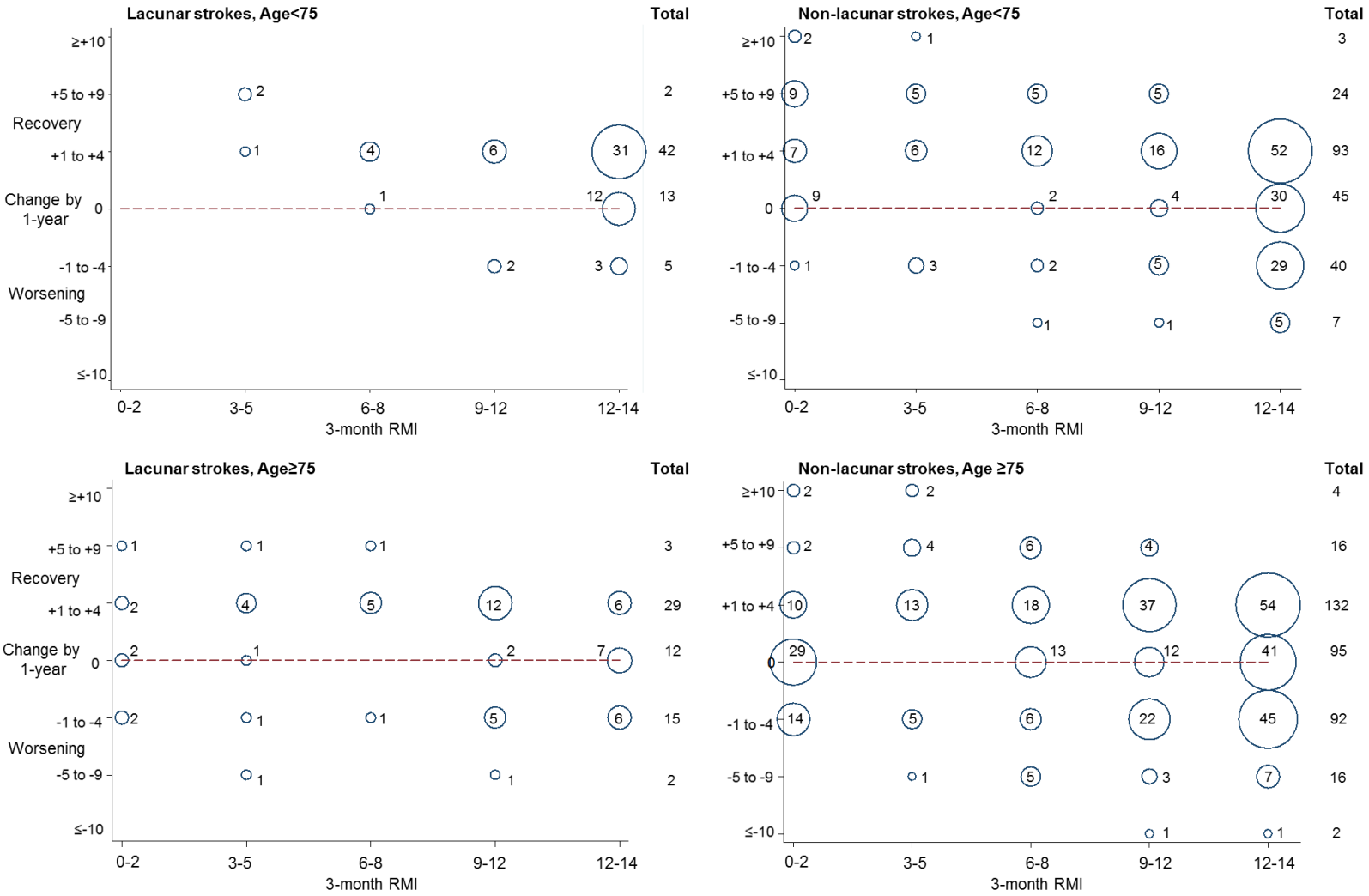

Figure VIII. Changes in RMI between 3-months and 1-year post-stroke for 1-year survivors with lacunar and non-lacunar stroke and a 3-month RMI<15, stratified by age<75 and ≥75. The size of each bubble represents the number of patients at that intersection. Bubbles falling along the dashed line indicate no change in RMI. Bubbles falling below this line indicate a worsening of RMI score in that time period, while those falling above it indicate recovery.

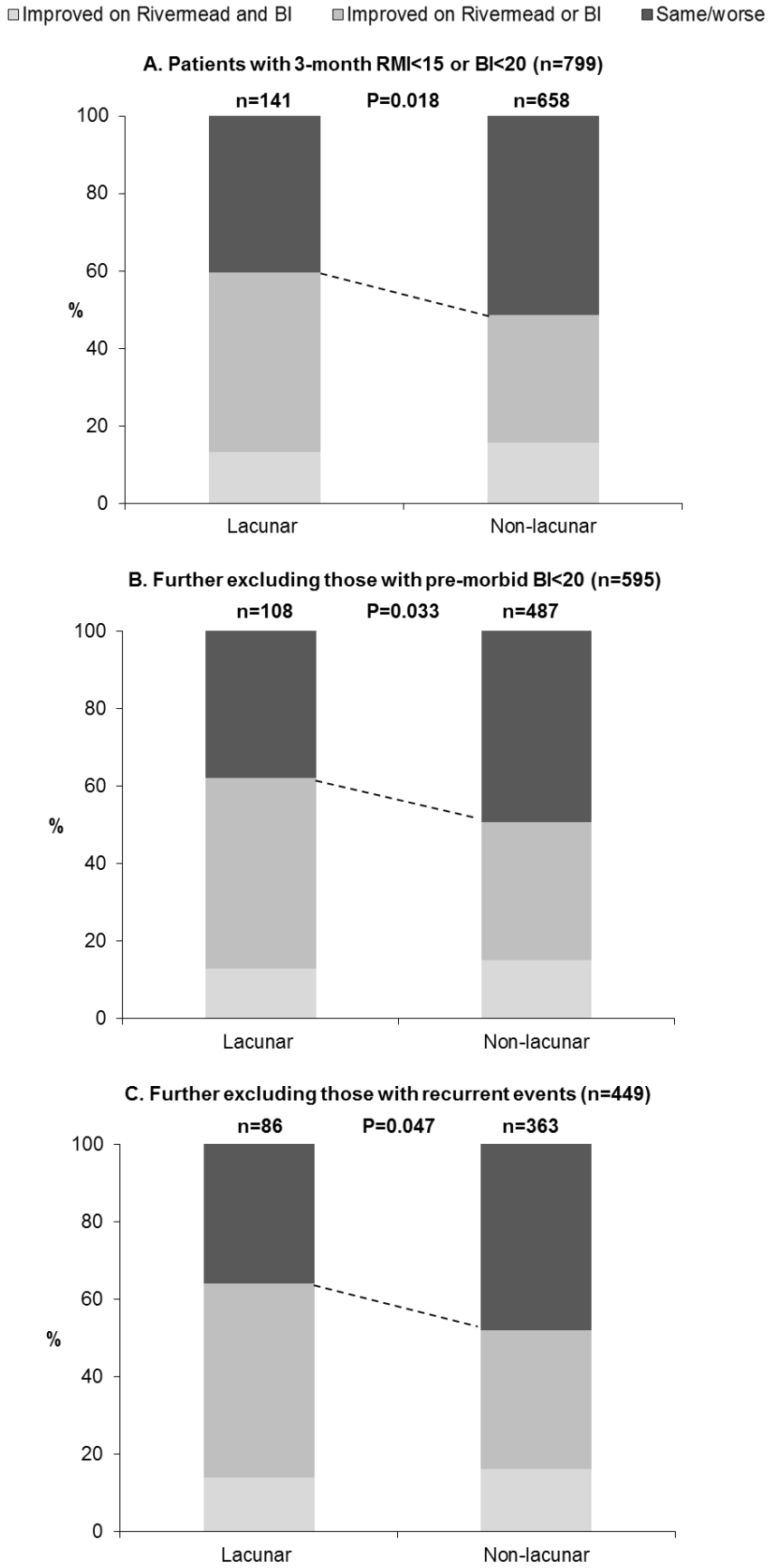

Figure IX. Changes in Rivermead Mobility Index (RMI) and/or Barthel Index (BI) between 3-months and 1-year post-stroke for 3-month survivors of lacunar versus non-lacunar stroke, (A) including all patients with 3-month RMI<15, and then progressively excluding those with (B) pre-morbid BI<20 and (C) recurrent vascular events over follow-up. P-values shown are from Wilcoxon rank-sum tests.

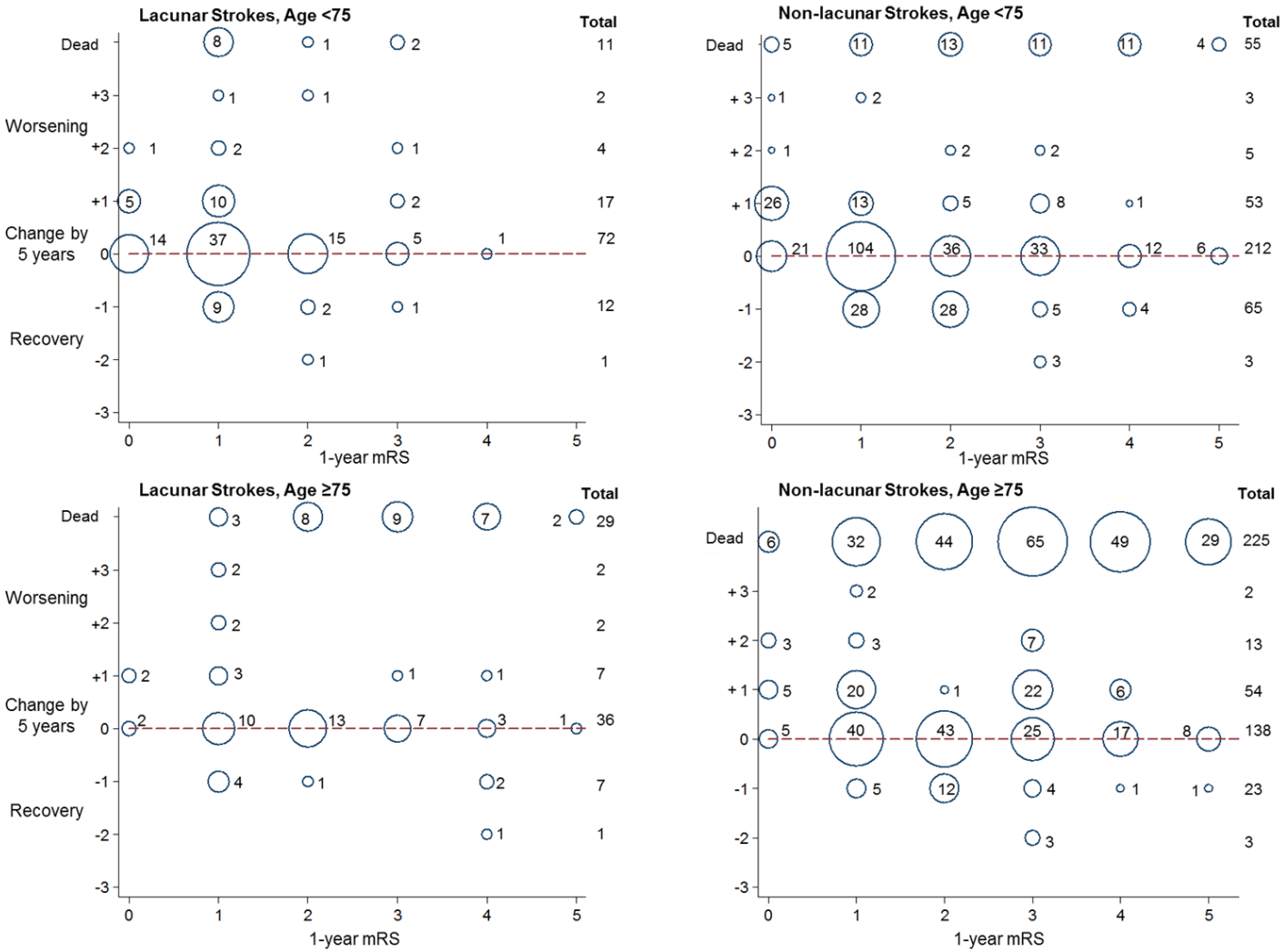

Figure X. Changes in mRS between 1-year and 5-years post-stroke for 1-year survivors with lacunar and non-lacunar stroke, stratified by age<75 and ≥75. The size of each bubble represents the number of patients at that intersection. Bubbles falling along the dashed line indicate no change in mRS. Bubbles falling above this line indicate a worsening of mRS score in that time period, while those falling below it indicate recovery.

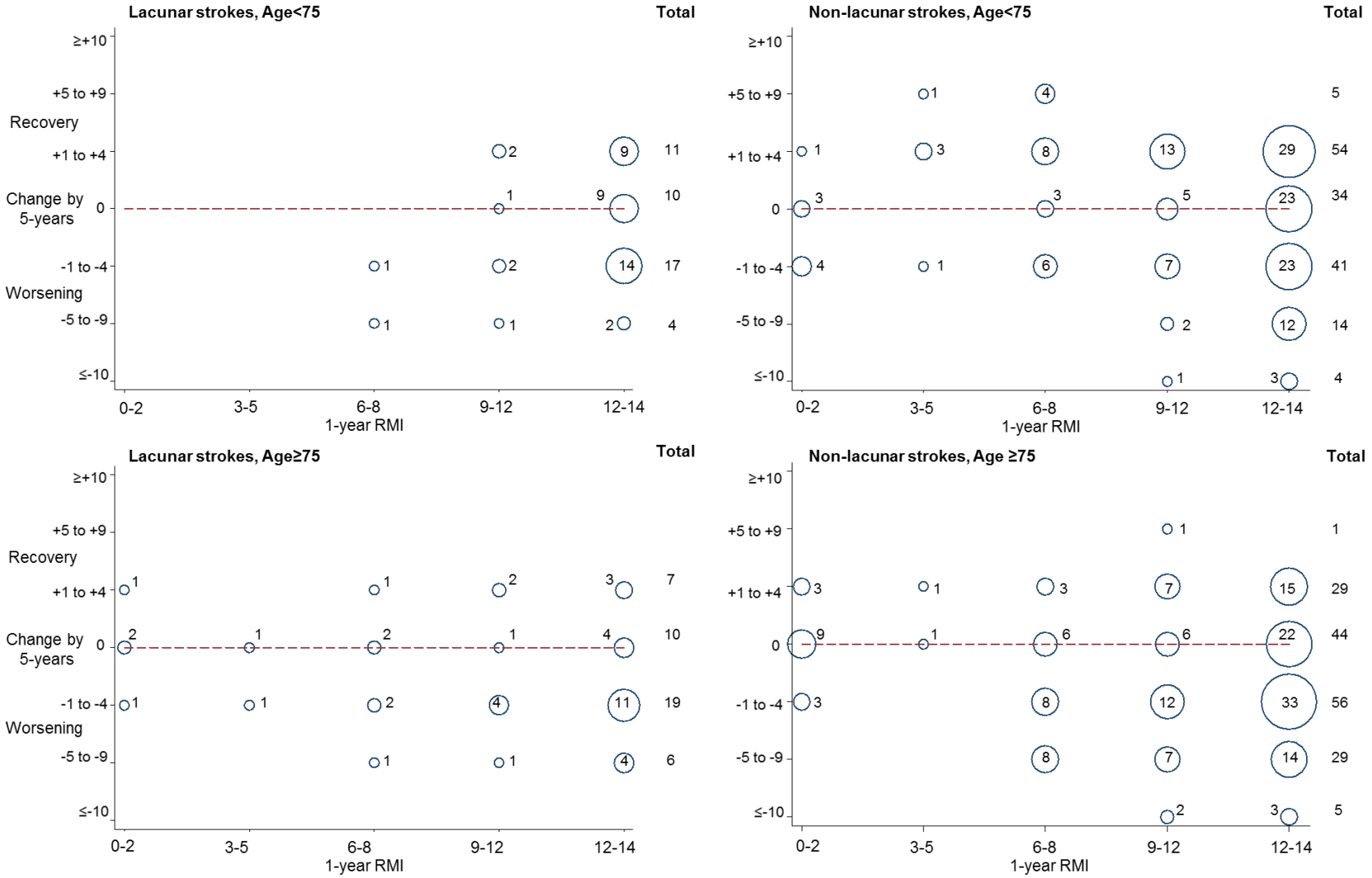

Figure XI. Changes in RMI between 1-year and 5-years post-stroke for 5-year survivors with lacunar and non-lacunar stroke, stratified by age<75 and ≥75. The size of each bubble represents the number of patients at that intersection. Bubbles falling along the dashed line indicate no change in mRS. Bubbles falling below this line indicate a worsening of mRS score in that time period, while those falling above it indicate recovery.

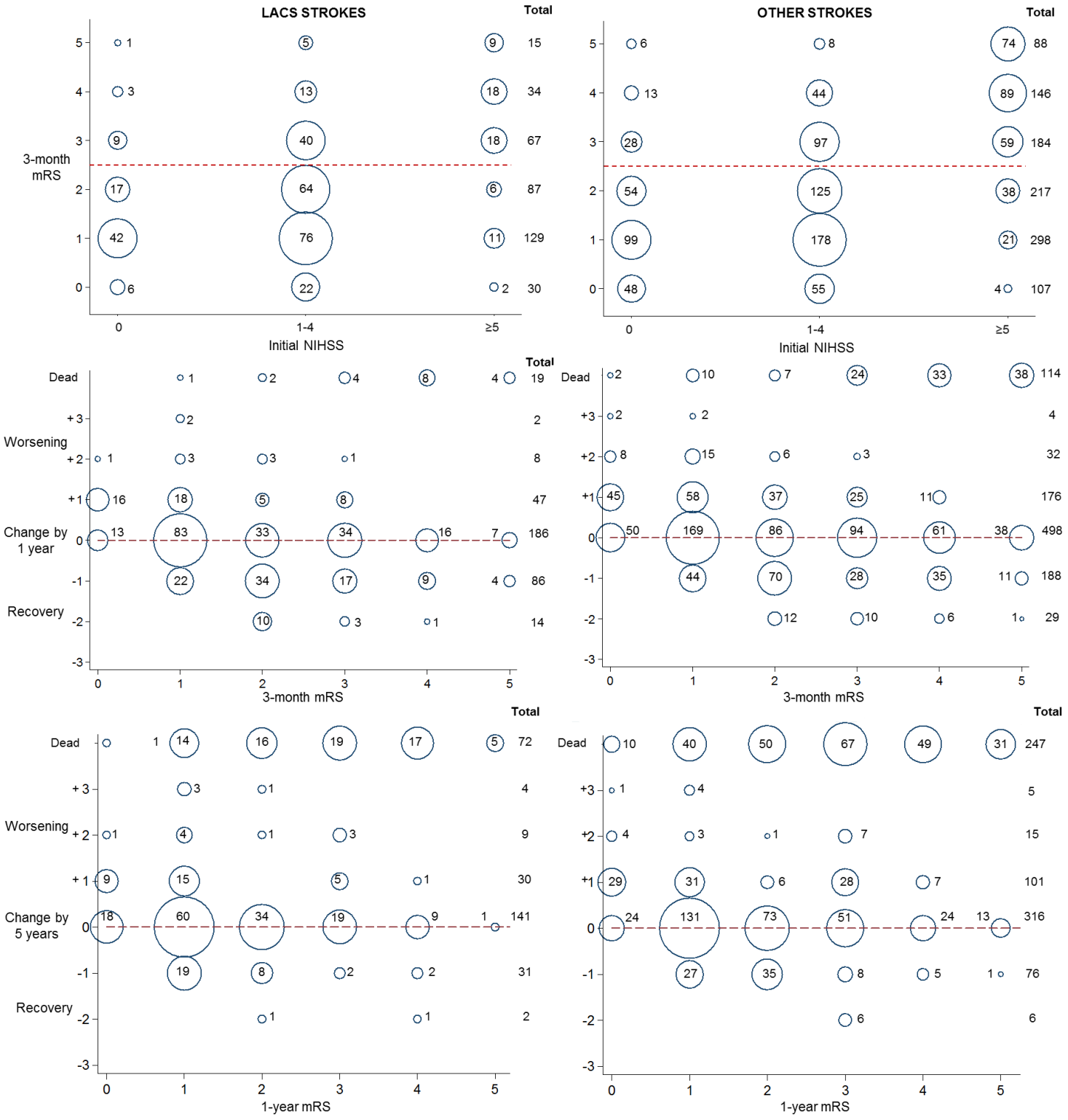

Figure XII. Early recovery (3-month mRS by initial NIHSS) and recovery from 3-months to 1-year, and 1-year to 5-years in 3-month survivors with lacunar stroke syndromes (LACS) versus other strokes. The size of each bubble represents the number of patients at that intersection. Bubbles falling along the dashed line indicate no change in mRS. Bubbles falling above this line indicate a worsening of mRS score in that time period, while those falling below it indicate recovery.

CHAPTER 5

Ordinal versus dichotomous analyses of the modified Rankin Scale in the prediction of 5-year outcomes and costs after ischaemic stroke

5.1 CHAPTER ABSTRACT

There is debate about the merits of ordinal vs dichotomous analysis of the mRS when it is used as a primary outcome measure in neurological trials, and about the 0-1/2-6 vs 0-2/3-6 dichotomy. In this chapter, I assessed the predictive power of these mRS representations for long-term outcome after ischaemic stroke and also quantified trial ineligibility rates based on pre-morbid mRS.

In consecutive ischaemic stroke survivors in OXVASC, I related 3-month mRS to 1-year and 5-year disability and death (logistic regressions), as well as health and social care costs (generalized linear model), adjusted for age/sex, and compared predictive values (Area under the Curve, AUC; Akaike information criterion, AIC). I also calculated the proportion of patients in whom a pre-morbid mRS >1 or >2 would result in exclusion from trials using dichotomous analysis.

Among 1,425 3-month survivors, 3-month mRS representations differed in predicting 5-year mortality ($p_{heterogeneity}$=0.0005), with ordinal superior to 0-1/2-5 (p=0.0004) and 0-2/3-5 somewhat better than 0-1/2-5 (p=0.02). Results were similar for 5-year disability, and 5-year care costs were also best predicted by the ordinal model (ΔAIC versus age/sex: -423 for ordinal, -374 for 0-2/3-5, -316 for 0-1/2-5; relative-likelihood<0.00001). 244 (17.1%) survivors had pre-morbid mRS>2 and 434 (30.5%) had mRS>1; both proportions increased with female sex, socio-economic deprivation, and age (all p<0.001), with age-specific rates of mRS>1 ranging from 9 (7.0%) patients aged <55 to 150 (60.7%) of those >85 years.

Thus, ordinal analysis of the 3-month mRS best predicts long-term outcomes after ischaemic stroke. Rates of pre-morbid disability that would usually necessitate exclusion of patients from trials using dichotomous analysis were high in several important groups. The implications of these findings of trial design and interpretation are discussed.

5.2 INTRODUCTION

In Chapter 2, I demonstrated that the 3-month mRS is a strong independent predictor of 5-year death and disability outcomes after ischaemic stroke. In Chapters 3 and 4, I demonstrated some of the vulnerabilities of considering the 3-month mRS in isolation as a post-stroke outcome, particularly with regards to apparent sex differences in stroke outcome (when failing to account for pre-morbid disability) and the greater capacity for late recovery between 3- and 12-months in lacunar stroke patients (when failing to control for this in recovery studies). But overall, my findings have reaffirmed the use of the 3-month mRS as the primary outcome measure in stroke trials. Yet despite its popularity, there remains a lack of consensus on how the mRS should be analysed when used as an outcome measure, as briefly discussed in Chapter 1. Over half of stroke trials since 2007 used dichotomous (binary) analysis, splitting the mRS into favourable/unfavourable outcomes, whilst about a quarter used ordinal (shift) analysis, assessing all changes across the range.[1] There is also disagreement about optimal dichotomy, with many recent trials using mRS 0-1 versus 2-6, instead of 0-2 versus 3-6.[2-5]

Dichotomous analyses provide results that are easily explained using the absolute risk reduction in outcome between treatment groups, but they are often statistically inefficient, requiring larger sample sizes, and risk overvaluing a beneficial transition at one end of the distribution whilst disregarding harm at the other.[6] The ordinal approach, first advocated for stroke trials by Bath[7] and Saver[8], reduces this risk and allows trials to reduce sample size by 14-53%[9] – particularly appealing for trials in rarer conditions – but might reduce statistical power if benefit is clustered at a few predictable state-transitions.[10] When seeking a clinically interpretable parameter (common odds-ratio), ordinal analysis is also limited by the proportional odds assumption, although alternatives have been proposed.[11] The dilemma is complicated by inter-rater variability, which is greatest for grades 1 and 2, around which the mRS is dichotomized.[12]

Aside from the issue of which approach is most statistically robust for short-term outcome analysis, the long-term trajectories of patients in different mRS grades might also be important in informing the choice of primary outcome analysis. Moreover, a dichotomous approach usually results in exclusion of patients with pre-morbid disability, since such patients are unlikely to achieve a favourable stroke outcome per that definition. For example, recent trials of thrombectomy in acute stroke generally excluded patients with pre-morbid mRS≥2.[13] However, such patients could still contribute in ordinal analysis, particularly if there are major differences in long-term outcomes across the range of mRS categories.

I therefore compared the predictive power of the three commonly used mRS representations (ordinal/full-range versus dichotomized as 0-1/2-6 or 0-2/3-6) for 5-year disability, survival, and health/social-care costs after ischaemic stroke in the OXVASC study. I also examined the proportion of patients who had pre-morbid mRS>1 or >2 – who would risk exclusion with dichotomous approaches – and examined whether the predictive power of the mRS representations would differ upon excluding these patients.

5.3 METHODS

Study Population

OXVASC methodology was previously described in Chapter 2. Since I sought to predict 5-year outcomes and costs based on the 3-month mRS (as used in trials), and 3-month mRS=6 (death) would perfectly predict 5-year death/disability, I focused on patients surviving 3-months past their index stroke (first stroke in the study period, 2002-2014) in this Chapter. However, since 3-month deaths would contribute to the primary outcome analysis of a trial and might improve the predictive ability of each mRS representation to different extents, I performed analyses for 1-year and 5-year death both including and excluding these patients.

Health and Social Care Resource Use

Resource use was obtained from the date of the first stroke in the study period ("index" stroke) until 5-years post-stroke or 15-May-2017, whichever was first. The methods on how resource use and costs were collected have been reported previously.[14,15] Patients' medical records from the Oxford University Hospitals Trust were reviewed for any A&E visit, emergency transport, outpatient care visit, day case, or hospitalisation. For each spell in hospital, the dates of admission, discharge, and transfers between different specialty wards were recorded. I estimated the number of institutionalized days as the difference between either date of 5-year follow-up or death, whichever was earliest, and the date of admission into the institution. Hospital resource use was valued using unit costs from the schedule of reference costs for NHS trusts.[16] Institutionalization was costed as the cost per week in a private nursing home, which in 2016 was £795 ($1,145).[17] Costs were presented in 2016 prices and converted from UK pounds sterling (£) to US dollars ($) using the 2016 rate of purchasing power parities ($=£0.694, http://stats.oecd.org/).

Statistical Analyses

The proportions of patients who had pre-morbid mRS of >2 or >1 were calculated both for the overall cohort and in relation to age (<45, 45-54, 55-64, 65-74, 75-84, ≥85 years), sex, and index of socioeconomic deprivation.[18] The proportions disabled, dead/disabled, or dead

at 1-year and 5-years were also calculated and stratified by 3-month mRS. Disability at 1-year or 5-years was defined as mRS>2, but analysis was repeated using mRS>1. Logistic regression was used to adjust associations of 3-month mRS and long-term outcomes for age/sex. Proportions of interest were compared using Chi-squared tests.

Since I did not have full 5-year data for patients recruited after 15-May-2012, I examined the effect of censoring on resource-use results,[19] partitioning the study period into smaller time-periods (by day) within each of which the total cost incurred for all patients alive at the beginning of the period was calculated. Estimated costs of patients with complete data for each time-period were weighted by the Kaplan-Meier sample average estimator, and summed over all periods to estimate mean censor-adjusted costs. Costs were stratified by 3-month mRS and reported as means with 95% confidence-intervals (CIs) from 1000-bootstrap estimates. To assess whether health/social care costs varied over time by 3-month mRS, I constructed generalized gamma linear models (GLMs) assuming a log identity, adjusted for age/sex. Statistical significance was set at $p<0.050$.

Model quality for predicting disability and/or death was assessed using the Area under the Receiver-Operating-Characteristics Curve (AUC) from the age/sex-adjusted logistic regressions, with each of the following forms of the 3-month mRS: (1) dichotomized as 0-2/3-5, (2) dichotomized as 0-1/2-5, and (3) including the full range of the mRS (0-5) in the models. I compared these AUCs using the standard nonparametric approach, and calculated the ΔAUC by subtracting the AUC obtained from a logistic model including only age/sex.[20] The quality of the GLMs for predicting health and social care costs with these mRS representations was compared using the Akaike information criterion (AIC), with which I calculated the relative likelihood, proportional to the probability that the lowest-quality model minimizes estimated information loss.[21] I also calculated the ΔAIC versus a GLM including only age/sex. These analyses were repeated after excluding patients with (1) pre-morbid mRS>2, and (2) pre-morbid mRS>1.

Statistical analyses were performed using STATA 13.1.

5.4 RESULTS

Pre-morbid disability

I presented the baseline characteristics for this cohort in Chapter 2. 244 (17.2%) 3-month survivors had pre-morbid mRS>2; this proportion rose with age from 5 (3.9%) patients <55 years, to 228 (20.6%) >65, and 92 (37.9%) >85 years (Figure 1A). On the other hand, 433 (30.5%) patients had pre-morbid mRS>1, including 9 (7.0%) patients aged <55 years, 402 (36.3%) >65, and 150 (60.7%) >85 years. Women were more likely than men to have

premorbid mRS>2 (155/670 [23.1%] versus 89/752 [11.8%]) or >1 (264/670 [39.4%] versus 170/752 [22.6%], p<0.001, Figure 1B). Patients at or worse than the median socio-economic deprivation index were more likely than those less deprived to have premorbid mRS>2 (175/828 [21.1%] versus 68/593 [11.5%]) or >1 (300/828 [36.2%] versus 133/593 [22.5%], p<0.001, Figure 1C). Age, female sex, and deprivation independently predicted premorbid disability on multivariable logistic regression even upon adjusting for significant comorbidities (Table I, Appendix).

Disability and death/disability outcomes

When disability was defined as mRS>2, the proportion of survivors who were disabled at 5-years increased with 3-month mRS (Figure IA, Appendix), with a bigger step-change when dichotomized as 0-2/3-5 versus 0-1/2-5 (Figure IB). Similar trends were observed with the composite outcome of 5-year death/disability (Figure IC-D). On age/sex-adjusted logistic regression, 3-month mRS strongly predicted 5-year disability (Tables II-III, Appendix), and 5-year death/disability (Tables IV-V), with AUC≥0.8 for all 3 models. Both when including/excluding patients with pre-morbid mRS>2, the AUCs for the ordinal model were consistently superior to the 0-2/3-5 and 0-1/2-5 dichotomies (e.g. for 5-year death/disability in all, ΔAUC[vs age/sex]=0.142 for ordinal versus 0.135 for 0-2/3-5, p=0.02; 0.086 for 0-1/2-5, p<0.0001; ROC curves in Figures II-III). When disability was defined as mRS>1 (Tables VI-IX), the two dichotomies became similar in predicting 5-year disability and death/disability but the ordinal model remained superior when including/excluding those with pre-morbid mRS>1 (ROC curves in Figures IV-VI; e.g. for 5-year death/disability in all, ΔAUC=0.112 for 0-2/3-5 versus 0.102 for 0-1/2-5, p=0.20; 0.131 for ordinal, p<0.0001).

1-year and 5-year deaths

3-month mRS strongly predicted 1-year mortality (Figure 2A), with 22/869 (2.5%) of patients with 3-month mRS of 0-2 dead at 1-year (no significant difference among 0,1, or 2) versus 28/251 (11.2%) with mRS 3, 41/180 (22.8%) with mRS 4, and 42/103 (40.8%) with mRS 5 (p≤0.001 for each comparison). Consequently, on age- and sex-adjusted logistic regression, the 0-2/3-5 dichotomy was more predictive of 1-year death than 0-1/2-5 whilst the ordinal scale was superior to both (Table X, ΔAUC[vs age/sex]=0.106 for ordinal versus 0.087 for 0-2/3-5, p=0.02; 0.045 for 0-1/2-5, p<0.0001). On examining 5-year death, the main change was that mortality differences emerged between mRS 1 (66/356,18.5%) and 2 (76/273, 27.8%, p=0.006) whilst mRS 3 and 4 became similar (Figure 2B). The ordinal model remained the best predictor of 5-year death (Table 1, ΔAUC=0.037 for ordinal versus 0.032 for 0-2/3-5 and 0.017 for 0-1/2-5, $p_{heterogeneity}$=0.0005, ROC curves in Figure VII) whist the 0-2/3-5 dichotomy performed better than 0-1/2-5 (p=0.02). In particular, jumps in odds of 5-year death were seen from mRS 2 to 3 and 3-4 to 5 (aOR versus 0 for mRS 2=1.64, 95%CI

0.85-3.17; mRS 3=3.81, 1.97-7.37; mRS 5=10.4, 4.83-22.6, p<0.0001). When patients with 3-month mRS of 6 were included in the regressions for 1-year and 5-year death, the ordinal model remained superior to both dichotomies (Tables XI-XII).

When patients with pre-morbid mRS>2 were excluded (Tables XIII-XIV), then the ordinal model no longer significantly outperformed the 0-2/3-5 dichotomy but was still consistently superior to 0-1/2-5 (e.g. for 5-year death, ΔAUC=0.028 for ordinal versus 0.022 for 0-2/3-5, p=0.09; 0.014 for 0-1/2-5, p=0.01; ROC curves in Figure VIII). On the other hand, the 0-2/3-5 dichotomy was slightly better than 0-1/2-5 only in predicting 1-year (ΔAUC=0.090 for 0-2/3-5 versus 0.047 for 0-1/2-5, p=0.01) but not 5-year deaths (p=0.25). When we further excluded those with pre-morbid mRS>1 (Tables XV-XVI), the 0-1/2-5 dichotomy became even less useful with an AUC similar to age/sex alone (e.g. for 5-year death: ΔAUC=0.011, p=0.10). The ordinal scale remained consistently superior to 0-1/2-5, whereas the 0-2/3-5 dichotomy again was superior to 0-1/2-5 only for predicting 1-year death (ROC curves in Figure IX, Appendix).

Health and social care costs

3-month mRS also predicted 5-year health and social care costs, which rose with each mRS grade; the proportion of total costs that were related to social care or institutionalization also rose with each grade, particularly going from mRS 3 to 4 to 5 (Figure 2C). Patients with 3-month mRS of 5 accrued the highest costs despite their high mortality, and there were significant differences in costs between patients with 3-month mRS of 1 versus 2, 2 versus 3, and 3 versus 4 (e.g. mean difference between mRS 2 and 3: $32,952, 95%CI $23,594-43,464), versus the insignificant difference between mRS 1 and 2 ($5,104, 95%CI –$1,090-10,614). 5-year costs were best predicted by the ordinal model, which had the lowest AIC i.e. minimized information-loss (Table 2, ΔAIC[vs age/sex]: -423 for ordinal versus -374 for 0-2/3-5 and -316 for 0-1/2-5; relative-likelihood <0.00001). Results were similar when cases with incomplete follow-up were included (Table XVII, Appendix); even upon excluding patients with pre-morbid mRS>2 (Table XVIII) and mRS>1 (Table XIX), ordinal analysis was consistently superior and the 0-1/2-5 inferior to the 0-2/3-5 dichotomy.

5.5 DISCUSSION

In this chapter, I have demonstrated that the ordinal mRS is superior to both the 0-1/2-6 and 0-2/3-6 dichotomies in predicting 5-year disability (whether defined as mRS>1 or >2), death/disability, mortality, and health/social care costs. The 0-1/2-6 dichotomy was generally inferior to 0-2/3-6 for predicting long-term outcomes. I also found that a substantial proportion of patients have pre-morbid disability, particularly the elderly (aged >85 years),

women, and those in lower socio-economic strata. These findings have implications for clinical trials using the mRS as the primary outcome measure.

Firstly, these findings favour using ordinal over dichotomous analysis of the mRS by adding clinical data to arguments about statistical efficiency. Efficiency depends on expected treatment effects and does not always favour ordinal analysis.[10,22] However, a clinically-robust primary outcome measure should capture differences in long-term disability, care needs (costs), and survival – objective treatment goals in neurological disease – and our analyses demonstrate that the ordinal mRS best reflects these outcomes, with differences seen across the range of the scale. These results imply that any shifts in mRS can be meaningful, and that it is misleading to consider certain states as being equivalent. It is also inappropriate to view patients with pre-morbid disability as having no potential to benefit from disability-lowering treatments, given significant differences in long-term outcome among patients with 3-month mRS grades 3, 4, and 5, and certainly between mRS 2 and 3.

Secondly, these results highlight the substantial proportion of patients with pre-morbid disability that risk exclusion with dichotomous approaches. The 0-1/2-6 dichotomy would have excluded 30.5% of our cohort from attaining a favourable outcome even pre-stroke, and was more likely to exclude older, female, and socioeconomically-deprived patients. Defining a favourable outcome as mRS 0-2 is less exclusionary, but would still have prevented 17.2% of our patients from demonstrating any treatment benefit. Previous inpatient studies have reported higher rates of pre-morbid disability.[23] Even when trials use block-randomization or actively enrol older patients – like the third International Stroke Trial (IST-3) – their sample will still be unrepresentative if they exclude patients with pre-morbid disability, as did IST-3.[24] Ageism has been noted in interventional stroke studies,[25] and older patients,[26] women,[27] and socio-economically deprived patients[28] are less likely to receive appropriate acute stroke care. By permitting patients with pre-morbid disability to demonstrate treatment benefit, ordinal analysis can encourage trials to enrol such patients and better represent the stroke population.

Thirdly, for acute stroke trials that still wish to dichotomize the mRS, my data support the use of the 0-2/3-6 dichotomy over 0-1/2-6, with a much more significant difference in long-term outcomes between mRS 3 and 2 (“step-change”) than between 2 and 1. This means that in addition to promoting exclusion of more patients, trials using the 0-1/2-6 dichotomy risk underestimating the benefit of their interventions by classifying patients with 3-month mRS of 2 as having an “unfavourable” outcome, when they are likely to fare much better over 5-years than those with mRS of 3. This is a pressing concern given the 0-1/2-6 dichotomy’s popularity in recent trials.[2-5]

Fourthly, these findings demonstrate non-linear trends in long-term outcomes predicted by different mRS grades, suggesting that not all shifts should be weighted equally in an ideal ordinal analysis. The shift from 0-2 to 3-6 appears to merit the highest weighting, but there are also jumps in mortality and care-costs from 3 to 4 to 5. The utility-weighted mRS may be one method to address this issue, although it most values transitions from 3 to 4 to 5.[29] I will examine this issue in greater detail in Chapter 6.

My analysis has several strengths, including a robust population-based design, high rates of ascertainment of all incident strokes, completeness of follow-up, replication of findings for several outcomes, and generalizability, with similar 5-year mortality and disability rates as prior population-based studies.[30,31] However, there are some potential shortcomings. Firstly, a randomized controlled trial is required to prove a causal association between shifting patients to lower mRS scores and reducing long-term disability, mortality, and costs, and validate the differential value of various state-transitions suggested by my analyses. Secondly, since assessors were not blinded to prior mRS scores, 1-year and 5-year disability assessments could have been unfavourably biased in patients with higher 3-month mRS. However, ordinal analysis remained superior with different disability definitions, and trends were similar for 5-year death and costs, which are untainted by disability assessments. Thirdly, I only studied ischaemic stroke patients; distinctions among mRS grades may differ in other diseases that use this scale for outcome analysis.

In conclusion, my findings show that ordinal analysis of the 3-month mRS better predicts long-term outcomes of ischaemic stroke than either dichotomy. Dichotomous analyses, particularly the 0-1/2-6 dichotomy, also promote selection bias against significant segments of the general stroke population.

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5.7 TABLES

Table 1. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year death in 3-month ischaemic stroke survivors with full 5-years of followup or death between 3-months and 5-years (n=1,235).

	Age and Sex alone (reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							1.20 (0.62-2.31)	0.591
2			2.89 (2.13-3.92)	<0.0001*			1.64 (0.85-3.17)	0.141
3					3.61 (2.74-4.75)	<0.0001*	3.81 (1.97-7.37)	<0.0001*
4							4.59 (2.31-9.10)	<0.0001*
5							10.4 (4.83-22.6)	<0.0001*
Age	1.12 (1.10-1.13)	<0.0001*	1.10 (1.09-1.12)	<0.0001*	1.10 (1.08-1.12)	<0.0001*	1.10 (1.08-1.12)	<0.0001*
Male	1.13 (0.87-1.48)	0.368	1.20 (0.91-1.57)	0.201	1.25 (0.94-1.65)	0.122	1.29 (0.97-1.71)	0.077
AUC (95% CI)	0.784 (0.758-0.810)		0.801 (0.776-0.826)		0.816 (0.791-0.840)		0.821 (0.798-0.845)	
ΔAUC (vs Age/Sex)	N/A		**0.017**		**0.032**		**0.037**	
p>|X^2| (vs Age/Sex)		N/A		0.0026*		<0.0001*		<0.0001*

P=0.02* for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy (favouring the latter).

P=0.0004* for comparison of AUC for 0-1/2-5 dichotomy versus ordinal mRS (favouring the latter).

P=0.04* for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS (favouring the latter).

Table 2. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year healthcare costs in 3-month ischaemic stroke survivors with full 5-years of followup, or death between 3-months and 5-years (n=1,241).

	Age and Sex alone (reference AIC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	Margins ($, 95% CI)	**p>|z|**	**Margins ($)**	**p>|z|**	**Margins ($)**	**p>|z|**	**Margins ($)**	**p>|z|**
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							9,808 (4,399-15,218)	0.001*
2			39,723 (28,972-50,474)	<0.0001*			12,032 (5,878-18,186)	0.001*
3					48,299 (36,295-60,304)	<0.0001*	39,851 (28,130-51,573)	<0.0001*
4							61,622 (42,105-79,139)	<0.0001*
5							80,052 (49,563-110,542)	<0.0001*
Age	1,465 (1,028-1,902)	<0.0001*	1,185 (782-1,588)	<0.0001*	1,169 (770-1,569)	<0.0001*	1,171 (773-1,570)	<0.0001*
Male	-10,417 (-16,487 to -4,347)	0.012*	-9,160 (-17,570 to -751)	0.030*	-10,189 (-18,583 to -1,796)	0.015*	-8,257 (-16,454 to -60)	0.044*
AIC	28,619		28,395		28,245		28,196	
ΔAIC (vs Age/Sex)	N/A		**-316**		**-374**		**-423**	

Relative likelihood <0.00001 for the first or second model versus the ordinal model i.e. Akaike Information Criterion analysis favours the ordinal model.

5.8 FIGURES

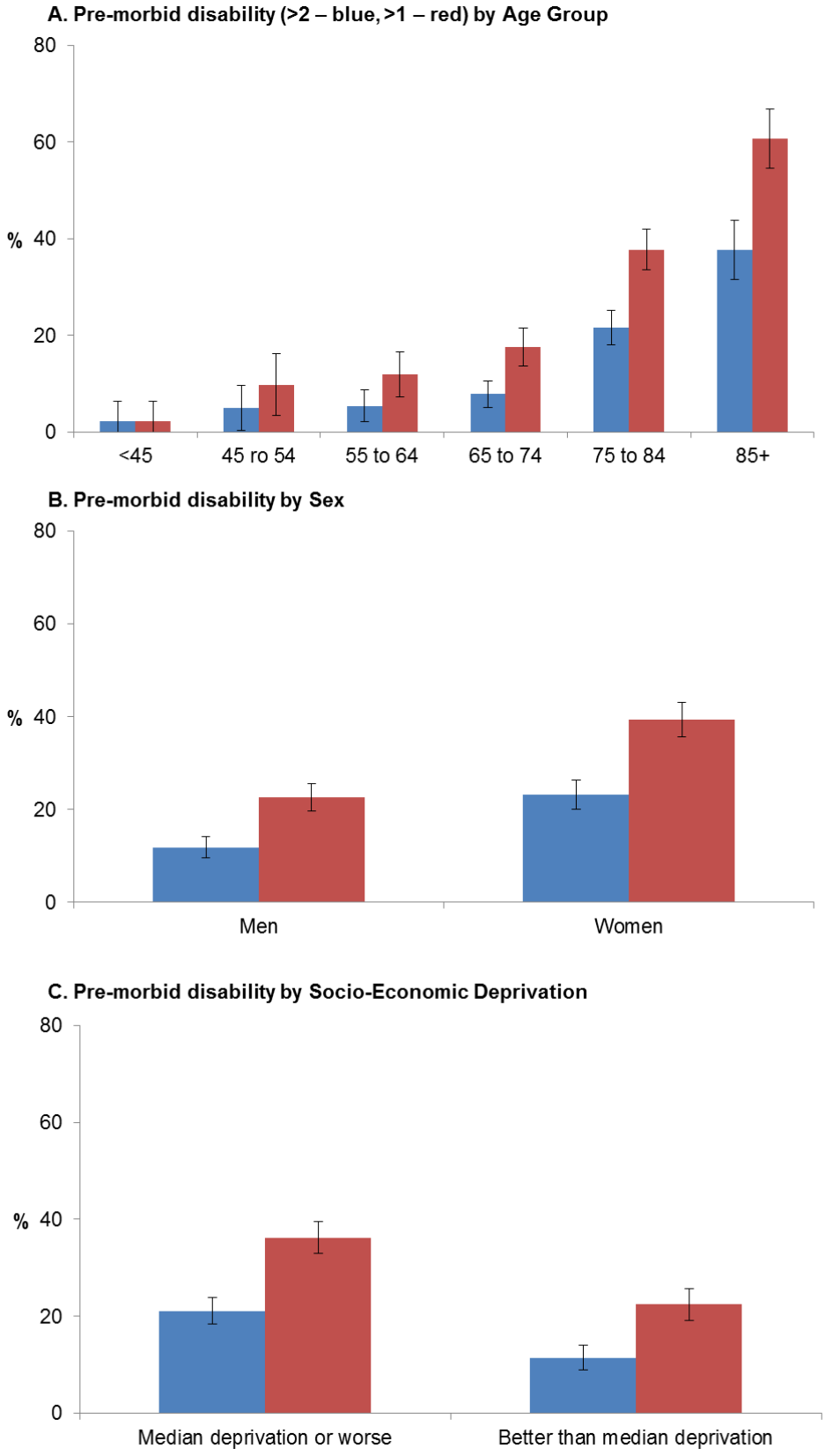

Figure 1. Proportion of 3-month survivors of ischaemic stroke with pre-morbid disability, defined as a pre-stroke mRS of >2 (blue) or >1 (red) by: (A) Age, (B) Sex, and (C) Socio-economic deprivation index. Bars represent 95% confidence intervals.

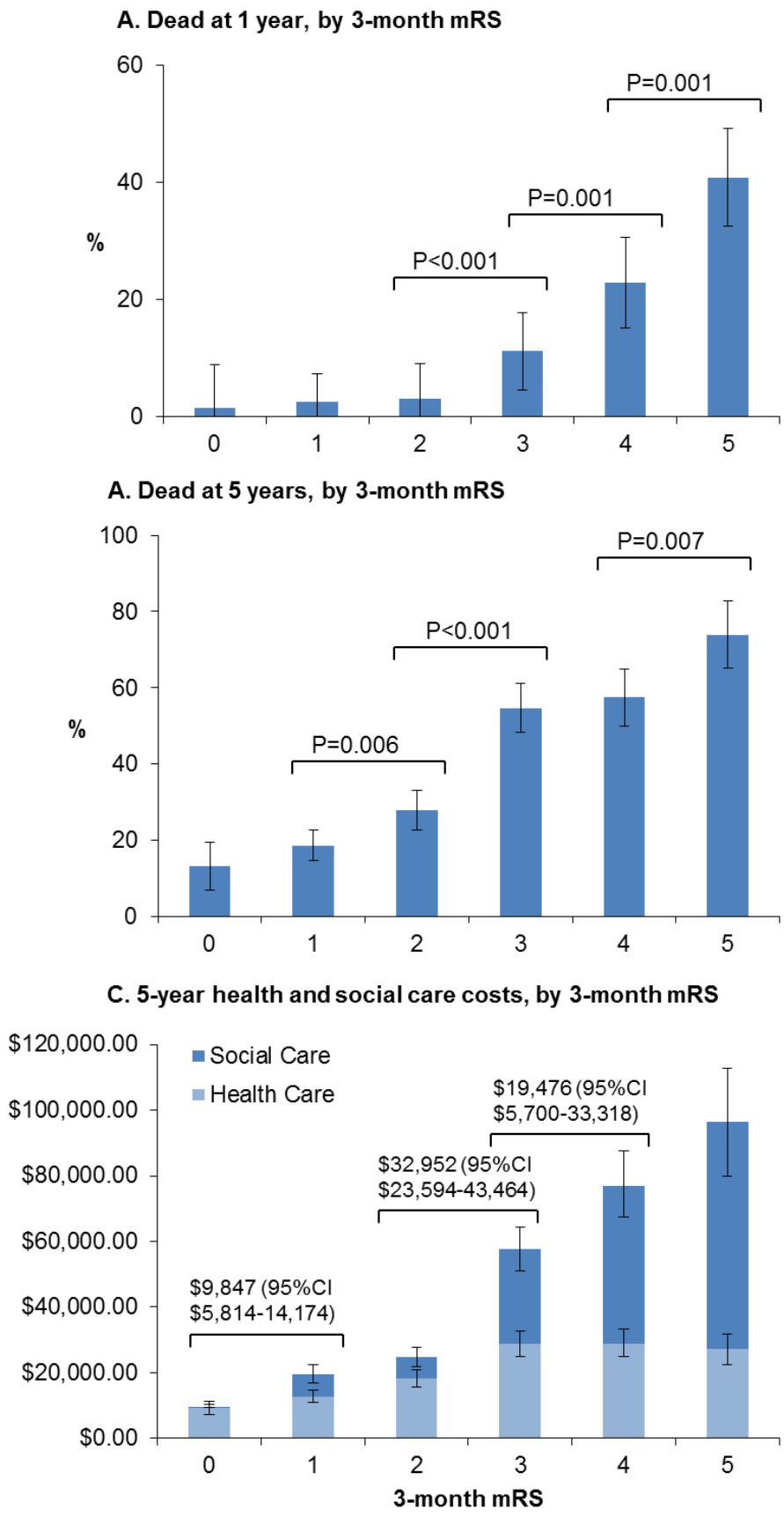

Figure 2. Proportion of 3-month survivors of ischaemic stroke with full 5-years of follow-up, who were dead at 1-year (A), dead at 5-years (B), and cumulative 5-year health and social care costs for all survivors (C), stratified by 3-month mRS. Bars represent 95% confidence intervals. Significant differences between mRS grades are indicated using P-values from chi-squared analysis (A-B) and mean cost differences with 95% confidence intervals (C).

5.9 APPENDIX
Supplementary Tables and Figures for Chapter 5

Table I. Association of age, sex, and socio-economic deprivation with pre-morbid disability – defined as mRS>2 or mRS>1 – in 3-month survivors of ischaemic stroke (n=1,421).

	Pre-morbid mRS>2		Pre-morbid mRS>1	
	aOR (95%CI)	**p>|z|**	**aOR (95%CI)**	**p>|z|**
Age	1.09 (1.07-1.10)	<0.0001*	1.09 (1.07-1.10)	<0.0001*
Female sex	1.66 (1.22-2.25)	0.001*	1.70 (1.32-2.19)	<0.0001*
≥Median deprivation	2.26 (1.65-3.12)	<0.0001*	2.27 (1.75-2.95)	<0.0001*
Significant comorbidity*	1.18 (0.80-1.76)	0.403	1.51 (1.09-2.10)	0.014*
AUC	0.77		0.77	
$p>\|X^2\|$		<0.0001*		<0.0001*

*This was a composite term coding for the presence of any comorbidity that was a significant predictor of pre-morbid disability (>2 or >1) on univariable logistic regression. This included prior myocardial infarction, stroke, transient ischaemic attack, valvular heart disease, heart failure, diabetes, hypertension, angina, or peripheral vascular disease.

Table II. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year disability (mRS>2) in 3-month survivors of ischaemic stroke, excluding those who died during follow-up (n=950).

	Age/Sex alone (Reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|		
3-month mRS								
0	N/A		**0-1=Reference**		**0-2=Reference**		**0=Reference**	
1							6.68 (0.88-50.5)	0.066
2			18.9 (11.7-30.5)	<0.0001*			16.5 (2.22-123)	0.006*
3					55.4 (35.3-87.0)	<0.0001*	270 (36.1-2021)	<0.0001*
4							1082 (131-8902)	<0.0001*
5							3230 (195-53593)	<0.0001*
Age	1.05 (1.03-1.06)	<0.0001*	1.03 (1.02-1.05)	<0.0001*	1.04 (1.02-1.06)	<0.0001*	1.04 (1.02-1.06)	<0.0001*
Male	0.58 (0.43-0.79)	<0.0001*	0.57 (0.40-0.81)	0.002*	0.61 (0.39-0.94)	0.026*	0.62 (0.39-0.97)	0.025*
AUC (95%CI)	0.674 (0.634-0.714)		0.841 (0.814-0.868)		0.907 (0.882-0.932)		0.925 (0.903-0.946)	
ΔAUC (vs Age/Sex)	N/A		**0.167**		**0.233**		**0.251**	
p>|X^2| (vs Age/Sex)		N/A		<0.0001*		<0.0001*		<0.0001*

P<0.0001* for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy or the ordinal mRS.
P=0.004* for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS (favouring the latter).

Table III. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year disability (mRS>2) in 3-month survivors of ischaemic stroke, excluding those who died and excluding those with pre-morbid mRS>2 (n=874).

	Age/Sex alone (Reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|		
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							6.65 (0.88-50.2)	0.067
2			14.3 (8.8-23.3)	<0.0001*			14.9 (1.99-111)	0.009*
3					48.9 (30.0-79.8)	<0.0001*	211 (27.8-1600)	<0.0001*
4							897 (106-7576)	<0.0001*
5							2580 (154-43314)	<0.0001*
Age	1.05 (1.03-1.06)	<0.0001*	1.03 (1.02-1.05)	<0.0001*	1.05 (1.02-1.07)	<0.0001*	1.04 (1.02-1.07)	<0.0001*
Male	0.58 (0.41-0.82)	0.002*	0.56 (0.38-0.81)	0.003*	0.58 (0.36-0.92)	0.021*	0.59 (0.37-0.96)	0.034*
AUC (95%CI)	0.665 (0.620-0.710)		0.829 (0.797-0.861)		0.891 (0.859-0.923)		0.910 (0.883-0.937)	
ΔAUC (vs Age/Sex)	N/A		**0.164**		**0.226**		**0.245**	
p>|X^2| (vs Age/Sex)		N/A		<0.0001*		<0.0001*		<0.0001*

P<0.0001* for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy or the ordinal mRS.
P=0.01* for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS (favouring the latter).

Table IV. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year disability (mRS>2) or death in 3-month ischaemic stroke survivors (n=1,403).

	Age/Sex alone (Reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS (sensitivity analysis)	
	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							1.74 (0.95-3.19)	0.074
2			9.34 (7.07-12.3)	<0.0001*			3.30 (1.80-6.05)	<0.0001*
3					32.4 (22.3-47.2)	<0.0001*	35.7 (18.2-70.0)	<0.0001*
4							147 (58.1-373)	<0.0001*
5							562 (72.0-4380)	<0.0001*
Age	1.09 (1.08-1.10)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	1.08 (1.06-1.09)	<0.0001*
Male	0.75 (0.59-0.95)	0.016*	0.77 (0.59-1.00)	0.053	0.84 (0.63-1.14)	0.266	0.88 (0.65-1.19)	0.415
AUC (95%CI)	0.764 (0.739-0.788)		0.850 (0.830-0.870)		0.899 (0.883-0.915)		0.906 (0.891-0.922)	
ΔAUC (vs Age/Sex)	N/A		**0.086**		**0.135**		**0.142**	
p>|X^2| (vs Age/Sex)		N/A		<0.0001*		<0.0001*		<0.0001*

P<0.0001* for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy or the ordinal mRS.
P=0.02* for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS (favouring the latter).

Table V. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year disability (mRS>2) or death in 3-month survivors of ischaemic stroke, excluding those with pre-morbid mRS>2 (n=1,171).

	Age/Sex alone (Reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|		
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							1.71 (0.93-3.13)	0.085
2			6.73 (5.04-8.97)	<0.0001*			3.22 (1.75-5.92)	<0.001*
3					24.2 (16.1-36.5)	<0.0001*	26.6 (13.2-53.4)	<0.0001*
4							106 (39.2-289)	<0.0001*
5							367 (46.5-2897)	<0.0001*
Age	1.08 (1.07-1.10)	<0.0001*	1.07 (1.06-1.09)	<0.0001*	1.08 (1.06-1.10)	<0.0001*	1.08 (1.06-1.10)	<0.0001*
Male	0.79 (0.61-1.02)	0.072	0.79 (0.59-1.04)	0.096	0.83 (0.61-1.13)	0.247	0.87 (0.64-1.19)	0.390
AUC (95%CI)	0.740 (0.711-0.768)		0.821 (0.797-0.845)		0.866 (0.845-0.888)		0.875 (0.854-0.895)	
ΔAUC (vs Age/Sex)	N/A		**0.081**		**0.126**		**0.135**	
p>|X^2| (vs Age/Sex)		N/A		<0.0001*		<0.0001*		<0.0001*

P<0.0001* for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy or the ordinal mRS, and versus the ordinal mRS.

P=0.03* for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS (favouring the latter).

Table VI. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year <u>disability (mRS>1)</u> in in 3-month survivors of ischaemic stroke, excluding those who died during follow-up (n=969).

	Age/Sex alone (Reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
			aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							3.28 (1.63-6.62)	0.001*
2			12.5 (9.0-17.2)	<0.0001*			12.3 (6.07-25.1)	<0.0001*
3					65.7 (31.3-138)	<0.0001*	196 (67.8-568)	<0.0001*
4							970 (120-7849)	<0.0001*
5							290 (35.3-2388)	<0.0001*
Age	1.06 (1.04-1.07)	<0.0001*	1.05 (1.04-1.07)	<0.0001*	1.05 (1.04-1.07)	<0.0001*	1.05 (1.04-1.07)	<0.0001*
Male	0.66 (0.50-0.87)	0.003*	0.66 (0.47-0.91)	0.012	0.74 (0.53-1.03)	0.075	0.73 (0.52-1.04)	0.086
AUC (95%CI)	0.698 (0.662-0.728)		0.847 (0.822-0.872)		0.845 (0.820-0.870)		0.882 (0.861-0.904)	
ΔAUC (vs Age/Sex)	N/A		**0.149**		**0.147**		**<u>0.184</u>**	
p>|X^2| (vs Age/Sex)		N/A		<0.0001*		<0.0001*		<0.0001*

P=0.88 for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy.
<u>P<0.0001*</u> for comparison of AUC for 0-1/2-5 dichotomy versus ordinal mRS (favouring the latter).
<u>P<0.0001</u>* for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS (favouring the latter).

Table VII. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year <u>disability (mRS>1)</u> in in 3-month survivors of ischaemic stroke, excluding those who died during follow-up and <u>excluding those with pre-morbid mRS>1</u> (n=773).

	Age/Sex alone (Reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
			aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							2.94 (1.40-6.17)	0.004*
2			10.6 (7.44-15.1)	<0.0001*			10.5 (4.97-22.3)	<0.0001*
3					78.7 (31.2-198)	<0.0001*	233 (59.9-909)	<0.0001*
4							669 (80.9-5538)	<0.0001*
5							219 (26.0-1853)	<0.0001*
Age	1.05 (1.03-1.06)	<0.0001*	1.05 (1.03-1.06)	<0.0001*	1.05 (1.03-1.07)	<0.0001*	1.05 (1.03-1.07)	<0.0001*
Male	0.74 (0.54-1.00)	0.05*	0.67 (0.47-0.96)	0.03*	0.75 (0.52-1.09)	0.128	0.73 (0.49-1.08)	0.115
AUC (95%CI)	0.664 (0.625-0.704)		0.823 (0.792-0.854)		0.813 (0.779-0.846)		0.857 (0.829-0.885)	
ΔAUC (vs Age/Sex)	N/A		**0.159**		**0.149**		**<u>0.193</u>**	
p>|X^2| (vs Age/Sex)		N/A		<0.0001*		<0.0001*		<0.0001*

P=0.49 for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy.
<u>P<0.0001*</u> for comparison of AUC for 0-1/2-5 dichotomy versus ordinal mRS (favouring the latter).
<u>P=0.0002</u>* for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS (favouring the latter).

Table VIII. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year disability (mRS >1) or death in in 3-month ischaemic stroke survivors (n=1,403).

	Age/Sex alone (Reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
			aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							2.29 (1.38-3.79)	0.001*
2			12.6 (9.46-16.9)	<0.0001*			7.94 (4.70-13.4)	<0.0001*
3					73.9 (35.7-153)	<0.0001*	141 (54.9-365)	<0.0001*
4							716 (93.6-5473)	<0.0001*
5							310 (40.7-2359)	<0.0001*
Age	1.09 (1.07-1.10)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	1.08 (1.06-1.09)	<0.0001*	1.07 (1.06-1.09)	<0.0001*
Male	0.72 (0.56-0.92)	0.008*	0.73 (0.55-0.98)	0.036*	0.81 (0.61-1.08)	0.156	0.82 (0.60-1.12)	0.207
AUC (95%CI)	0.775 (0.750-0.800)		0.877 (0.858-0.895)		0.887 (0.870-0.903)		0.906 (0.891-0.921)	
ΔAUC (vs Age/Sex)	N/A		**0.102**		**0.112**		**0.131**	
p>|X^2| (vs Age/Sex)		N/A		<0.0001*		<0.0001*		<0.0001*

P=0.20 for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy.
P<0.0001* for comparison of AUC for 0-1/2-5 dichotomy versus ordinal mRS (favouring the latter).
P=0.0001* for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS (favouring the latter).

Table IX. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year disability (mRS >1) or death in in 3-month ischaemic stroke survivors, excluding those with pre-morbid mRS>1 (n=984).

	Age/Sex alone (Reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
			aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							1.96 (1.17-3.29)	0.011*
2			9.26 (6.76-12.7)	<0.0001*			6.49 (3.77-11.2)	<0.0001*
3					72.8 (29.0-183)	<0.0001*	137 (38.9-482)	<0.0001*
4							396 (50.4-3109)	<0.0001*
5							164 (21.3-1267)	<0.0001*
Age	1.07 (1.06-1.08)	<0.0001*	1.07 (1.05-1.08)	<0.0001*	1.07 (1.05-1.08)	<0.0001*	1.07 (1.05-1.08)	<0.0001*
Male	0.80 (0.60-1.05)	0.106	0.75 (0.55-1.03)	0.073	0.85 (0.62-1.17)	0.313	0.83 (0.60-1.16)	0.282
AUC (95%CI)	0.730 (0.699-0.761)		0.836 (0.811-0.861)		0.840 (0.815-0.864)		0.865 (0.842-0.887)	
ΔAUC (vs Age/Sex)	N/A		**0.106**		**0.110**		**0.135**	
p>|X^2| (vs Age/Sex)		N/A		<0.0001*		<0.0001*		<0.0001*

P=0.72 for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy.
P<0.0001* for comparison of AUC for 0-1/2-5 dichotomy versus ordinal mRS (favouring the latter).
P=0.001* for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS (favouring the latter).

Table X. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on <u>1-year death</u> in 3-month ischaemic stroke survivors (n=1,403).

	Age/Sex alone (reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	aOR (95%CI)	**p>|z|**	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							1.55 (0.34-7.14)	0.575
2			4.84 (2.67-8.79)	<0.0001*			1.52 (0.32-7.22)	0.597
3					7.33 (4.50-12.0)	<0.0001*	4.81 (1.10-21.0)	0.036*
4							12.6 (2.91-54.1)	0.001*
5							31.8 (7.31-139)	<0.0001*
Age	1.09 (1.07-1.12)	<0.0001*	1.07 (1.05-1.10)	<0.0001*	1.06 (1.04-1.09)	<0.0001*	1.07 (1.04-1.09)	<0.0001*
Male	1.36 (0.93-1.98)	0.112	1.46 (0.99-2.14)	0.056	1.58 (1.06-2.34)	0.023*	1.92 (1.26-2.91)	0.002*
AUC (95%CI)	0.728 (0.686-0.770)		0.773 (0.735-0.810)		0.814 (0.779-0.850)		**<u>0.834</u>** (0.797-0.870)	
ΔAUC (vs Age/Sex)	N/A		**0.045**		**0.086**		**0.106**	
p>|X^2| (vs Age/Sex)		N/A		0.0003*		<0.0001*		<0.0001*

P<0.0001* for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy, and 0-1/2-5 dichotomy versus ordinal mRS.
P=0.0161* for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS (favouring the latter).

Table XI. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 1-year death in in all ischaemic stroke patients (n=1,584). This analysis also includes patients who were already dead by 3-months (mRS=6, n=181). Since 3-month mRS=6 would "predict" subsequent death perfectly, patients with mRS of 5 and 6 were combined for the ordinal analysis.

	Age/Sex alone (reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1			12.0 (6.74-21.3)	<0.0001*			1.58 (0.34-7.27)	0.557
2					19.4 (12.3-30.7)	<0.0001*	1.57 (0.33-7.41)	0.571
3							5.05 (1.17-21.9)	0.030*
4							13.1 (3.05-56.1)	0.001*
5-6							172 (40.8-726)	<0.0001*
Age	1.09 (1.07-1.11)	<0.0001*	1.07 (1.05-1.09)	<0.0001*	1.05 (1.04-1.07)	<0.0001*	1.06 (1.04-1.08)	<0.0001*
Male	1.05 (0.80-1.37)	0.714	1.14 (0.86-1.51)	0.356	1.27 (0.94-1.72)	0.112	1.87 (1.28-2.73)	0.001*
AUC	0.733		0.797		0.851		0.922	
(95%CI)	(0.702-0.763)		(0.773-0.821)		(0.831-0.872)		(0.904-0.940)	
ΔAUC (vs Age/Sex)	N/A		**0.064**		**0.118**		**0.189**	
p>|X^2| (vs Age/Sex)		N/A		<0.0001*		<0.0001*		<0.0001*

P<0.0001* for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy (favouring the latter).
P<0.0001* for comparison of AUC for either dichotomy versus ordinal mRS (favouring the latter).

Table XII. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year death in all ischaemic stroke patients with full 5-years of followup or death before 5-years (n=1,416). This analysis also includes patients who were already dead by 3-months (mRS=6, n=181). Since 3-month mRS=6 would "predict" subsequent death perfectly, patients with mRS of 5 and 6 were combined for the ordinal analysis.

	Age and Sex alone (reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							1.21 (0.63-2.33)	0.570
2			4.29 (3.19-5.76)	<0.0001*			1.66 (0.86-3.21)	0.128
3					5.93 (4.56-7.70)	<0.0001*	3.89 (2.02-7.50)	<0.0001*
4							4.67 (2.36-9.24)	<0.0001*
5-6							38.7 (18.6-80.7)	<0.0001*
Age	1.11 (1.10-1.13)	<0.0001*	1.10 (1.08-1.11)	<0.0001*	1.09 (1.08-1.11)	<0.0001*	1.10 (1.08-1.12)	<0.0001*
Male	1.05 (0.82-1.34)	0.690	1.13 (0.88-1.46)	0.338	1.22 (0.93-1.59)	0.151	1.29 (0.98-1.71)	0.070
AUC	0.787		0.816		0.843		0.867	
(95% CI)	(0.763-0.811)		(0.794-0.838)		(0.822-0.863)		(0.848-0.886)	
ΔAUC (vs Age/Sex)	N/A		**0.029**		**0.056**		**0.080**	
p>|X^2| (vs Age/Sex)		N/A		<0.0001*		<0.0001*		<0.0001*

P<0.0001* for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy (favouring the latter).
P<0.0001* for comparison of AUC for either dichotomy versus ordinal mRS (favouring the latter).

Table XIII. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on <u>1-year death</u> in 3-month ischaemic stroke survivors, <u>excluding those with pre-morbid mRS>2</u> (n=1,171).

	Age/Sex alone (reference AUC)		**mRS dichotomized as 0-1 versus 2-5**		**mRS dichotomized as 0-2 versus 3-5**		**Full range of mRS**	
	aOR (95%CI)	**p>|z|**	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							1.41 (0.30-6.57)	0.662
2			3.80 (2.00-7.22)	<0.0001*			1.41 (0.29-6.83)	0.667
3					6.44 (3.72-11.14)	<0.0001*	5.11 (1.13-23.0)	0.034*
4							8.73 (1.90-40.1)	0.005*
5							22.7 (4.97-104)	<0.0001*
Age	1.08 (1.05-1.11)	<0.0001*	1.07 (1.04-1.10)	<0.0001*	1.06 (1.03-1.09)	<0.0001*	1.07 (1.03-1.10)	<0.0001*
Male	1.16 (0.71-1.90)	0.547	1.22 (0.74-2.01)	0.438	1.30 (0.78-2.16)	0.317	1.56 (0.91-2.66)	0.105
p>|X^2|		<0.0001*		<0.0001*		<0.0001*		<0.0001*
AUC (95%CI)	0.714 (0.659-0.770)		0.761 (0.710-0.811)		0.804 (0.753-0.855)		0.811 (0.759-0.863)	
ΔAUC (vs Age/Sex)	N/A		**0.047**		**0.090**		**0.097**	
p>|X^2| (vs Age/Sex)		N/A		0.0122*		0.0001*		0.0001*

P=0.01* for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy.
P=0.005* for 0-1/2-5 dichotomy versus ordinal mRS (favouring the latter in each case).
P=0.34 for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS.

Table XIV. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year death in 3-month ischaemic stroke survivors, excluding those with pre-morbid mRS>2 (n=1,013).

	Age/Sex alone (reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							1.18 (0.61-2.28)	0.616
2			2.30 (1.67-3.17)	<0.0001*			1.71 (0.89-3.31)	0.109
3					2.74 (2.00-3.77)	<0.0001*	3.40 (1.70-6.77)	0.001*
4							2.73 (1.29-5.81)	0.009*
5							7.80 (3.37-18.0)	<0.0001*
Age	1.11 (1.09-1.13)	<0.0001*	1.10 (1.08-1.12)	<0.0001*	1.10 (1.08-1.12)	<0.0001*	1.10 (1.08-1.12)	<0.0001*
Male	1.16 (0.86-1.57)	0.341	1.21 (0.89-1.64)	0.235	1.22 (0.89-1.67)	0.212	1.26 (0.92-1.73)	0.146
AUC (95%CI)	0.766 (0.735-0.797)		0.780 (0.750-0.811)		0.788 (0.758-0.818)		0.794 (0.765-0.824)	
ΔAUC (vs Age/Sex)	N/A		**0.014**		**0.022**		**0.028**	
p>|X^2| (vs Age/Sex)		N/A		0.02*		0.004*		0.0007*

P=0.25 for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy, P=0.01* for 0-1/2-5 dichotomy versus ordinal mRS.
P=0.09 for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS.

Table XV. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 1-year death in 3-month ischaemic stroke survivors, excluding those with pre-morbid mRS>1 (n=984).

	Age/Sex alone (reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|	aOR (95%CI)	p>|z|
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							1.30 (0.27-6.17)	0.741
2			2.96 (1.47-5.97)	0.002*			0.83 (0.15-4.67)	0.834
3					6.06 (3.17-11.58)	<0.0001*	3.01 (0.60-14.94)	0.179
4							6.15 (1.24-30.54)	0.026*
5							17.67 (3.76-83.14)	<0.0001*
Age	1.09 (1.05-1.13)	<0.0001*	1.08 (1.04-1.12)	<0.0001*	1.07 (1.03-1.11)	<0.0001*	1.08 (1.04-1.12)	<0.0001*
Male	0.95 (0.52-1.75)	0.878	0.96 (0.52-1.77)	0.901	1.00 (0.53-1.86)	0.988	1.27 (0.66-2.45)	0.483
AUC (95%CI)	0.738 (0.670-0.806)		0.767 (0.705-0.830)		0.808 (0.743-0.873)		0.816 (0.745-0.887)	
ΔAUC (vs Age/Sex)	N/A		**0.029**		**0.070**		**0.078**	
p>|X^2| (vs Age/Sex)		N/A		0.15		0.006*		0.004*

P=0.02* for comparison of AUC for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy, P=0.03* for 0-1/2-5 dichotomy versus ordinal mRS.
P=0.47 for comparison of AUC for 0-2/3-5 dichotomy versus ordinal mRS.

Table XVI. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year death in 3-month ischaemic stroke survivors, excluding those with pre-morbid mRS>1 (n=843).

	Age/Sex alone (reference AUC)		mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	aOR (95%CI)	**p>|z|**	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							1.05 (0.54-2.06)	0.880
2			2.10 (1.48-3.00)	<0.0001*			1.52 (0.77-3.01)	0.229
3					2.48 (1.72-3.58)	<0.0001*	2.77 (1.33-5.79)	0.007*
4							1.92 (0.83-4.41)	0.125
5							5.92 (2.48-14.1)	<0.0001*
Age	1.11 (1.09-1.13)	<0.0001*	1.10 (1.08-1.12)	<0.0001*	1.10 (1.08-1.12)	<0.0001*	1.10 (1.08-1.12)	<0.0001*
Male	1.12 (0.79-1.59)	0.508	1.15 (0.81-1.64)	0.431	1.18 (0.83-1.68)	0.366	1.21 (0.84-1.73)	0.312
$p>\|X^2\|$		<0.0001*		<0.0001*		<0.0001*		<0.0001*
AUC (95%CI)	0.770 (0.728-0.803)		0.781 (0.747-0.816)		0.786 (0.750-0.821)		0.793 (0.758-0.828)	
ΔAUC (vs Age/Sex)	N/A		**0.011**		**0.016**		**0.023**	
$p>\|X^2\|$ (vs Age/Sex)		N/A		0.10		0.046*		0.0088*

P=0.04* for comparison of AUC for 0-1/2-5 dichotomy versus ordinal mRS (favouring the latter).
P=0.55 for 0-1/2-5 dichotomy versus 0-2/3-5 dichotomy; P=0.09 for 0-2/3-5 dichotomy versus ordinal mRS.

Table XVII. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year healthcare costs in 3-month ischaemic stroke survivors including censored cases (n=1,403).

			mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	Margins ($, 95%CI)	**p>|z|**	**Margins ($)**	**p>|z|**	**Margins ($)**	**p>|z|**	**Margins ($)**	**p>|z|**
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							8,959 (4,453-13,466)	<0.0001*
2			40,068 (30,107-50,026)	<0.0001*			12,283 (6,847-17,719)	<0.0001*
3					47,899 (36,603-59,194)	<0.0001*	39,272 (28,317-50,227)	<0.0001*
4							60,781 (42,914-78,648)	<0.0001*
5							80,442 (50,678-110,206)	<0.0001*
Age	1,447 (1,053-1,841)	<0.0001*	1,1168 (805-1,532)	<0.0001*	1,153 (795-1,511)	<0.0001*	1,151 (795-1,508)	<0.0001*
Male	-10,060 (-17,979 to -2,141)	0.011*	-8,515 (-16,120 to -910)	0.025*	-9,659 (-17,260 to -2,060)	0.010*	-7,421 (-14,809 to -32)	0.045*
AIC	32,144		31,844		31,678		31,611	
ΔAIC (vs Age/Sex)	N/A		**-300**		**-466**		**-533**	

Relative likelihood <0.00001* for the first or second model versus the ordinal model i.e. Akaike Information Criterion (AIC) analysis favours the ordinal model.

Table XVIII. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year healthcare costs in 3-month ischaemic stroke survivors excluding those with pre-morbid mRS >2 (n=1,171; censored patients retained).

			mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	Margins ($, 95%CI)	**p>|z|**	**Margins ($)**	**p>|z|**	**Margins ($)**	**p>|z|**	**Margins ($)**	**p>|z|**
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							8,723 (4,149-13,297)	0.001*
2			33,362 (23,795-42,929)	<0.0001*			10,528 (5,192-15,864)	<0.0001*
3					46,542 (33,924-59,161)	<0.0001*	36,522 (23,444-49,601)	<0.0001*
4							69,887 (42,050-97,724)	<0.0001*
5							102,050 (54,092-150,009)	<0.0001*
Age	1,503 (1,102-1,903)	<0.0001*	1,238 (871-1,605)	<0.0001*	1,208 (850-1,566)	<0.0001*	1,205 (846-1,565)	<0.0001*
Male	-13,165 (-21,096 to -5,233)	0.001*	-10,799 (-18,414 to -3,183)	0.004*	-12,148 (-19,792 to -4,503)	0.001*	-9,505 (-16,960 to -2,050)	0.010*
AIC	26,479		26,240		26,051		25,983	
ΔAIC (vs Age/Sex)	N/A		**-239**		**-428**		**-496**	

Relative likelihood <0.00001 for the first or second model versus the ordinal model i.e. Akaike Information Criterion (AIC) analysis favours the ordinal model.

Table XIX. Impact of 3-month mRS – dichotomized as 0-1/2-5 or 0-2/3-5, or included as the full ordinal scale – on 5-year healthcare costs in 3-month ischaemic stroke survivors excluding those with pre-morbid mRS >1 (n=984; censored patients retained).

			mRS dichotomized as 0-1 versus 2-5		mRS dichotomized as 0-2 versus 3-5		Full range of mRS	
	Margins ($, 95%CI)	**p>|z|**	**Margins ($)**	**p>|z|**	**Margins ($)**	**p>|z|**	**Margins ($)**	**p>|z|**
3-month mRS								
0	N/A		**0-1 = Reference**		**0-2 = Reference**		**0 = Reference**	
1							6,760 (2,418-11,101)	0.005*
2			32,886 (22,906-42,865)	<0.0001*			10,214 (4,629-15,799)	<0.001*
3					45,289 (31,517-59,062)	<0.0001*	37,818 (21,332-54,305)	<0.0001*
4							66,399 (34,572-98,227)	<0.0001*
5							99,311 (47,013-151,608)	<0.0001*
Age	1,353 (952-1,754)	<0.0001*	1,118 (760-1,476)	<0.0001*	1,072 (722-1,421)	<0.0001*	1,067 (714-1,421)	<0.0001*
Male	-10,935 (-18,941 to -2,927)	0.005*	-9,115 (-16,694 to -1,536)	0.015*	-10,737 (-18,389 to -3,085)	0.004*	-7,852 (-15,373 to -329)	0.035
AIC	22,085		21,769		21,615		21,562	
ΔAIC (vs Age/Sex)	N/A		**-316**		**-470**		**-523**	

Relative likelihood <0.00001* for the first or second model versus the ordinal model i.e. Akaike Information Criterion (AIC) analysis favours the ordinal model.

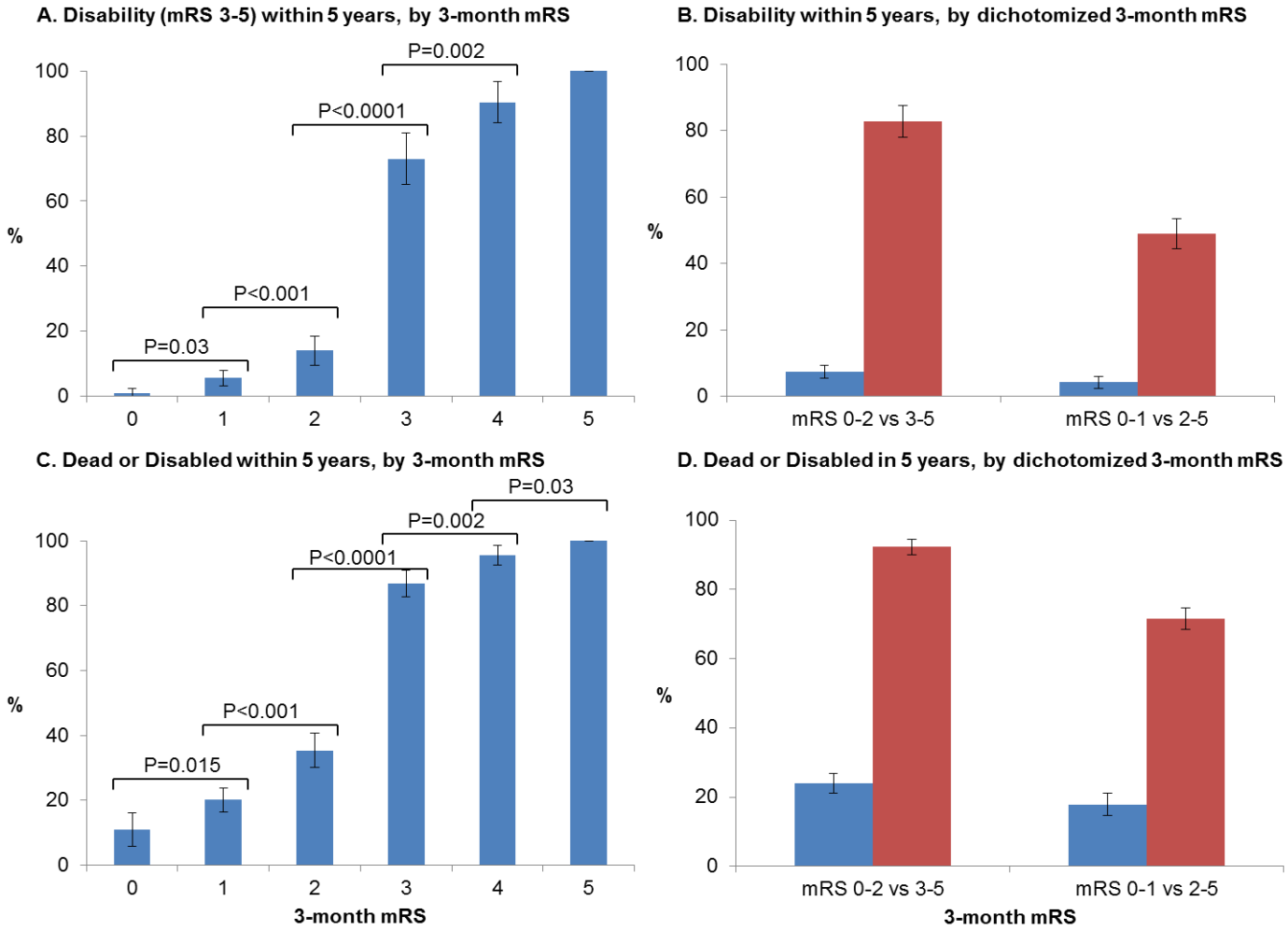

Figure I. Proportion of 3-month survivors of ischaemic stroke who were alive and disabled within 5 years (A-B) and dead/disabled within 5 years (C-D), stratified by 3-month mRS, with disability defined as 5-year mRS>2. For patients who had not yet reached their 5-year follow-up, 1-year disability status was used.

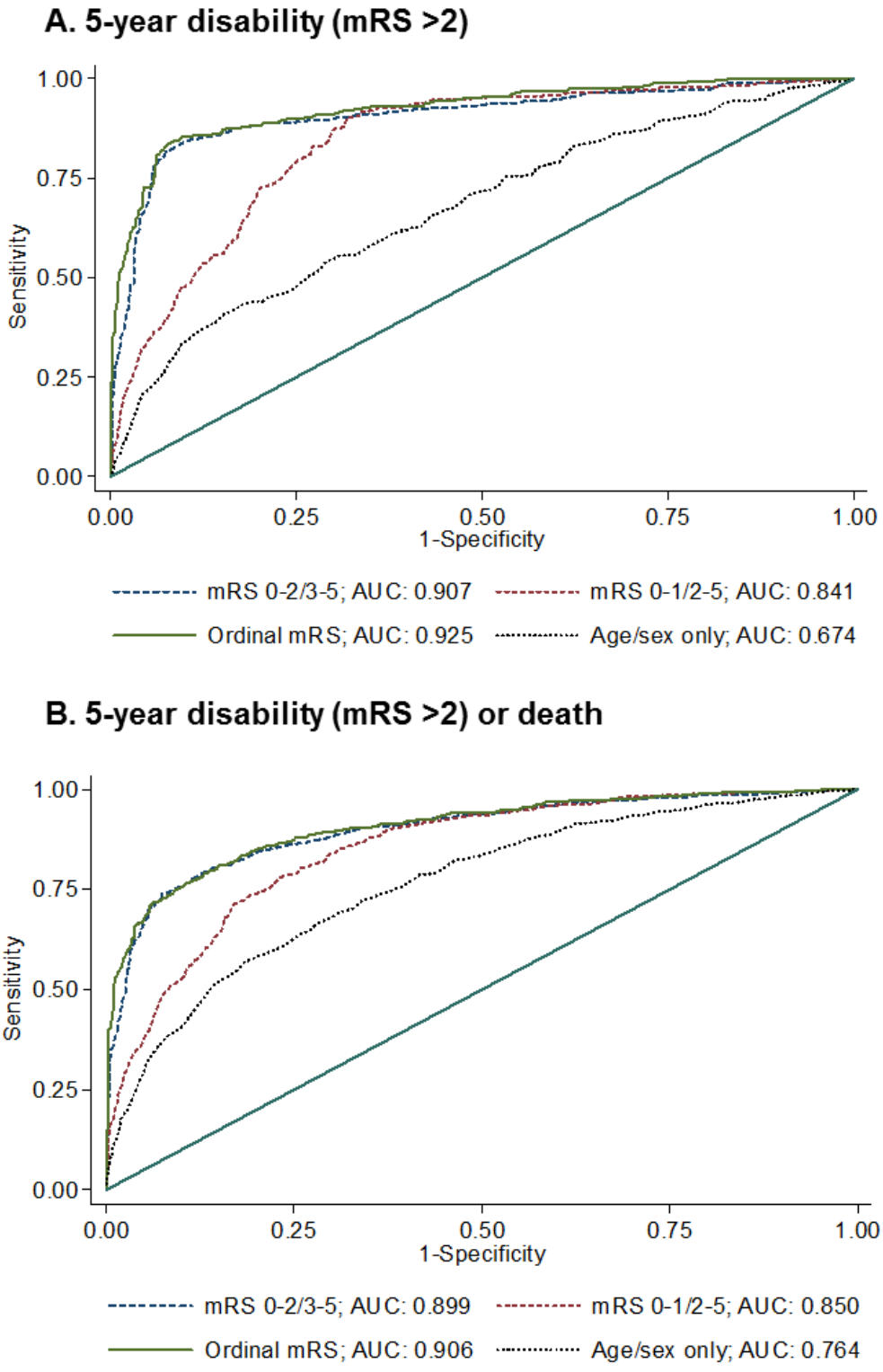

Figure II. Receiver-operating-characteristics curves for the age- and sex-adjusted logistic regression models for predicting (A) 5-year disability and (B) 5-year death or disability (or 1-year disability for those with incomplete follow-up) for each of the three mRS representations (ordinal and dichotomized as 0-2/3-5 or 0-1/2-5), with disability defined as a 5-year mRS >2. The ROC curves for logistic regression including only age and sex are included for comparison.

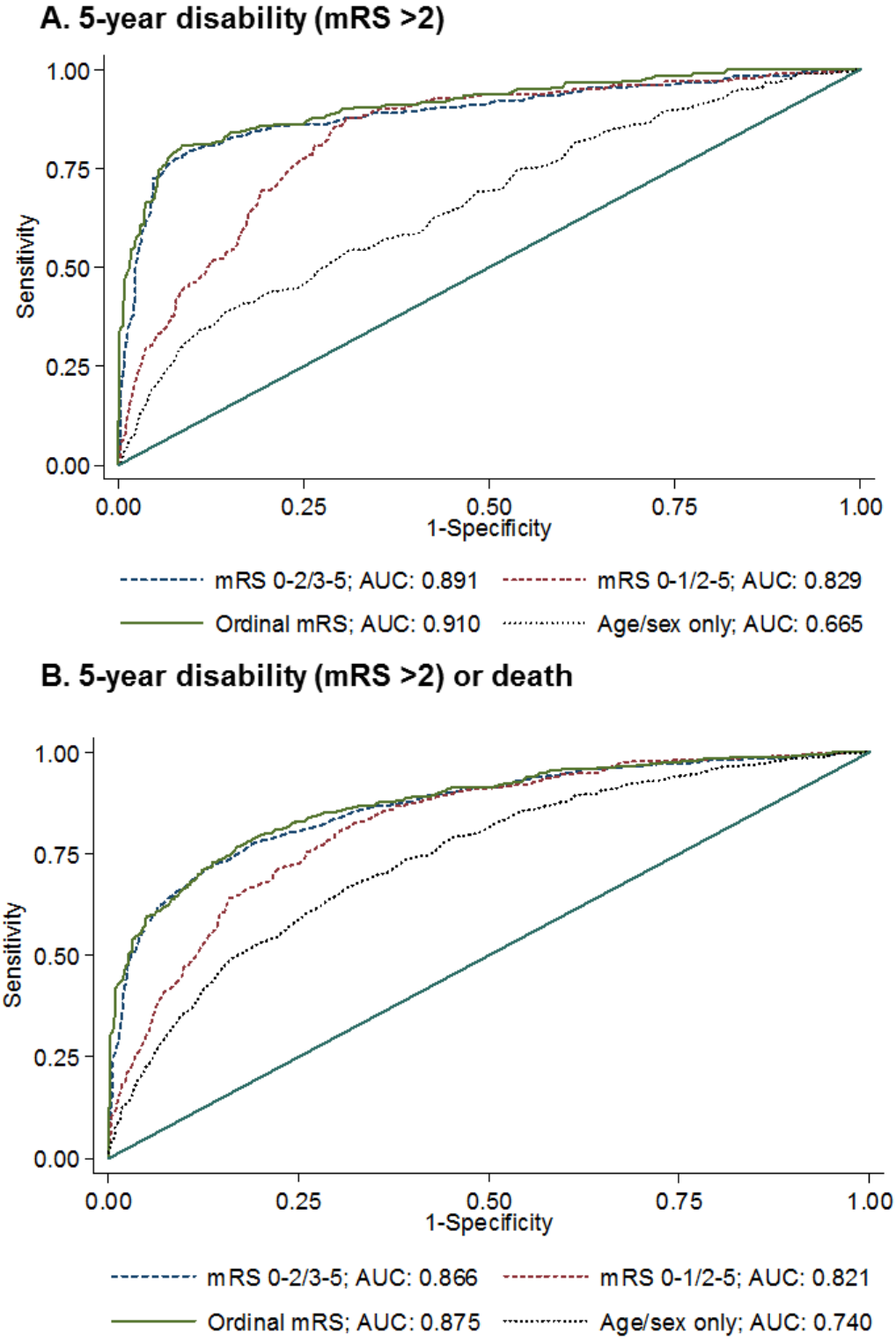

Figure III. Receiver-operating-characteristics curves for the age- and sex-adjusted logistic regression models for predicting (A) 5-year disability and (B) 5-year death or disability (or 1-year disability for those with incomplete follow-up), excluding those with pre-morbid mRS>2, for each of the three mRS representations (ordinal and dichotomized as 0-2/3-5 or 0-1/2-5), with disability defined as a 5-year mRS>2. The ROC curve for logistic regression including only age and sex is included in each case for comparison.

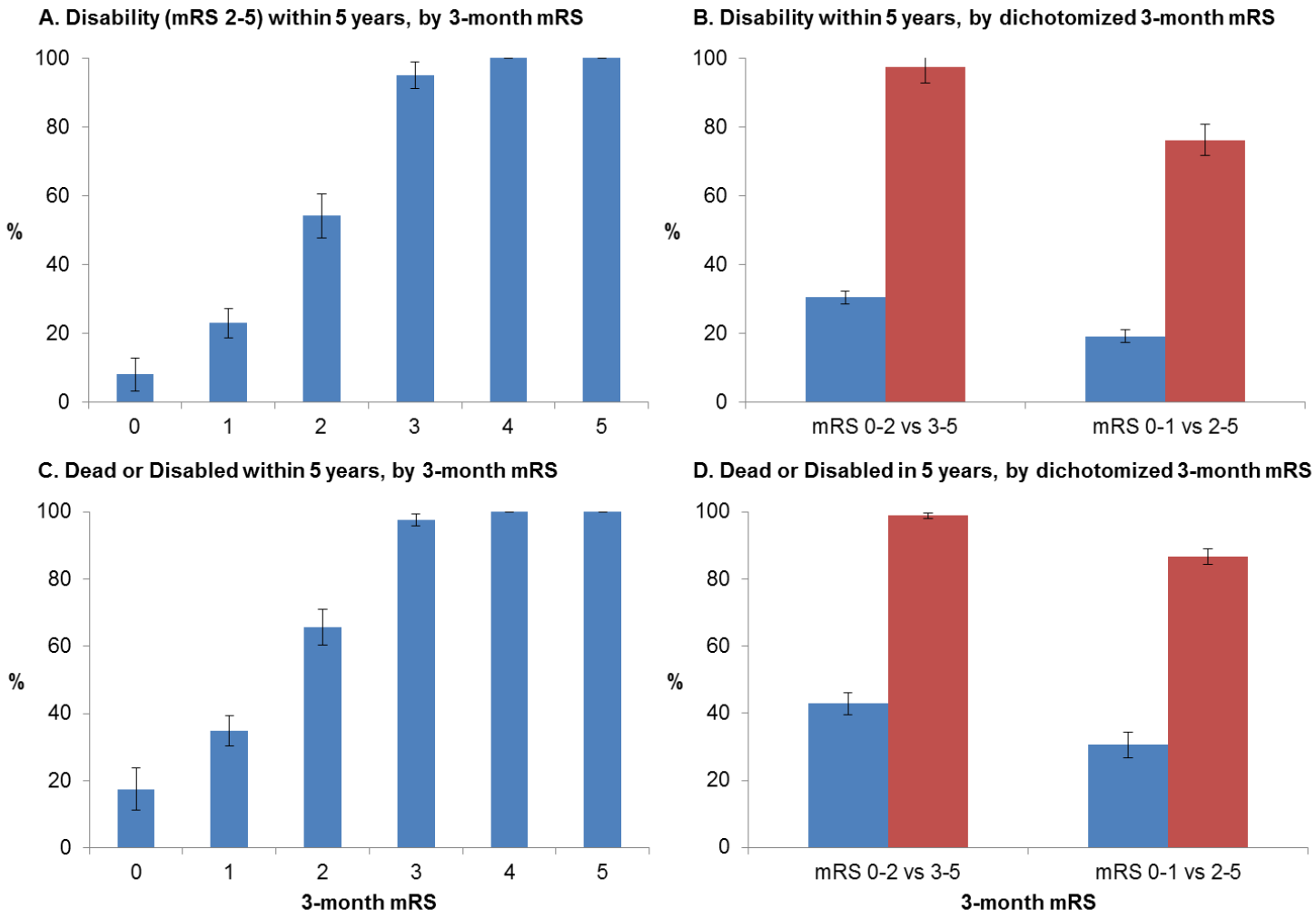

Figure IV. Proportion of 3-month survivors of ischaemic stroke who were alive and disabled within 5 years (A-B) and dead/disabled within 5 years (C-D), stratified by 3-month mRS, with disability defined as 5-year mRS>1. For patients who had not yet reached their 5-year follow-up, 1-year disability status was used.

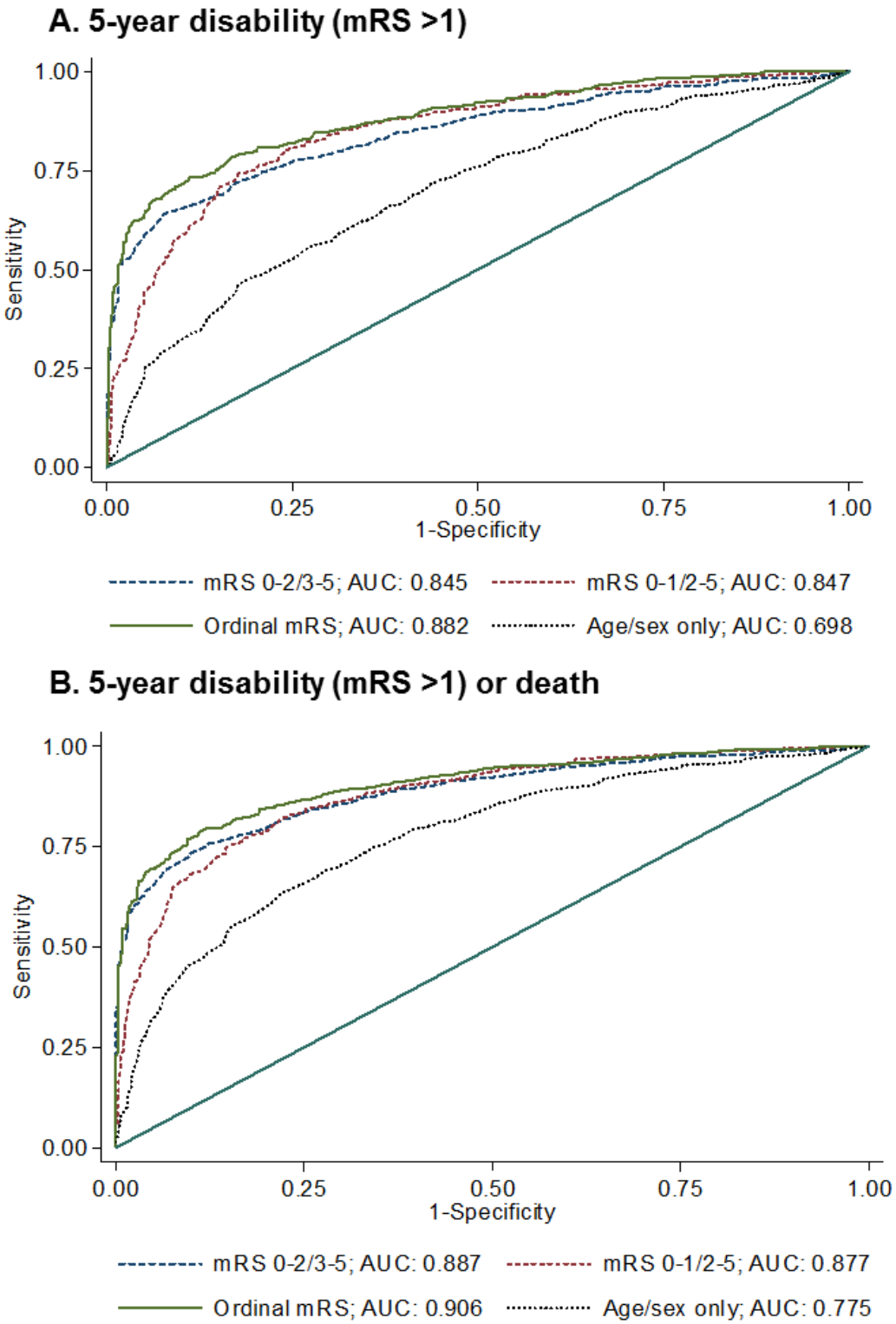

Figure V. Receiver-operating-characteristics curves for the age- and sex-adjusted logistic regression models for predicting (A) 5-year disability and (B) 5-year death or disability (or 1-year disability for those with incomplete follow-up) for each of the three mRS representations (ordinal and dichotomized as 0-2/3-5 or 0-1/2-5), with disability defined as 5-year mRS>1. The ROC curves for logistic regression including only age and sex are included for comparison.

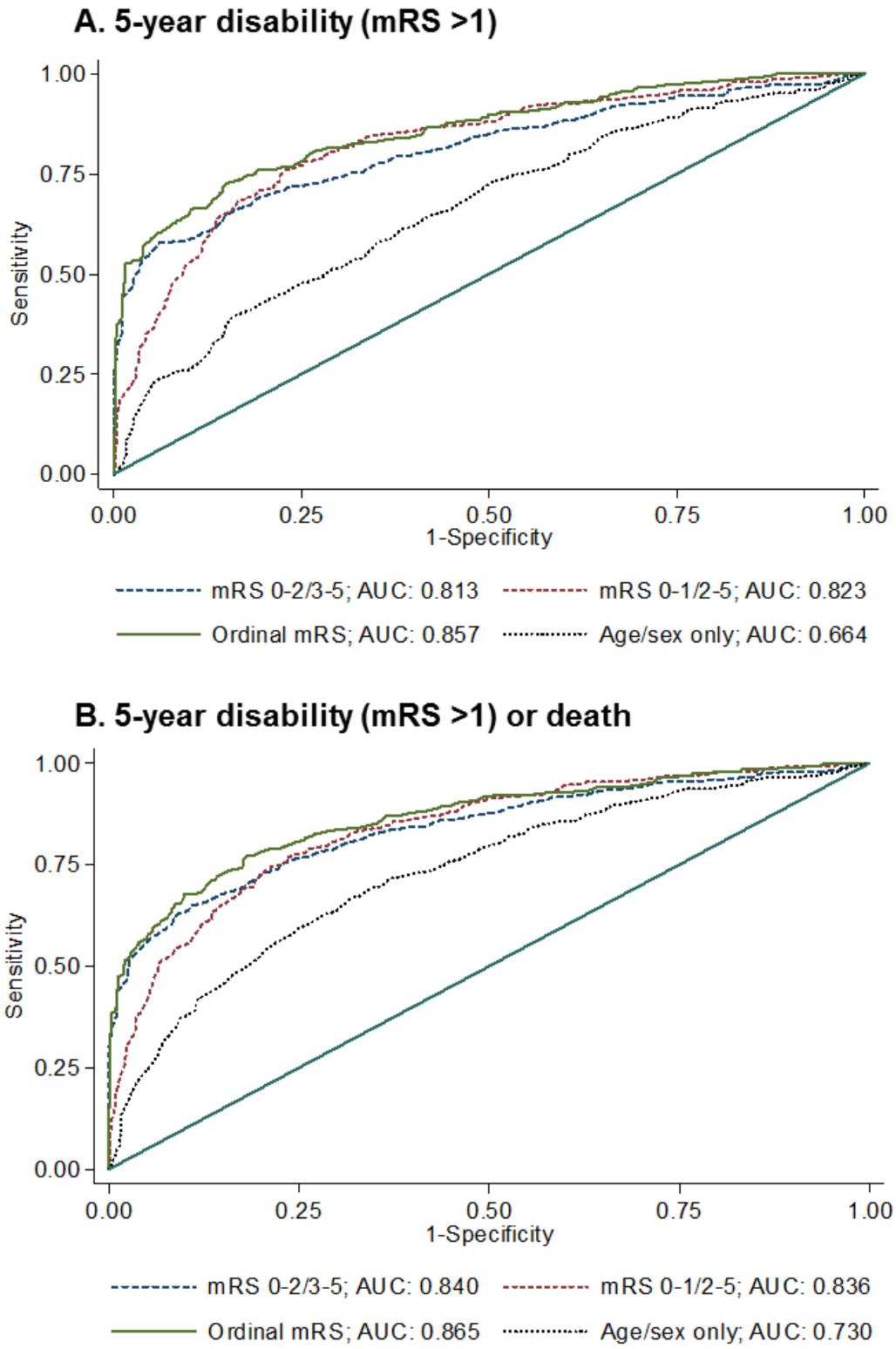

Figure VI. Receiver-operating-characteristics curves for the age- and sex-adjusted logistic regression models for predicting (A) 5-year disability and (B) 5-year death or disability (or 1-year disability for those with incomplete follow-up), excluding those with pre-morbid mRS>1, for each of the three mRS representations (ordinal and dichotomized as 0-2/3-5 or 0-1/2-5), with disability defined as 5-year mRS>1. The ROC curve for logistic regression including only age and sex is included in each case for comparison.

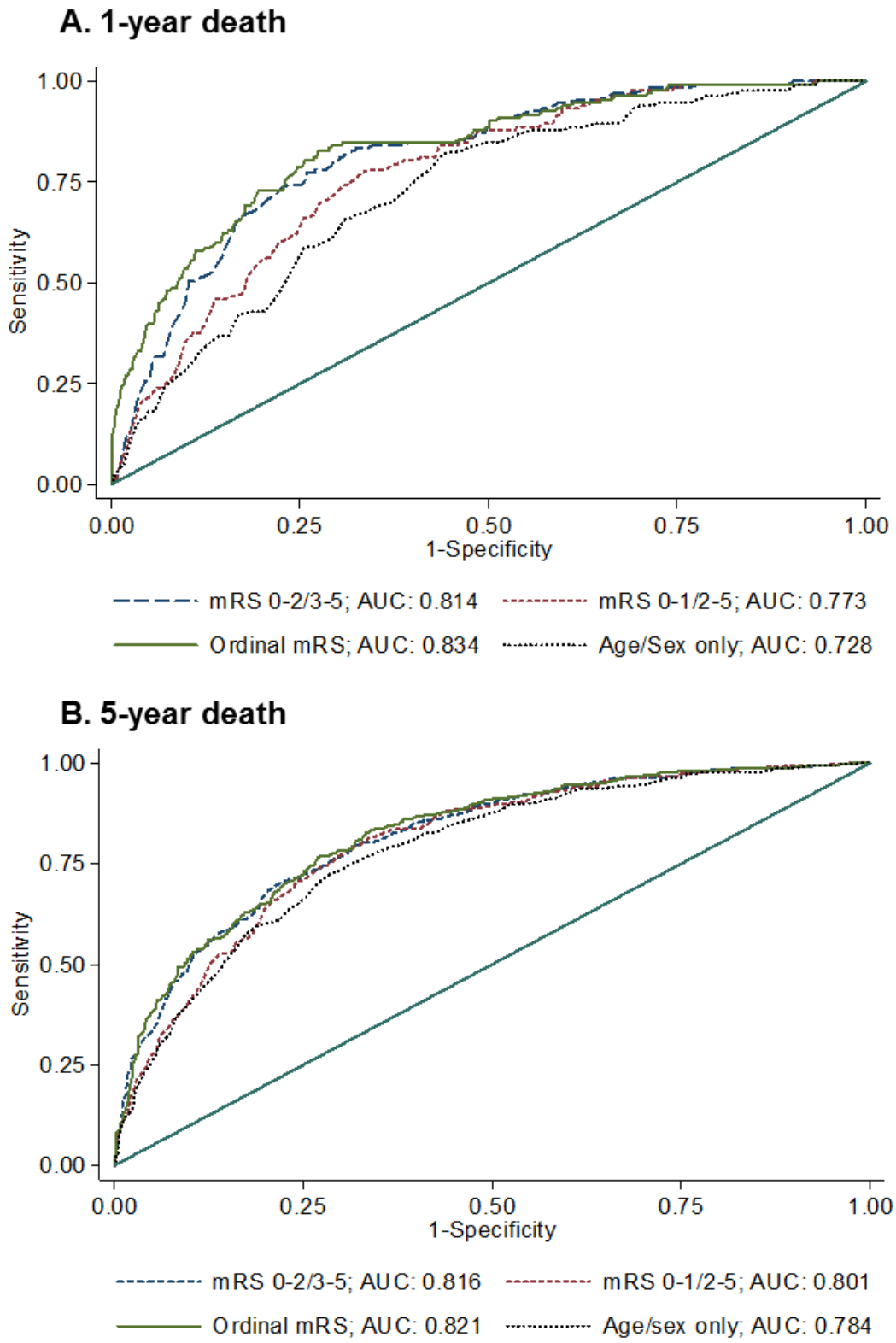

Figure VII. Receiver-operating-characteristics (ROC) curves for the age- and sex-adjusted logistic regression models for predicting the outcome of death at (A) 1-year and (B) 5-years for each of the three mRS representations (ordinal and dichotomized as 0-2/>2 or 0-1/>1). The ROC curve for logistic regression including only age and sex is included in each case for comparison.

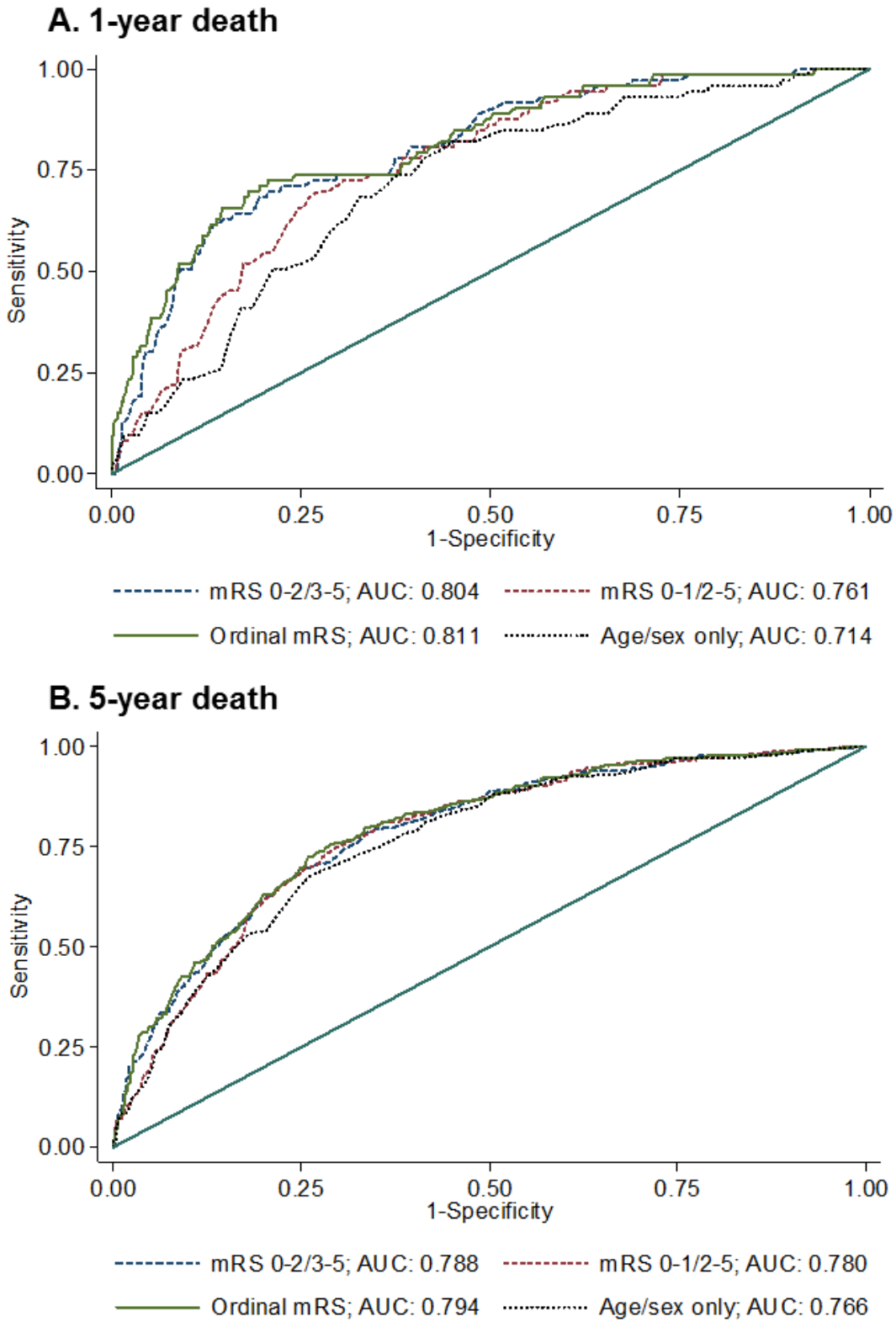

Figure VIII. Receiver-operating-characteristics (ROC) curves for the age- and sex-adjusted logistic regression models for predicting the outcome of death at (A) 1-year and (B) 5-years for each of the three mRS representations (ordinal and dichotomized as 0-2/3-5 or 0-1/2-5), excluding patients with pre-morbid mRS>2. The ROC curve for logistic regression including only age and sex is included in each case for comparison.

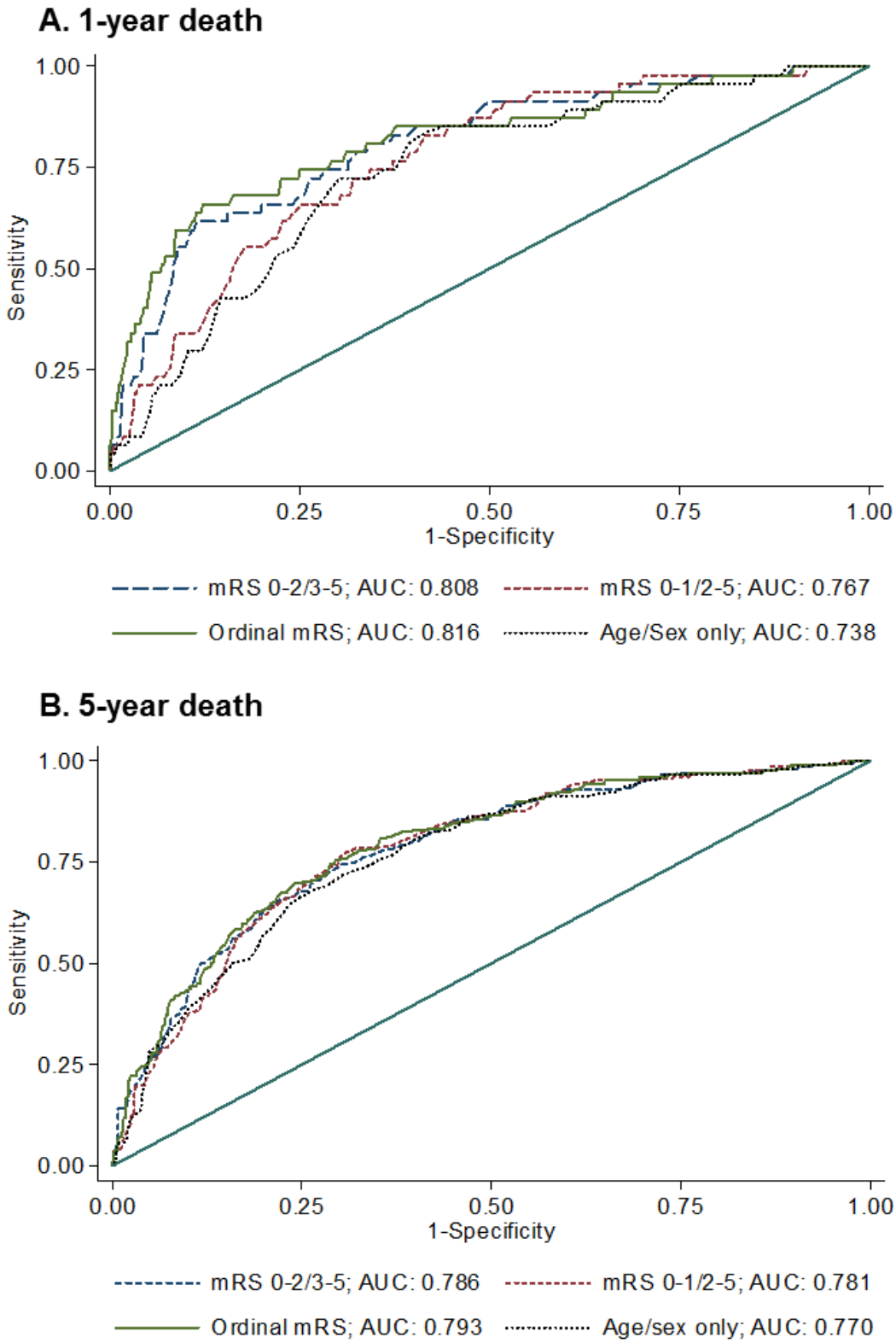

Figure IX. Receiver-operating-characteristics (ROC) curves for the age- and sex-adjusted logistic regression models for predicting the outcome of death at (A) 1-year and (B) 5-years for each of the three mRS representations (ordinal and dichotomized as 0-2/3-5 or 0-1/2-5), excluding patients with pre-morbid mRS>1. The ROC curve for logistic regression including only age and sex is included in each case for comparison.

CHAPTER 6

Developing cohort-derived weights to inform ordinal analysis of the modified Rankin Scale in stroke trials

6.1 CHAPTER ABSTRACT

Ordinal analyses of the mRS continue to be poorly adopted as primary outcome measures in stroke trials, despite their statistical superiority and the pitfalls of dichotomization. The use of ordinal analyses is hindered by the poor clinical interpretability of conventional approaches, which also tend to treat all state-transitions as equal. Weighting the mRS based on the probability of attaining relevant post-stroke clinical endpoints, or expected long-term costs and utilities, may facilitate the adoption of ordinal mRS analysis as the primary outcome measure in stroke trials.

In consecutive ischaemic stroke patients in OXVASC, I used age/sex-adjusted logistic regressions to derive probability weights for 1-year to 5-year death, post-stroke dementia, and/or institutionalization outcomes for the 3-month mRS. I derived similar weights from 1000-bootstrap estimates of 5-year costs and EQ5D-derived quality-adjusted life expectancy (QALE). To assess the consistency of these trends, I also stratified the patients by age (<75 versus >75) and sex (men versus women), and excluded patients with pre-morbid mRS>2 and then mRS>1.

Among 1,606 patients (1,425 3-month survivors), a sigmoid (S-shaped) relationship was observed between the 3-month mRS and death, post-stroke dementia, and/or institutionalization from 1-year to 5-years, with the following age/sex-adjusted probability weights for attaining any of these outcomes at 5-years: mRS 0=0.19; 1=0.27; 2=0.41; 3=0.73; 4=0.77; 5=0.94 (mRS 6 by definition having a probability of 1). Similar trends were seen on examining 1-year to 5-year healthcare costs and QALE, with predicted 5-year QALE as follows: mRS 0=3.88; 1=3.49; 2=3.01; 4=1.30; 5=0.06 (mRS 6 by definition having a QALE of 0). Results were also similar upon stratifying all these outcomes by age and sex, and excluding patients with pre-morbid disability.

These findings underscore the need to weight the mRS in ordinal analyses, as different state transitions in the scale differ in both their clinical prognosis and the quality-of-life experienced by patients, as well as the associated costs of care. Cohort-derived natural history data for objective clinical endpoints of interest – such as death, dementia, or institutionalization post-stroke – can be used to derive these weights. Costs and QALEs could also be used but these are likely to be more vulnerable to variability across practice settings or cultures. In addition to their usefulness for outcome analyses in trials, such weights can also be used by clinicians for prognostication and by health economists for cost-effectiveness analyses of stroke therapies.

6.2 INTRODUCTION

In Chapter 5, I demonstrated that the ordinal form of the modified Rankin Scale (mRS) better predicts 5-year disability, death, and healthcare costs compared to the commonly-used dichotomies, and that the dichotomies risk excluding key segments of the stroke population from trials owing to their pre-morbid disability. As noted previously, several groups have demonstrated additional pitfalls of collapsing ordinal measures like the mRS into a binary scale for dichotomous analysis, including loss of information,[1,2] statistical inefficiency (larger sample sizes),[3, 4] and the risk of ignoring bi-directional effects.[3]

Despite these pitfalls of dichotomization, adoption of ordinal analyses remains poor; for instance, only a quarter of all acute stroke trials since 2007 have used ordinal analysis.[5] One major reason for this is the poor clinical interpretability of conventional approaches to ordinal analysis. Assumption-free approaches like the Cochran-Mantel-Haenszel test simply provide p-values, and it is difficult to get a sense of the expected effect size from such outputs as a common odds-ratio (based on the proportional-odds assumption) or "number-needed-to-treat"[6, 7] as one does not know whether group differences are due to many individuals improving a little bit, a few individuals improving greatly, or a mix of these outcomes. On the other hand, dichotomous analyses provide an easily understood result: X% difference in the proportion of those dead/dependent at 3-months versus control arm. Furthermore, conventional ordinal approaches run into the fundamental problem of valuing all mRS state transitions equally. Informing treatment decisions with such a paradigm is misleading as the differences between ranks on ordinal scales are often non-linear. For instance, a transition from mRS=3 (requiring care/assistance) to mRS=2 (functional independence) is likely to be more clinically-valuable than a transition from mRS=1 (some symptoms) to mRS=0 (no symptoms), although they may both be statistically significant.

To reflect clinically-meaningful treatment effects whilst retaining the full range of the outcome measure, ordinal scales could be weighted to reflect real-world differences between various health-states. Recently, utility-weighting of the mRS was proposed as one method of converting the spacing between mRS ranks to distances that reflect societal valuation of disability states.[8] These weights were derived by averaging values from two different papers – one of these was from the OXVASC study itself,[9] in which mRS scores were mapped to European Quality of Life Scale (EQ-5D) scores in stroke/TIA survivors and then to utilities using utility values for the 243 possible EQ-5D health states obtained via time-tradeoff methods in the general British population. The other paper actually derived disability weights for the mRS generated by an international panel of neurovascular and cardiovascular physicians and nurses through the WHO-GBD (World Health Organization Global Burden of Disease Project) person-tradeoff method.[10] These disability weights – sans patient input – were converted to utility weights by taking their inverse to help derive

the utility-weighted mRS. But even setting aside the issue of whether true utility weights were used, utilities themselves are often not truly patient-centred as they are ultimately derived from the general population rather than the patients themselves, and also differ markedly based on individual and cultural belief systems and sociodemographic factors.[11]

On the other hand, objective long-term outcomes such as death, institutionalization, or disease-specific endpoints (like post-stroke dementia) are less vulnerable to bias, reflect the natural history of the condition, and their value is immediately apparent to patients and clinicians. Weighting ordinal scales based on the probability of attaining such outcomes – as furnished by appropriate prospective cohort studies – could provide a clinically-grounded paradigm for the statistical analysis of randomized-controlled trials. Quality-adjusted life expectancies (QALEs, total quality-adjusted life-years expected over a given time-period for a person in a given health-state) could also be used to temper the uncertainty of utility-weights with the relative definitiveness of mortality data. Together with health/social care cost weights, such QALE weights would also be better suited for cost-effectiveness analyses. Therefore, I sought to derive probability weights for 5-year death, institutionalization, and dementia outcomes, as well as 5-year cost and QALE weights, for the various 3-month mRS scores in the OXVASC study. Given that further recovery is uncommon in ischaemic stroke patients beyond 1-year post-stroke (as discussed in Chapter 2 and more specifically for lacunar strokes in Chapter 4), I hypothesized that the non-linearity of the relationship between 3-month mRS and long-term outcome (seen for 5-year death/disability and costs in Chapter 5) would be preserved across all these long-term clinical and health-economic outcomes at all follow-up points beyond 1-year.

6.3 METHODS

Study Population

OXVASC methodology was previously described in Chapter 2. I again focused on patients surviving 3-months past their index stroke (first stroke in the study period, April 2002 to March 2014) in this Chapter.

Determination of Institutionalization

At the time of 1-month, 3-month, 6-month, 1-year, 2-year, and 5-year follow-up, patients and/or carers were asked whether they lived in their own home, with friends or relatives, warden housing (in which a trained warden is available 24 hours a day), care home (either residential or nursing care), hospital, or in an intermediate care facility (e.g. community hospital). In addition to these interviews, patients' medical records from the Oxford University Hospitals Trust and their GP practices were also reviewed to identify if and when they were institutionalized. Long-term institutionalization was defined as admission into a

nursing or residential care home. I did not include temporary post-acute care and in-hospital rehabilitation stays.

Determination of Post-stroke Dementia

The details of dementia diagnosis in OXVASC, made through overlapping methods of cognitive testing, interview-based assessments of patients and carers, and ongoing searches of primary care and hospital records, have been previously reported.[12-14] Briefly, cognitive testing was done at all follow-ups using ≥1 of the Mini-Mental State Examination (MMSE),[15] Montreal Cognitive Assessment (MoCA),[16] or Telephone Interview for Cognitive Status-modified (TICSm),[17] all of which have been validated against the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery.[18-21] The MMSE was done at all time points until April 1, 2005, when the baseline MMSE was replaced by the 10 point Abbreviated Mental Test Score (AMTS).[22, 23] From April 2007, the MoCA was introduced for the 6-month, 1-year, and 5-year follow-ups as recommended by the NINDS-CSN Vascular Cognitive Impairment Harmonization Standards Working Group.[18] The TICSm or telephone MoCA (out of 12)[20] was done by telephone when face-to-face follow-up was not feasible. The Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) was also administered to an informant whenever possible to further assess pre-morbid cognitive functioning.[24]

Dementia was defined as pre- or post-stroke. Pre-stroke dementia was recorded if dementia was a listed diagnosis in the primary care record at the time of the index stroke. Pre-stroke dementia was excluded when there was no listed dementia diagnosis and baseline cognitive testing was above the cut-off for dementia (see below). For the remaining cases, pre-stroke dementia diagnosis was made by Dr. Sarah T. Pendlebury (a senior geriatrician with expertise in dementia) after reviewing all available study assessment data and hand-searching of the entire primary care record, including individual consultation records, all hospital outpatient clinic letters, and hospitalization documentation to establish pre-stroke dementia diagnosis on the basis of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) criteria and by IQCODE score ≥3.6. Post-stroke dementia diagnosis was made after exclusion of patients with pre-stroke dementia, and required MMSE<24[25] (remaining <24 for all subsequent follow-ups) or MoCA<20 or TICSm<22 or T-MoCA<9.[20] For subjects with an incomplete test (i.e. testing performed but there was a problem like dysphasia, visual impairment, inability to use the dominant arm, or English as a second language that interfered with test completion), individual patient scores were reviewed, and patients with cognitive scores above cut-off were designated as no-dementia. For those scoring below cut-off, individual patient study records including those from primary care and informant-derived information were used to determine whether the DSM-

IV criteria were met, to avoid spurious classifications on the basis of a low cognitive score. For patients without a direct study assessment, post-stroke dementia was diagnosed if a diagnosis of dementia was recorded in the primary care record, or if DSM-IV criteria[26] were met after hand-searching of the entire primary care record as described by Kokmen et al[27] and dementia was listed on the death certificate. Previous assessments have established that there is no under-diagnosis of dementia in OXVASC using this methodology.[12]

Assessment of Quality-of-life

Methods for quality-of-life assessment in OXVASC have been previously described.[28] At 6-month, 1-year, and 5-year follow-up appointments, patients were asked about their current health-related quality-of-life using the EQ-5D-3 levels questionnaire,[29] where patients are asked to report any problems (none, some, or unable/extreme) in five attributes: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D has been found to be a valid quality-of-life measure after stroke.[30] EQ-5D responses were converted into utilities using UK population tariffs developed in the 1990s,[31] when a sample of health states was valued using the time-trade-off method by 3,337 members of the general public,[14] and regression equations were fitted to obtain a tariff for all 243 possible EQ-5D health states, generating tariffs ranging from -0.59 to 1.[31]

Statistical analyses

Analyses were censored at 15-May-2017 and were performed using STATA 13.1.

Logistic regression was used to adjust associations of 3-month mRS and long-term outcomes of death, institutionalization, and/or post-stroke dementia for age/sex, and estimate the age/sex-adjusted probability (and thereby “weights”) of these outcomes at 1-year, 2-years, 3-years, 4-years, and 5-years for each mRS grade. I was particularly interested in examining composite outcomes of death/dementia, death/institutionalization, and death/institutionalization/dementia, in order to capture the dual burden of disability and mortality carried by each step up the mRS (as discussed in Chapter 2 on the time-course of post-stroke death and disability outcomes). I decided against using death/disability as a composite outcome in these analyses (as previously used in Chapters 2 and 5); since disability assessments in follow-up were also performed using the mRS, probability weights generated using this approach may have been perceived as being somewhat tautological. Using institutionalization or dementia – both untainted by mRS assessments – as surrogates for disability burden, would circumvent this issue whilst testing my hypothesis about the “non-linearity” of the mRS in relation to other long-term outcomes.

The collection and analysis of 5-year health and social care costs were previously described in Chapter 5. For this Chapter, costs stratified by 3-month mRS were estimated not only for 5-years but also for 1-year, 2-years, 3-years, and 4-years using the same approach.[32]

A quality-adjusted survival curve was generated by plotting, against time, the product of the mean utility at each follow-up and the probability of surviving to that follow-up. This area under the curve represents the mean quality-adjusted survival (i.e. quality-adjusted life years [QALYs] generated between 3-months and 5-years after index stroke).[33] QALYs were stratified by 3-month mRS score and reported as means alongside 95% CIs, calculated using 1,000 bootstrap estimates. We did not perform multiple imputation of missing EQ-5D data, given that a recent analysis of utilities after stroke and TIA in OXVASC found little difference in overall results upon imputing this missing data.[28]

All these analyses were repeated after excluding patients with (1) pre-morbid mRS>2, and (2) pre-morbid mRS>1 to reflect the exclusion criteria of many acute stroke trials. I also stratified these analyses by age (>75 versus <75) and sex.

Statistical significance was set at $p<0.050$.

6.4 RESULTS

Baseline characteristics of this cohort were previously presented in Chapter 2, Table 1. Among 1,425 3-month survivors, 42 (3.0%) were institutionalized pre-stroke, and 144 (9.3%) had pre-stroke dementia. EQ-5D data were missing for 236 (16.5%) 3-month survivors, representing 14.7% of the overall sample including 3-month deaths. Reasons included patient refusal of face-to-face or telephone follow-up (n=18), patients being too ill/disabled (n=89) or refusing to complete the EQ-5D questionnaire (n=33), and patients not attending follow-up appointments or simply being lost to follow-up (n=96).

Death, institutionalization, and dementia outcomes

Over the course of 5-year follow-up, 465 (32.6%) 3-month survivors died, 338 (24.1%) of those who were dementia-free pre-stroke developed new dementia, and 229 (16.6%) became newly institutionalized (of whom 121 [52.8%] had dementia). At 5-years, 144 (18.3%) of those alive had developed dementia whilst 85 (10.9%) were institutionalized. 652/1,281 (50.9%) patients with complete followup met the endpoints of death, dementia, or institutionalization by 5-years; this included 29 patients who had not yet reached 5-year follow-up but had already met the endpoints of post-stroke dementia or institutionalization.

On age/sex-adjusted logistic regression, the odds of 5-year death, dementia, and/or institutionalization rose non-linearly with rising 3-month mRS scores, with a step-change in particular between mRS 2 and 3 (Table 1). Upon plotting the probability-weights derived for

each mRS score from these regressions, an S-shaped (sigmoid) curve was obtained in each case beyond 1-year (Figure 1; dementia and institutionalization curves in Figure I of Appendix). There was generally little difference in probability of death, dementia, and/or institutionalization at 1-year between mRS scores 0, 1, and 2 with probabilities being quite low for these scores (e.g. estimated probability of death/dementia/institutionalization [Pr_{DDI}] at 1-year for mRS 0=0.058, mRS 1=0.061, mRS 2=0.098), and small differences gradually emerging over the subsequent years (e.g. Pr_{DDI} at 5-years for mRS 0=0.19, mRS 1=0.27, mRS 2=0.41). On the other hand, distinctions between mRS 3 and 4 were often most apparent at 1-year (e.g. Pr_{DDI} at 1-year for mRS 3=0.33, mRS 4=0.53) and then progressively became attenuated as patients with mRS 3 "caught up" in attaining these outcomes (e.g. Pr_{DDI} at 5-years for mRS 3=0.73, mRS 4=0.77). Additional jumps were also seen between mRS 4 and 5 across all outcomes (see probability weights in Tables I-IV, Appendix). Similar results were obtained for these outcomes upon excluding patients with pre-morbid mRS>2 (Figure II, Appendix) and pre-morbid mRS>1 (Figure III, Appendix).

When the results were stratified by age (Figures IV-V, Appendix) and sex (Figures VI-VII, Appendix), similar non-linear relationships were observed. The probabilities of attaining the endpoints (especially death) were generally lower in younger patients, and whereas the rise in probability was most pronounced between mRS 4 and 5 in younger patients (Figure IV), it was most pronounced from mRS 2 and 3 in those aged >75 years (Figure V). Although men were generally younger than women in the cohort (mean age in men: 71.6 years, women: 77.0 years, t-test p<0.0001), the probability rise was most pronounced between mRS 2 and 3 in men (Figure VI). The probability "weights" from the models with men and women were similar to those obtained from the whole cohort, generally differing by ≤0.05 or ≥-0.05, but many of the weights for those aged<75 and aged>75 fell well outside this range (Table V, Appendix).

Cost and QALE outcomes

Similar non-linear relationships were observed between the 3-month mRS and outcomes of health/social care costs and QALE over post-stroke years 1 through 5 (Tables 2-3, Figure 2). Health/social care costs generally rose and QALE fell with rising mRS scores, but again the curves were generally flatter between mRS scores 0, 1, and 2 with a step-change going from 2 to 3 (e.g. mean difference in 5-year QALE for mRS 0 versus 1=0.38, 95%CI 0.19-0.57; mRS 1 vs 2=0.48, 0.31-0.66; mRS 2 vs 3=1.15, 0.94-1.33). However, whereas the QALEs showed a much greater drop between mRS 4 and 5 than between mRS 3 and 4 (e.g. mean difference in 5-year QALE for mRS 3 vs 4: 0.57, 95%CI 0.31-0.81; mRS 4 vs 5= 1.23, 0.90-1.57), there was essentially a linear trend in the health and social care costs between mRS 3, 4, and 5 with these parts of the curves being fairly parallel for years 1 through 5 (e.g. mean difference at 5-years for mRS 3 vs 4: $19,476, 95%CI $5,700-33,318,

and for mRS 4 vs 5: $19,272, 95%CI $-1,141-40,510). There was also no overlap in the confidence intervals for QALE among the different mRS grades. Similar results were obtained for these outcomes upon excluding patients with pre-morbid mRS>2 (Figure VIII, Appendix) and pre-morbid mRS>1 (Figure IX, Appendix).

Again, when the results were stratified by age (Figures X-XI, Appendix) and sex (Figures XII-XIII, Appendix), similar non-linear relationships were observed, with the main difference being that the cost curves between mRS 0-2 were much flatter and changed little over 5-years of follow-up for men and those aged<75 (Figures X, XII). Generally higher rates of healthcare utilization among women meant that the step-change in costs between mRS 2 and 3 was less pronounced in women (e.g. mean difference in 5-year costs for mRS 2 vs 3 in men: $38,462, 95%CI $25,768-51,242; in women: $25,275, $11,314-37,979). A 3-month mRS of 5 was associated with a near-zero QALE at all follow-up years, with a mean 5-year QALE<0 (-0.22) in those aged <75 years. Compared to other patient groups, women and patients aged >75 years also showed a greater drop in mean 5-year QALE between mRS 0 and 1 (e.g. ΔQALE=-0.63 for age>75 vs -0.19 for age<75), and patients aged>75 also showed a greater drop between mRS 3 and 4 (e.g. ΔQALE=-0.80 vs -0.11 for age<75). Overall, the 5-year QALE "weights" estimated for different groups were fairly similar to those obtained from the whole cohort, generally differing by <0.50 or >-0.50 (Table VI, Appendix).

6.5 DISCUSSION

In this population-based prospective cohort of ischaemic stroke survivors, I have demonstrated that there is a non-linear, S-shaped relationship between the 3-month mRS and clinically-relevant outcomes of death, dementia, and/or institutionalization from 1-year to 5-years post-stroke. Similar trends were seen upon excluding patients with pre-morbid disability and upon stratifying the cohort by age and sex. Using age/sex-adjusted logistic regressions, I generated probability weights for each mRS grade for death, death/dementia, death/institutionalization, and death/dementia/institutionalization at 1-year through 5-years, and found similar non-linear relationships upon estimating health/social-care costs and quality-adjusted life expectancy for each mRS grade. The outcomes stratified by 3-month-mRS presented in this chapter provide normative data for clinical prognostication or cost-effectiveness analyses, and can be applied in service planning or population health management. For instance, using information about stroke incidence and observed 3-month mRS outcomes for stroke patients in an area, one can predict the healthcare costs and nursing home admissions expected for that patient population over the next five years and take this into account for resource allocation. In addition to these applications, my findings also have relevant implications for the analysis and interpretation of trials using the mRS.

Firstly, the incremental rise in odds of institutionalization and dementia, and incremental fall in QALE (with no overlapping confidence intervals) with each step up the mRS ladder, further establish the predictive validity (prognostic value) of the mRS outcome scale in ischaemic stroke,[34] and further imply that any shifts in the 3-month mRS from 5-6 towards lower mRS grades are likely to be clinically meaningful and valuable for patients. Studies examining minimally clinically important differences for utility in other diseases have found such differences to be in the range of 0.04 to 0.10 (which over 1 year of life would equal 0.04-0.10 QALYs);[35-38] in this regard, it is worth highlighting that the lowest mean difference in QALYs at 5 years between two mRS grades in the OXVASC cohort was 0.38 (between mRS 0 and 1). This further highlights the importance of using ordinal rather than dichotomous analyses of the mRS in trials to capture transitions across the scale, as discussed in Chapter 5 using death, disability, and care costs.

Secondly, these findings underscore the need to weight the mRS in ordinal analyses, as different state transitions in the scale clearly differ in both their clinical prognosis and the quality-of-life experienced by patients, as well as the associated costs of care. By acknowledging that certain state-transitions are more valuable than others whilst retaining the full range of the scale, this approach can facilitate ordinal analyses that identify treatment differences that are not just statistically significant but also clinically meaningful.

Thirdly, building upon the recently-proposed utility-weighted mRS, the estimated probabilities (5-year death, dementia, institutionalization), costs, and QALEs in this chapter have the added advantage of providing weights that reflect the long-term trajectories of these patients and the burden of their disease, versus a cross-sectional quality-of-life rating. The shape of the utility-weighted mRS curve differs considerably from that observed for the long-term outcomes in our cohort, including the QALE curves; in particular, the greatest utility value steps on the UW-mRS are between mRS 3, 4, and 5 and there is no step-change between mRS 2 to 3. Outcome analysis using the weights provided in this chapter could be performed using a t-test, similar what was proposed by Chaisinanunkul and colleagues for the utility-weighted mRS,[8] wherein the mRS scores for patients in the trial are simply replaced with the corresponding weight of interest (e.g. 5-year probability of death, dementia, or institutionalization) and then the means in treatment and control group compared. For the t-test to be valid, the sampling distribution of the average score needs to approximate the normal distribution; Chaisinanunkul and colleagues compared t-test results with exact modelling of the 7 mRS outcomes using a Dirichlet distribution and found them to be reasonably close.[8] Importantly, the mean difference between treatment/control groups provided through this t-test approach can provide a meaningful “effect size” that reflects the predicted long-term difference of the treatment (e.g. predicted lowering of the probability of 5-year death/institutionalization, predicted lowering of 5-year costs, or predicted increase in

5-year QALE). For healthcare policy planners and economists, such results offer greater immediate interpretability than conventional ordinal mRS, since treatment group differences could be expressed in terms typically used in healthcare population-level decision making.

Nonetheless, the question of which weights should be favoured for primary outcome analysis of the mRS is more complicated. Cost-based weights would appear to reflect the burden of disease to both the patient and the health system, but is unclear how an mRS of 6 should be weighted in such an analysis, since dead patients would incur zero costs beyond 3-months. One might weight mRS 5 and 6 equally given that many people consider such severe disability as mRS 5 to be even worse than death;[10] indeed, the near-zero 5-year QALE for patients with a 3-month mRS of 5 in our cohort (negative in those aged<75) supports such an approach. However, costs varied substantially by age and sex, and would also vary considerably depending on the healthcare system and payer model. In this regard, it would seem that the probability weights directly focussing on concrete post-stroke outcomes (e.g. composite of death, dementia, institutionalization) are most favourable. Patients with a 3-month mRS of 6 would be assigned a weight of 1.00 since they have already attained one of these composite endpoints. However, probability weights also varied considerably by age in the cohort. Like the cost weights, the overall probability weights would tend to over-estimate adverse outcome rates in younger populations whilst under-estimating them in older populations. One might suggest that different weights should be used in different trials depending on their demographic characteristics, but this seems needlessly complex. On the other hand, 5-year QALE weights were relatively consistent across different groups. One would also simply assign patients with 3-month mRS of 6 a QALE weight of 0 since they could not accumulate any further QALYs. In this regard, QALE weights seem most appealing; indeed, QALYs combine both mortality and quality-of-life data, and are widely favoured to inform treatment evaluations and resource allocation. That being said, they have their flaws, since the raters from whom utilities are ultimately derived are non-patients making a judgement about quality based on a presentation of disability (e.g. patient's score on EQ-5D domains), influenced profoundly by disease labels, presented prognosis, and actually having the disease.[39, 40]

My analysis has several strengths, including a robust population-based design with high rates of ascertainment of all incident strokes; completeness of follow-up for death, institutionalization, and cost data; and replication of findings for a range of outcomes and subgroups (age, sex, pre-morbidly disability-free patients). However, there are some potential limitations. Firstly, 14.7% of patients did not have EQ-5D data, which we did not impute; however, a recent analysis of utilities after stroke and TIA in OXVASC found that overall results did not differ upon imputing missing EQ-5D data.[28] Secondly, whilst I have presented best-fit curves for years 1 through 5 to better illustrate the shape of the

relationship between the 3-month mRS and various long-term outcomes, in reality the mRS is of course an ordinal scale and not a continuous one, so there cannot actually be any data points on those lines between the possible mRS scores. Thirdly, although OXVASC has similarly rates of long-term disability and mortality as other population-based studies,[41, 42] the generalizability of probability-, cost-, and QALE-weights seen in the OXVASC population may be limited by differences in practice settings or payer systems (with respect to healthcare costs and potentially mortality), ethnicity or cultural values (with respect to quality-of-life assessments and rates of institutionalization versus care-at-home; OXVASC is >95% White), and/or case-mix. The OXVASC population is also relatively elderly (mean age 73 years), and we did find that death, dementia, institutionalization rates and health/social-care costs were unsurprisingly much lower in those aged<75. Fourthly, the weights generated for the 3-month mRS may not be generalizable to mRS measurements made at considerably earlier or later time-points. Fifthly, if a new therapy or intervention directly modifies the risk of long-term dementia, institutionalization, or mortality over and above a reduction in stroke-related disability, then a probability-weighted mRS approach would likely under-estimate that benefit. However, this would still be an improvement over conventional approaches that do not take any such prognostic implications into account and could serve as a “shorthand” approach to estimate the cost-effectiveness of new therapies.

In conclusion, cohort-derived natural history data for objective clinical endpoints or health-economic outcomes of interest can be used to inform weighted ordinal analyses of the mRS in clinical trials. Comparing the performance of such probability-weighted or QALE-weighted mRS approaches against conventional ordinal analysis using published clinical trial data may help identify which weights best discriminate among effective and ineffective treatments, and may facilitate the adoption of weighted mRS analyses in stroke trials.

6.6 REFERENCES

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6.7 TABLES

Table 1. Odds of 5-year death, dementia, or institutionalization for each 3-month mRS score (age/sex-adjusted) in 3-month ischaemic stroke survivors with full 5-years of follow-up or who met the endpoint of interest between 3-months and 5-years. For the regressions of dementia and institutionalization, we excluded those who had a pre-stroke diagnosis of dementia and were institutionalized pre-stroke, respectively.

	Death at 5-years		Dementia at 5-years (or prior to death)		Death or Dementia		Institutionalization at 5-years (or prior to death)		Death or Institutionalization		Death, Dementia, or Institutionalization	
3-month mRS	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**	**aOR (95%CI)**	**p>|z|**
0	**Reference**		**Reference**		**Reference**		**Reference**		**Reference**		**Reference**	
1	1.20 (0.62-2.31)	0.591	0.86 (0.43-1.73)	0.668	1.16 (0.66-2.04)	0.615	2.96 (0.68-12.9)	0.149	1.57 (0.81-3.01)	0.180	1.31 (0.74-2.32)	0.356
2	1.64 (0.85-3.17)	0.141	1.61 (0.81-3.19)	0.174	1.92 (1.09-3.40)	0.025*	2.81 (0.64-12.4)	0.172	1.94 (1.00-3.75)	0.049*	1.99 (1.12-3.55)	0.019*
3	3.81 (1.97-7.37)	<0.001*	2.97 (1.50-5.88)	0.002*	4.96 (2.76-8.91)	<0.0001*	10.1 (2.39-43.1)	0.002*	6.21 (3.19-12.1)	<0.0001*	5.94 (3.26-10.8)	<0.0001*
4	4.59 (2.31-9.10)	<0.0001*	4.30 (2.11-8.77)	<0.0001*	5.87 (3.14-11.0)	<0.0001*	19.0 (4.44-81.0)	<0.0001*	8.57 (4.25-17.3)	<0.0001*	8.31 (4.39-16.1)	<0.0001*
5	10.4 (4.83-22.6)	<0.0001*	11.5 (5.13-25.7)	<0.0001*	16.5 (7.41-36.6)	<0.0001*	44.2 (10.1-194)	<0.0001*	38.0 (15.1-95.3)	<0.0001*	43.2 (15.8-118)	<0.0001*
Age	1.10 (1.08-1.12)	<0.0001*	1.06 (1.05-1.08)	<0.0001*	1.10 (1.08-1.11)	<0.0001*	1.07 (1.05-1.09)	<0.0001*	1.11 (1.09-1.13)	<0.0001*	1.11 (1.09-1.13)	<0.0001*
Male	1.29 (0.97-1.71)	0.077	0.83 (0.62-1.12)	0.232	1.04 (0.79-1.37)	0.781	0.65 (0.46-0.92)	0.014*	1.07 (0.80-1.43)	0.635	0.94 (0.71-1.25)	0.665
N	1235		1154		1255		1210		1244		1262	
AUC	**0.821**		**0.788**		**0.834**		**0.843**		**0.858**		**0.860**	
p>|X^2|		<0.0001*		<0.0001*		<0.0001*		<0.0001*		<0.0001*		<0.0001*

Table 2. Estimated total health and social care costs at 1-year, 2-years, 3-years, 4-years, and 5-years post-stroke for each 3-month mRS score in 3-month ischaemic stroke survivors.

3-month mRS	Year 1 $ (95%CI)	Year 2 $ (95%CI)	Year 3 $ (95%CI)	Year 4 $ (95%CI)	Year 5 $ (95%CI)
0	1,596 (1,125-2,113)	3,812 (2,738-5,139)	5,863 (4,239-7,988)	7,716 (5,850-9,933)	9,692 (7,486-12,037)
1	2,266 (1,799-2,785)	6,113 (5,039-7,285)	10,265 (8,457-12,312)	14,256 (11,804-17,077)	19,539 (16,133-23,242)
2	3,776 (2,928-4,664)	8,594 (6,767-10,447)	13,921 (11,208-16,851)	19,653 (16,035-23,438)	24,643 (20,115-29,436)
3	11,197 (9,063-13,327)	21,914 (18,227-25,680)	34,170 (28,966-39,805)	45,952 (39,225-53,434)	57,595 (49,150-66,445)
4	25,523 (22,315-29,050)	40,800 (35,306-46,310)	55,450 (47,695-63,518)	66,369 (57,074-75,876)	77,071 (66,663-88,926)
5	36,946 (32,308-42,070)	56,228 (48,109-64,298)	72,368 (60,883-84,221)	84,963 (70,027-99,936)	96,343 (78,692-113,998)
N	1403	1403	1403	1319	1235

Table 3. Estimated quality-adjusted life expectancy (QALE) at 1-year, 2-years, 3-years, 4-years, and 5-years post-stroke for each 3-month mRS score in 3-month ischaemic stroke survivors.

3-month mRS	Year 1 QALYS (95%CI)	Year 2 QALYS (95%CI)	Year 3 QALYS (95%CI)	Year 4 QALYS (95%CI)	Year 5 QALYs (95%CI)*
0	0.67 (0.65-0.68)	1.52 (1.48-1.56)	2.32 (2.25-2.40)	3.11 (3.00-3.22)	3.88 (3.73-4.03)
1	0.62 (0.60-0.63)	1.39 (1.36-1.42)	2.12 (2.07-2.18)	2.83 (2.75-2.91)	3.49 (3.39-3.61)
2	0.55 (0.53-0.56)	1.24 (1.20-1.28)	1.89 (1.81-1.95)	2.48 (2.37-2.57)	3.01 (2.87-3.14)
3	0.42 (0.39-0.44)	0.88 (0.83-0.93)	1.27 (1.19-1.36)	1.60 (1.48-1.72)	1.87 (1.72-2.02)
4	0.26 (0.23-0.30)	0.58 (0.51-0.66)	0.85 (0.74-0.97)	1.09 (0.93-1.25)	1.30 (1.10-1.51)
5	0.042 (-0.0060-0.099)	0.055 (-0.039-0.16)	0.058 (-0.091-0.22)	0.061 (-0.15-0.29)	0.063 (-0.20-0.34)
N	1403	1403	1403	1319	1235

***** Mean difference in QALYs at 5 years for mRS 0 vs 1: 0.38 (95%CI 0.19-0.57), mRS 1 vs 2: 0.48 (0.31-0.66), mRS 2 vs 3: 1.15 (0.94-1.33), mRS 3 vs 4: 0.57 (0.31-0.81), mRS 4 vs 5: 1.23 (0.90-1.57).

6.8 FIGURES

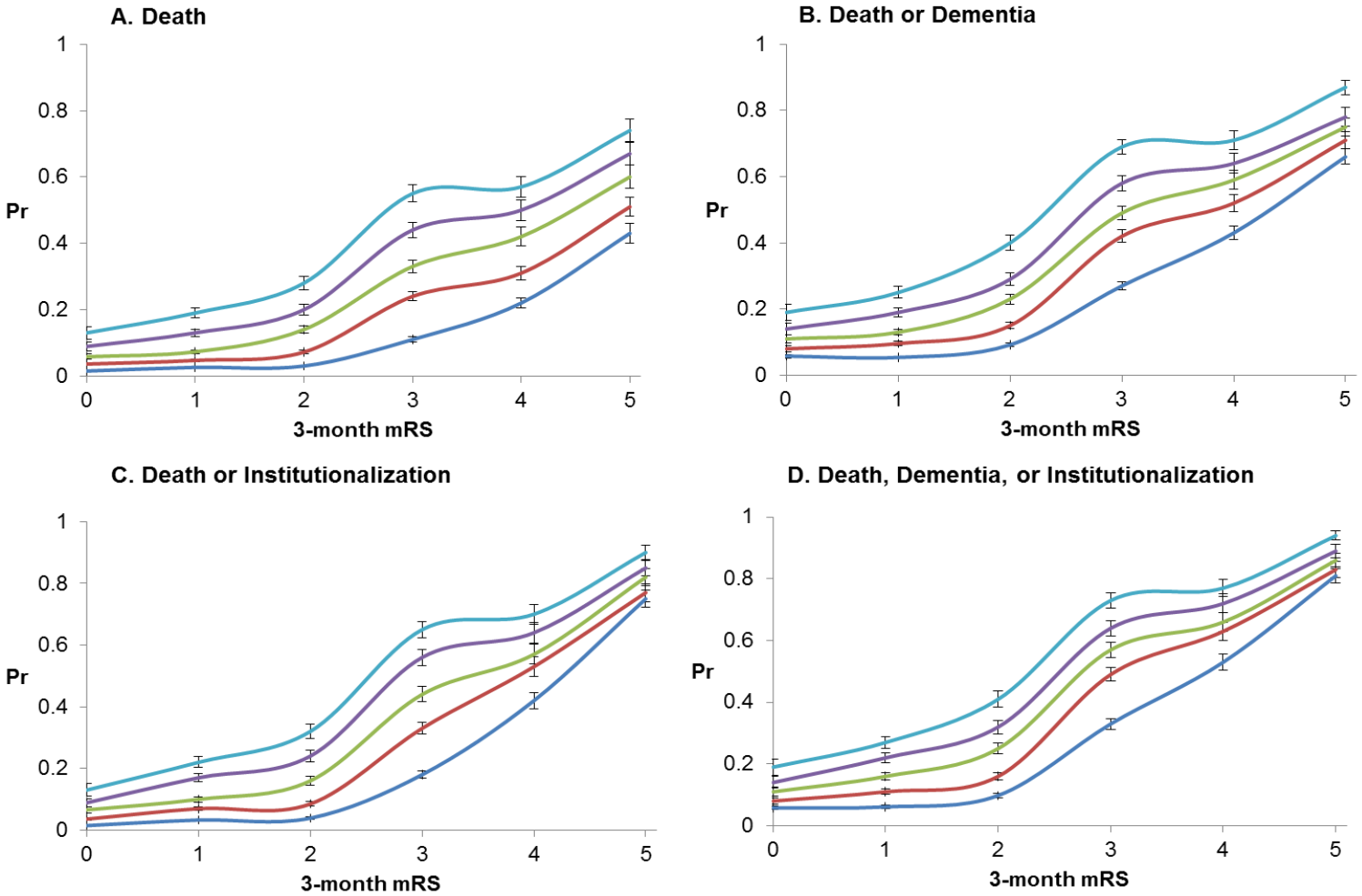


Figure 1. Age- and sex-adjusted probabilities estimated from logistic regressions for 1-year (dark blue), 2-year (red), 3-year (green), 4-year (purple), and 5-year (light blue) outcomes of (A) death, (B) death or post-stroke dementia, (C) death or post-stroke institutionalization, and (D) death, dementia, or institutionalization, for 3-month survivors of ischaemic stroke, stratified by 3-month mRS (n=1,403). Bars represent 95% confidence intervals.

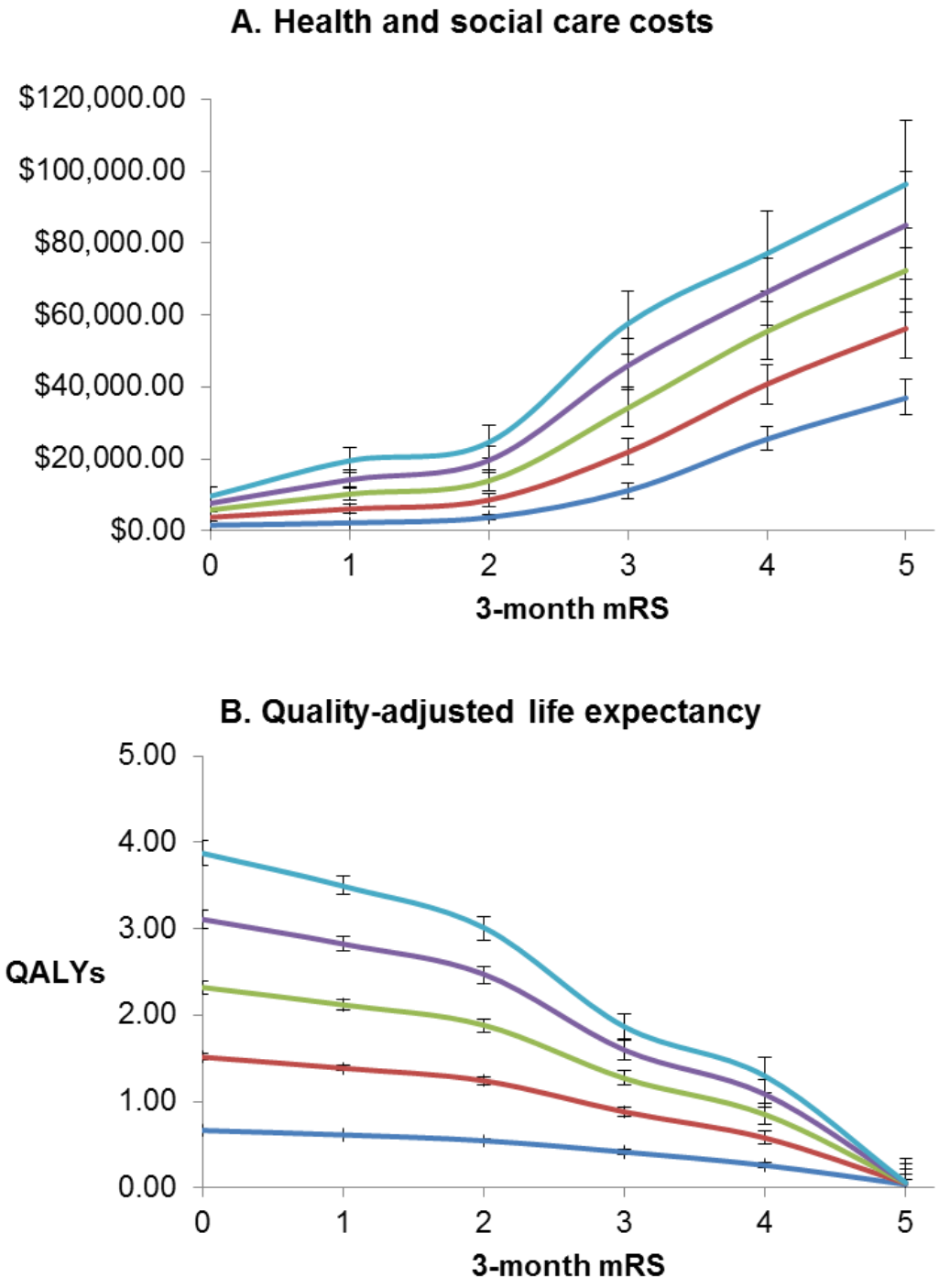


Figure 2. Estimated (A) 5-year health and social care costs and (B) quality-adjusted life expectancy (in quality-adjusted life-years, QALYs) for 1-year (dark blue), 2-years (red), 3-years (green), 4-years (purple), and 5-years (light blue) post-stroke for 3-month survivors of ischaemic stroke, stratified by 3-month mRS (n=1,403). Bars represent 95% confidence intervals.

6.9 APPENDIX – SUPPLEMENTARY TABLES AND FIGURES FOR CHAPTER 6

SUPPLEMENTARY TABLES

Table I – Age- and sex-adjusted probabilities of death in Years 1 through 5, estimated from logistic regressions in 3-month survivors of ischaemic stroke, grouped by 3-month mRS. All probabilities (Pr) are presented with two significant figures and alongside the number of individuals contributing to that estimate.

	Year 1		Year 2		Year 3		Year 4		Year 5	
3-month mRS	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**
0	0.015 (0.013-0.017)	137	0.036 (0.032-0.040)	137	0.058 (0.050-0.066)	137	0.089 (0.076-0.10)	124	0.13 (0.11-0.15)	107
1	0.026 (0.024-0.028)	427	0.047 (0.043-0.051)	427	0.073 (0.067-0.079)	427	0.13 (0.12-0.14)	385	0.19 (0.18-0.20)	356
2	0.030 (0.028-0.032)	305	0.072 (0.067-0.077)	305	0.14 (0.13-0.15)	305	0.20 (0.18-0.22)	290	0.28 (0.26-0.30)	273
3	0.11 (0.10-0.12)	251	0.24 (0.23-0.25)	251	0.33 (0.31-0.35)	251	0.44 (0.42-0.46)	243	0.55 (0.52-0.58)	234
4	0.22 (0.20-0.24)	180	0.31 (0.29-0.33)	180	0.42 (0.39-0.45)	180	0.50 (0.47-0.53)	174	0.57 (0.54-0.60)	169
5	0.43 (0.40-0.46)	103	0.51 (0.48-0.54)	103	0.60 (0.57-0.63)	103	0.67 (0.64-0.70)	103	0.74 (0.71-0.77)	96
Total N		1403		1403		1403		1319		1235

Table II – Age- and sex-adjusted probabilities of death or post-stroke dementia in Years 1 through 5, estimated from logistic regressions in 3-month survivors of ischaemic stroke, grouped by 3-month mRS. All probabilities (Pr) are presented with two significant figures and alongside the number of individuals contributing to that estimate.

	Year 1		Year 2		Year 3		Year 4		Year 5	
3-month mRS	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**
0	0.058 (0.052-0.064)	137	0.080 (0.072-0.088)	137	0.11 (0.098-0.12)	137	0.14 (0.12-0.16)	127	0.19 (0.17-0.21)	112
1	0.054 (0.051-0.057)	427	0.096 (0.090-0.10)	427	0.13 (0.12-0.14)	427	0.19 (0.18-0.20)	385	0.25 (0.23-0.27)	359
2	0.092 (0.087-0.097)	305	0.15 (0.14-0.16)	305	0.23 (0.22-0.24)	305	0.29 (0.27-0.31)	292	0.40 (0.38-0.42)	275
3	0.27 (0.26-0.28)	251	0.42 (0.40-0.44)	251	0.49 (0.47-0.51)	251	0.58 (0.56-0.60)	248	0.69 (0.67-0.71)	242
4	0.43 (0.41-0.45)	180	0.52 (0.50-0.54)	180	0.59 (0.56-0.62)	180	0.64 (0.61-0.67)	174	0.71 (0.68-0.74)	170
5	0.66 (0.64-0.68)	103	0.71 (0.68-0.74)	103	0.75 (0.72-0.78)	103	0.78 (0.75-0.81)	103	0.87 (0.85-0.89)	97
Total N		1403		1403		1403		1329		1255

Table III – Age- and sex-adjusted probabilities of death or post-stroke institutionalization in Years 1 through 5, estimated from logistic regressions in 3-month survivors of ischaemic stroke, grouped by 3-month mRS. All probabilities (Pr) are presented with two significant figures and alongside the number of individuals contributing to that estimate.

	Year 1		Year 2		Year 3		Year 4		Year 5	
3-month mRS	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**
0	0.015 (0.013-0.017)	137	0.036 (0.031-0.041)	137	0.066 (0.056-0.076)	137	0.089 (0.075-0.10)	124	0.13 (0.11-0.15)	107
1	0.033 (0.030-0.036)	427	0.070 (0.064-0.076)	427	0.10 (0.091-0.11)	427	0.17 (0.16-0.18)	385	0.22 (0.20-0.24)	356
2	0.039 (0.036-0.042)	305	0.085 (0.078-0.092)	305	0.16 (0.15-0.17)	305	0.24 (0.22-0.26)	290	0.32 (0.30-0.34)	273
3	0.18 (0.17-0.19)	251	0.33 (0.31-0.35)	251	0.44 (0.42-0.46)	251	0.56 (0.53-0.59)	243	0.65 (0.62-0.68)	234
4	0.42 (0.39-0.45)	180	0.53 (0.50-0.56)	180	0.57 (0.54-0.60)	180	0.64 (0.61-0.67)	174	0.70 (0.67-0.73)	169
5	0.75 (0.72-0.78)	103	0.77 (0.74-0.80)	103	0.82 (0.79-0.85)	103	0.85 (0.82-0.88)	103	0.90 (0.88-0.92)	96
Total N		1403		1403		1403		1319		1235

Table IV – Age- and sex-adjusted probabilities of death, post-stroke dementia, or institutionalization in Years 1 through 5, estimated from logistic regressions in 3-month survivors of ischaemic stroke, grouped by 3-month mRS. All probabilities (Pr) are presented with two significant figures and alongside the number of individuals contributing to that estimate.

	Year 1		Year 2		Year 3		Year 4		Year 5	
3-month mRS	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**	**Pr (95%CI)**	**N**
0	0.058 (0.051-0.065)	137	0.080 (0.070-0.090)	137	0.11 (0.096-0.12)	137	0.14 (0.12-0.16)	127	0.19 (0.16-0.22)	112
1	0.061 (0.057-0.065)	427	0.11 (0.10-0.12)	427	0.16 (0.15-0.17)	427	0.22 (0.20-0.24)	386	0.27 (0.25-0.29)	360
2	0.098 (0.091-0.11)	305	0.16 (0.15-0.17)	305	0.25 (0.23-0.27)	305	0.32 (0.30-0.34)	292	0.41 (0.38-0.44)	275
3	0.33 (0.31-0.35)	251	0.49 (0.47-0.51)	251	0.57 (0.55-0.59)	251	0.64 (0.62-0.66)	248	0.73 (0.71-0.75)	244
4	0.53 (0.50-0.56)	180	0.63 (0.60-0.66)	180	0.66 (0.63-0.69)	180	0.72 (0.69-0.75)	176	0.77 (0.74-0.80)	172
5	0.81 (0.79-0.83)	103	0.83 (0.80-0.86)	103	0.86 (0.84-0.88)	103	0.89 (0.87-0.91)	103	0.94 (0.93-0.95)	99
Total N		1403		1403		1403		1332		1262

Table V – Comparison of probability weights for 5-year death, dementia, or post-stroke institutionalization, derived from logistic regressions in 3-month survivors of ischaemic stroke and grouped by 3-month mRS, in: all patients, excluding premorbid mRS>2, excluding premorbid mRS>1, age<75, age>75, men, and women. All probabilities (Pr) are presented with two significant figures and alongside the number of individuals contributing to that estimate. Regressions in the first three groups were adjusted for age and sex. Below the probabilities for the 5 subgroups, the difference compared to the estimated probability for the overall cohort is presented (ΔPr = Pr for group – Pr for all patients). ΔPr's >0.10 or <-0.10, representing a >10% absolute difference in probability, are flagged with *.

3-month mRS	All Patients		Excluding Pre-morbid mRS>2		Excluding Pre-morbid mRS>1		Age <75 years		Age >75 years		Men		Women	
	Pr	N	Pr (ΔPr)	N	Pr (ΔPr)	N	Pr (ΔPr)	N	Pr (ΔPr)	N	Pr (ΔPr)	N	Pr (ΔPr)	N
0	0.19	112	0.19 (0.00)	112	0.19 (0.00)	108	0.13 (-0.06)	82	0.33 (0.14*)	30	0.19 (0.00)	70	0.19 (0.00)	42
1	0.27	360	0.27 (0.00)	358	0.25 (-0.02)	326	0.12 (-0.15*)	221	0.52 (0.25*)	139	0.22 (-0.05)	210	0.34 (0.07)	150
2	0.41	275	0.40 (-0.01)	265	0.36 (-0.05)	213	0.21 (-0.20*)	128	0.59 (0.18*)	147	0.37 (-0.04)	152	0.46 (0.05)	123
3	0.73	244	0.70 (-0.03)	152	0.65 (-0.08)	101	0.46 (-0.27*)	71	0.84 (0.11*)	173	0.74 (0.01)	122	0.72 (-0.01)	122
4	0.77	172	0.67 (-0.10)	89	0.59 (-0.18*)	64	0.49 (-0.28*)	49	0.89 (0.12*)	123	0.75 (-0.02)	71	0.79 (0.02)	101
5	0.94	99	0.93 (-0.01)	59	0.92 (-0.02)	50	0.88 (-0.06)	26	0.96 (0.02)	72	0.89 (-0.05)	37	0.97 (0.03)	62
Total N		1262		1035		862		577		684		662		600

Table VI – Comparison of 5-year quality-adjusted life expectancies (QALE weights) for 3-month survivors of ischaemic stroke, grouped by 3-month mRS, in: all patients, excluding premorbid mRS>2, excluding premorbid mRS>1, age<75, age>75, men, and women. All QALEs are presented with two decimal places and alongside the number of individuals contributing to that estimate. Below the QALEs for the 5 subgroups, the difference compared to the estimated QALE for the overall cohort is presented (ΔQALE = QALE for group – QALE for all patients). ΔQALEs >0.50 or <-0.50, representing 10% of the maximal 5-year QALE of 5.00, are flagged with *.

3-month mRS	All Patients		Excluding Pre-morbid mRS>2		Excluding Pre-morbid mRS>1		Age <75 years		Age >75 years		Men		Women	
	QALE	N	QALE (ΔQALE)	N	QALE (ΔQALE)	N	QALE (ΔQALE)	N	QALE (ΔQALE)	N	QALE (ΔQALE)	N	QALE (ΔQALE)	N
0	3.88	132	3.88 (0.00)	132	3.88 (0.00)	128	3.94 (0.06)	96	3.68 (-0.20)	36	3.88 (0.00)	87	3.88 (0.00)	45
1	3.49	379	3.51 (0.02)	378	3.57 (0.08)	349	3.75 (0.26)	239	3.05 (-0.44)	140	3.66 (0.17)	217	3.26 (-0.23)	162
2	3.01	276	3.03 (0.02)	265	3.20 (0.19)	217	3.50 (0.49)	137	2.74 (-0.27)	139	3.15 (0.14)	158	2.82 (-0.19)	118
3	1.87	219	2.05 (0.18)	139	2.22 (0.35)	94	2.17 (0.30)	69	1.73 (-0.14)	150	1.90 (0.03)	111	1.84 (-0.03)	108
4	1.30	112	1.71 (0.41)	73	1.91 (0.61*)	56	2.06 (0.76*)	39	0.93 (-0.37)	73	1.43 (0.13)	43	1.23 (-0.07)	69
5	0.06	49	0.02 (-0.04)	34	0.02 (-0.04)	27	-0.22 (-0.28)	14	0.23 (0.17)	35	-0.04 (-0.10)	16	0.14 (0.08)	33
Total N		1167		1021		871		594		573		632		535

SUPPLEMENTARY FIGURES

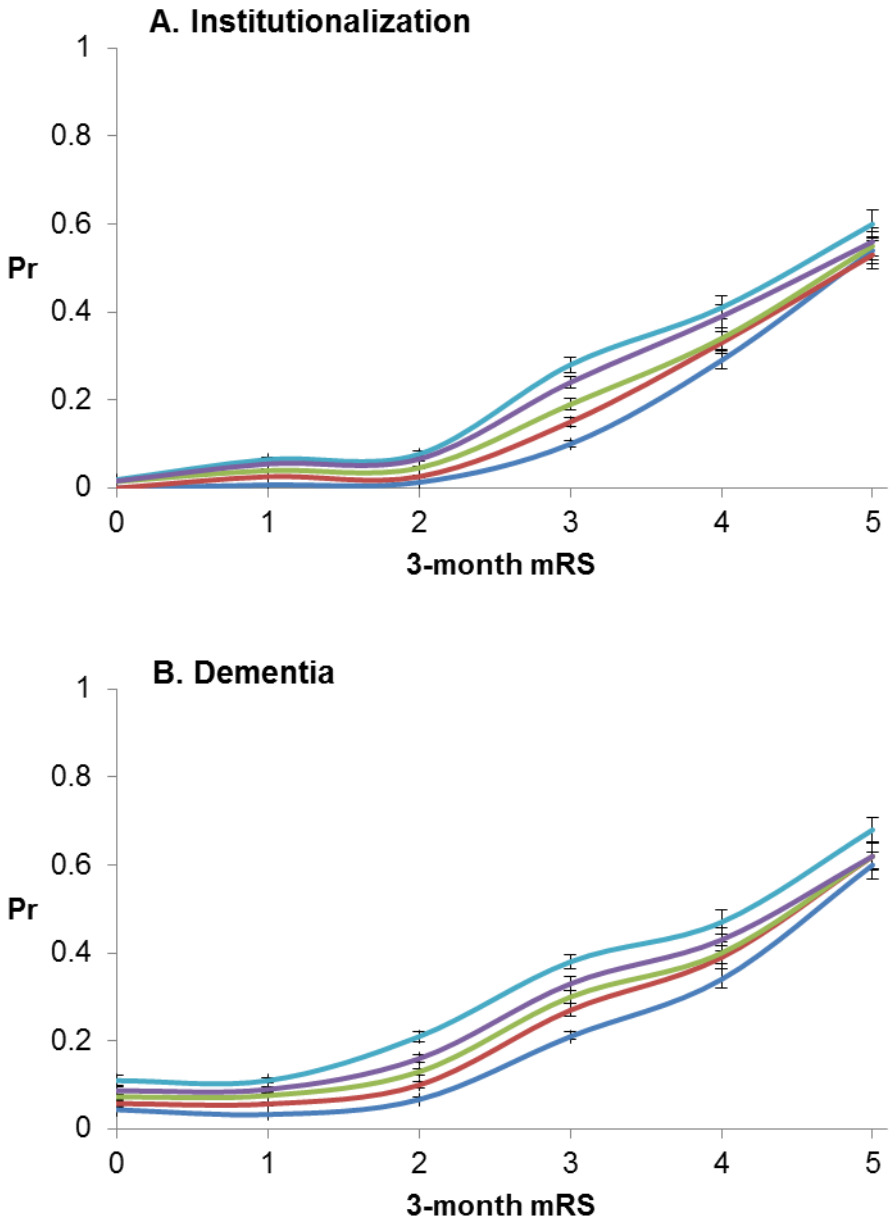


Figure I. Age- and sex-adjusted probabilities estimated from logistic regressions for 1-year (dark blue), 2-year (red), 3-year (green), 4-year (purple), and 5-year (light blue) outcomes of (A) post-stroke institutionalization and (B) post-stroke dementia for 3-month survivors of ischaemic stroke (n=1,425), stratified by 3-month mRS. Bars represent 95% confidence intervals.

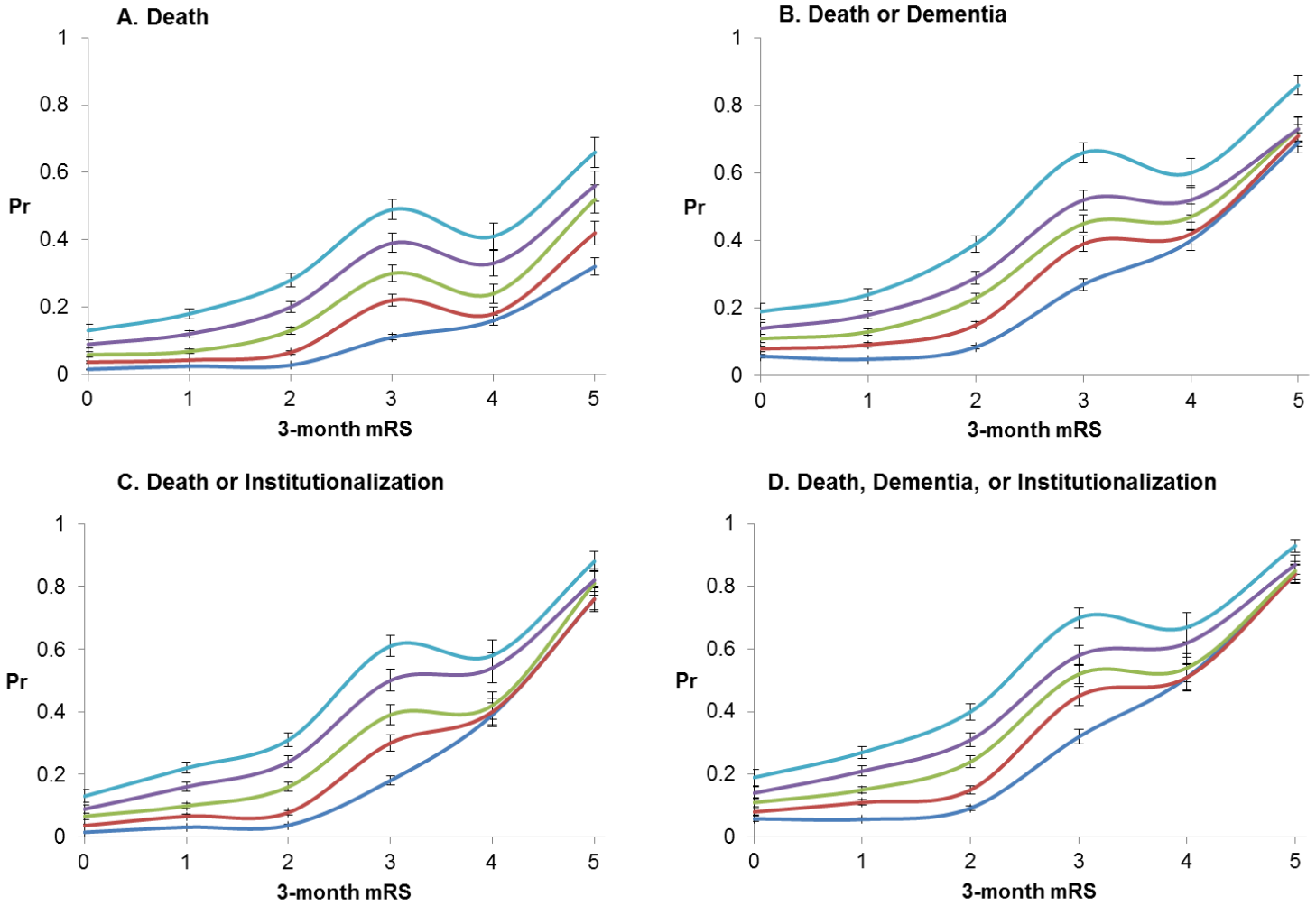


Figure II. Age- and sex-adjusted probabilities estimated from logistic regressions for 1-year (dark blue), 2-year (red), 3-year (green), 4-year (purple), and 5-year (light blue) outcomes of (A) death, (B) death or post-stroke dementia, (C) death or post-stroke institutionalization, and (D) death, dementia, or institutionalization for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, excluding patients with pre-morbid mRS>2 (n=1,171).

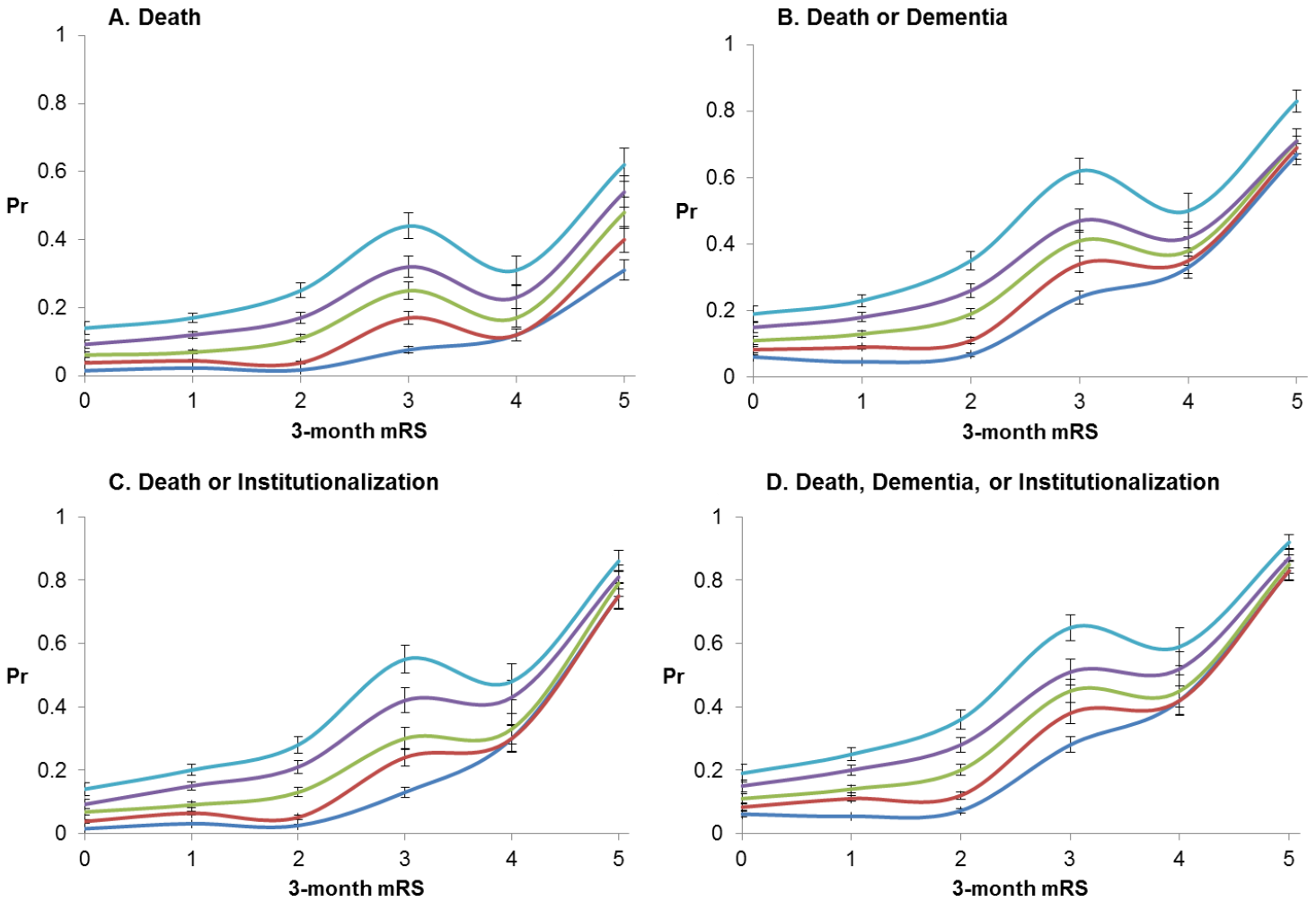


Figure III. Age- and sex-adjusted probabilities estimated from logistic regressions for 1-year (dark blue), 2-year (red), 3-year (green), 4-year (purple), and 5-year (light blue) outcomes of (A) death, (B) death or post-stroke dementia, (C) death or post-stroke institutionalization, and (D) death, dementia, or institutionalization for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, excluding patients with pre-morbid mRS>1 (n=984).

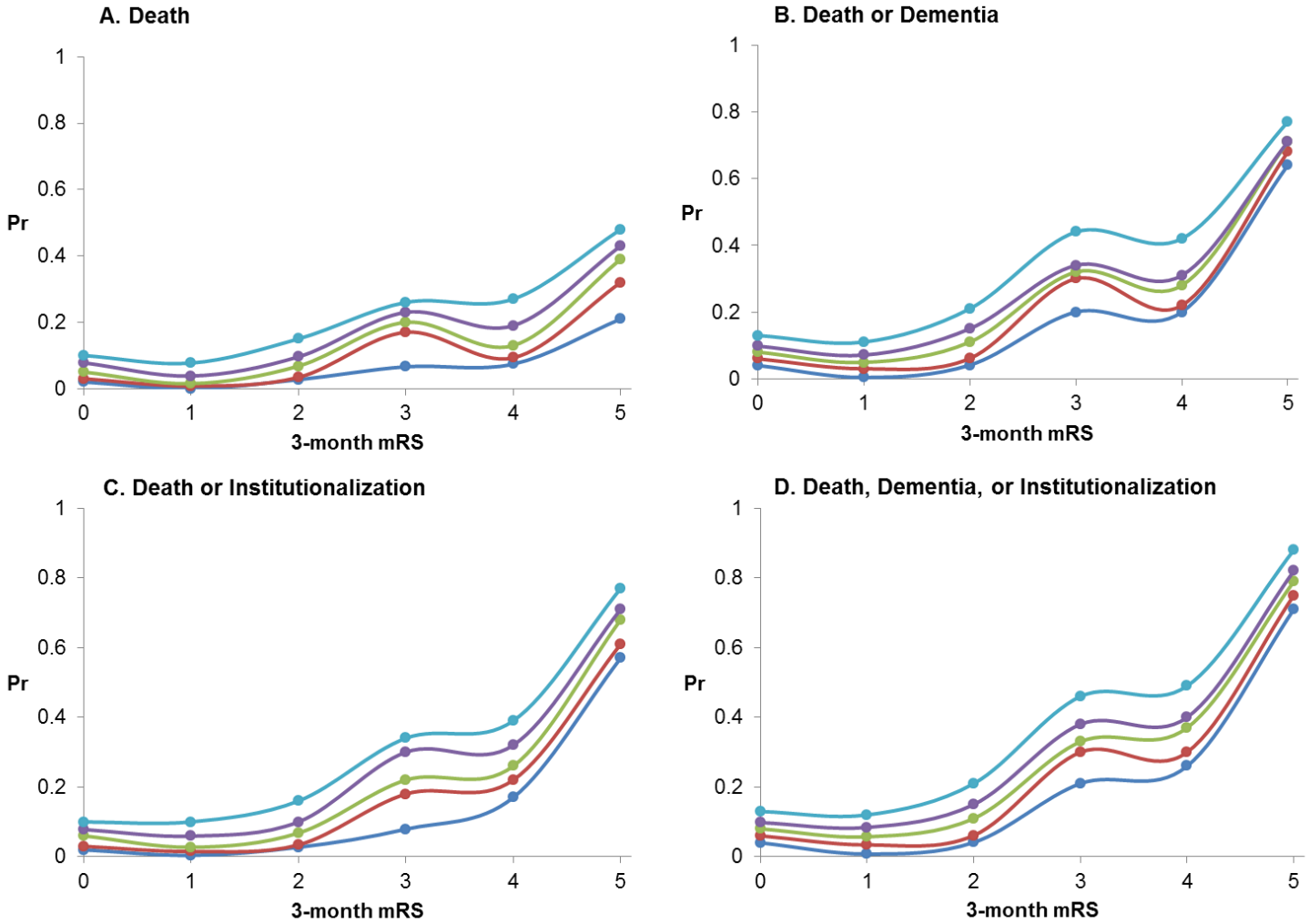


Figure IV. Unadjusted probabilities estimated from logistic regressions for 1-year (dark blue), 2-year (red), 3-year (green), 4-year (purple), and 5-year (light blue) outcomes of (A) death, (B) death or post-stroke dementia, (C) death or post-stroke institutionalization, and (D) death, dementia, or institutionalization for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, restricted to those aged <75 years (n=669).

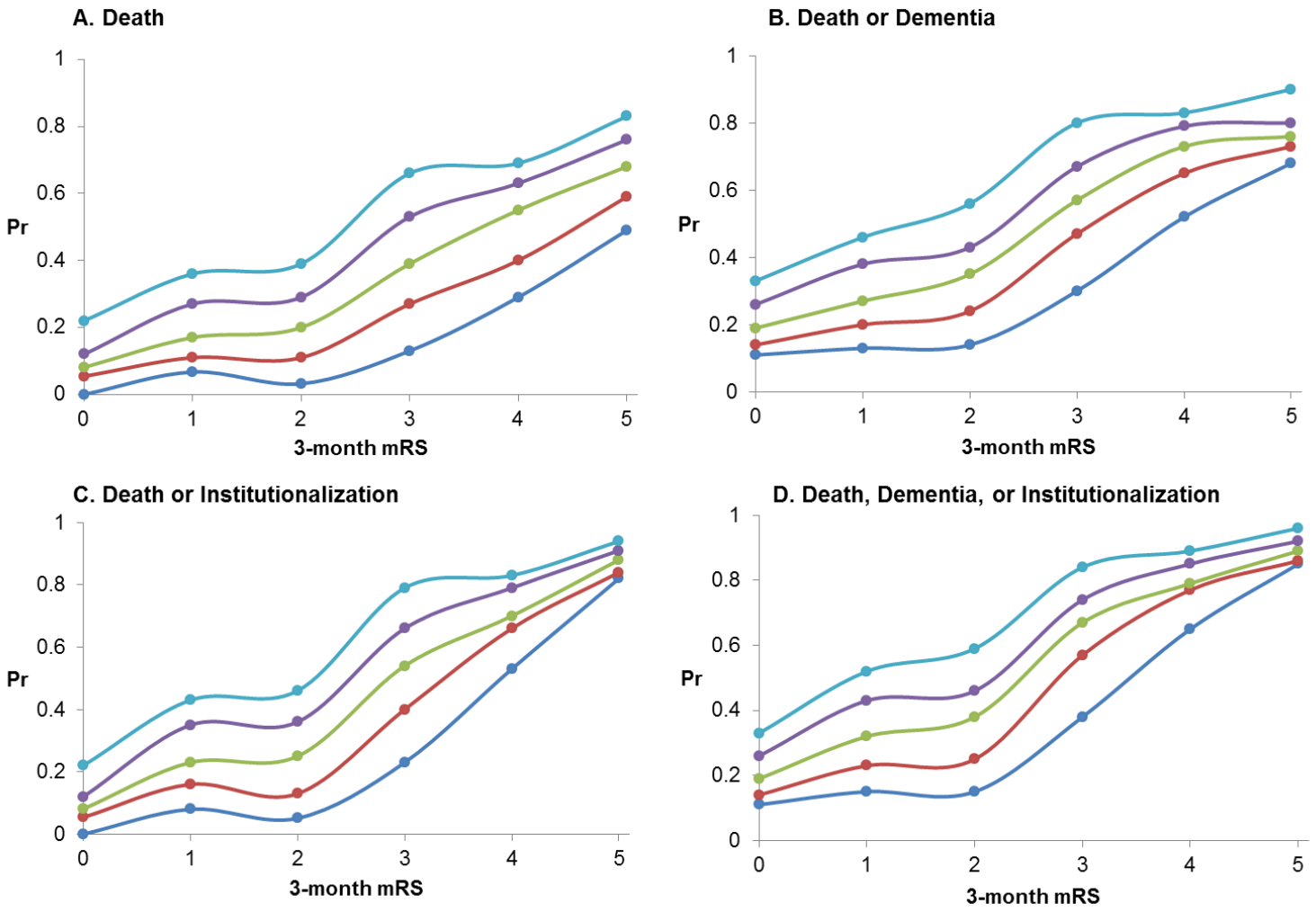


Figure V. Unadjusted probabilities estimated from logistic regressions for 1-year (dark blue), 2-year (red), 3-year (green), 4-year (purple), and 5-year (light blue) outcomes of (A) death, (B) death or post-stroke dementia, (C) death or post-stroke institutionalization, and (D) death, dementia, or institutionalization for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, restricted to those aged >75 years (n=733).

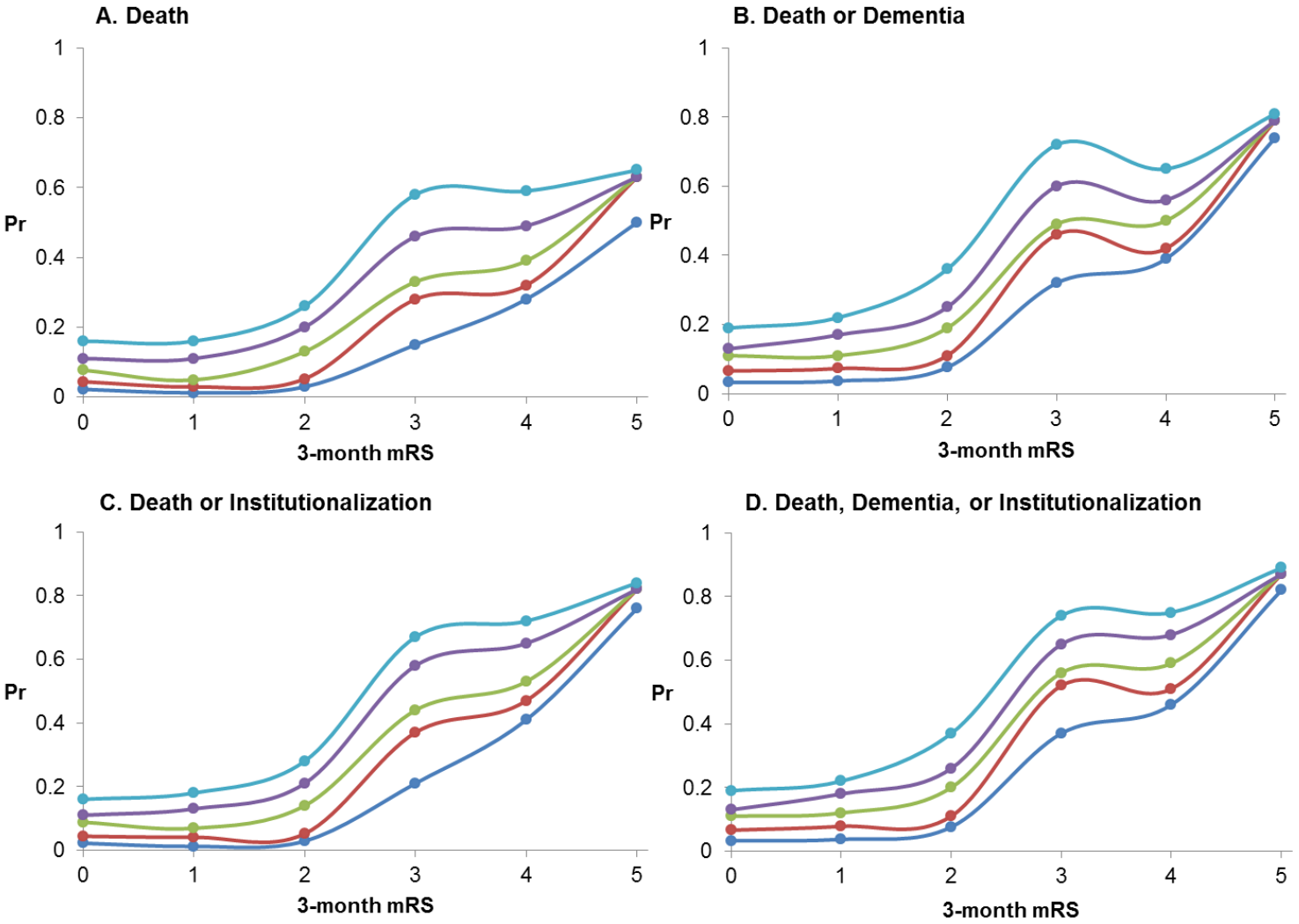


Figure VI. Unadjusted probabilities estimated from logistic regressions for 1-year (dark blue), 2-year (red), 3-year (green), 4-year (purple), and 5-year (light blue) outcomes of (A) death, (B) death or post-stroke dementia, (C) death or post-stroke institutionalization, and (D) death, dementia, or institutionalization for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, restricted to male sex (n=748).

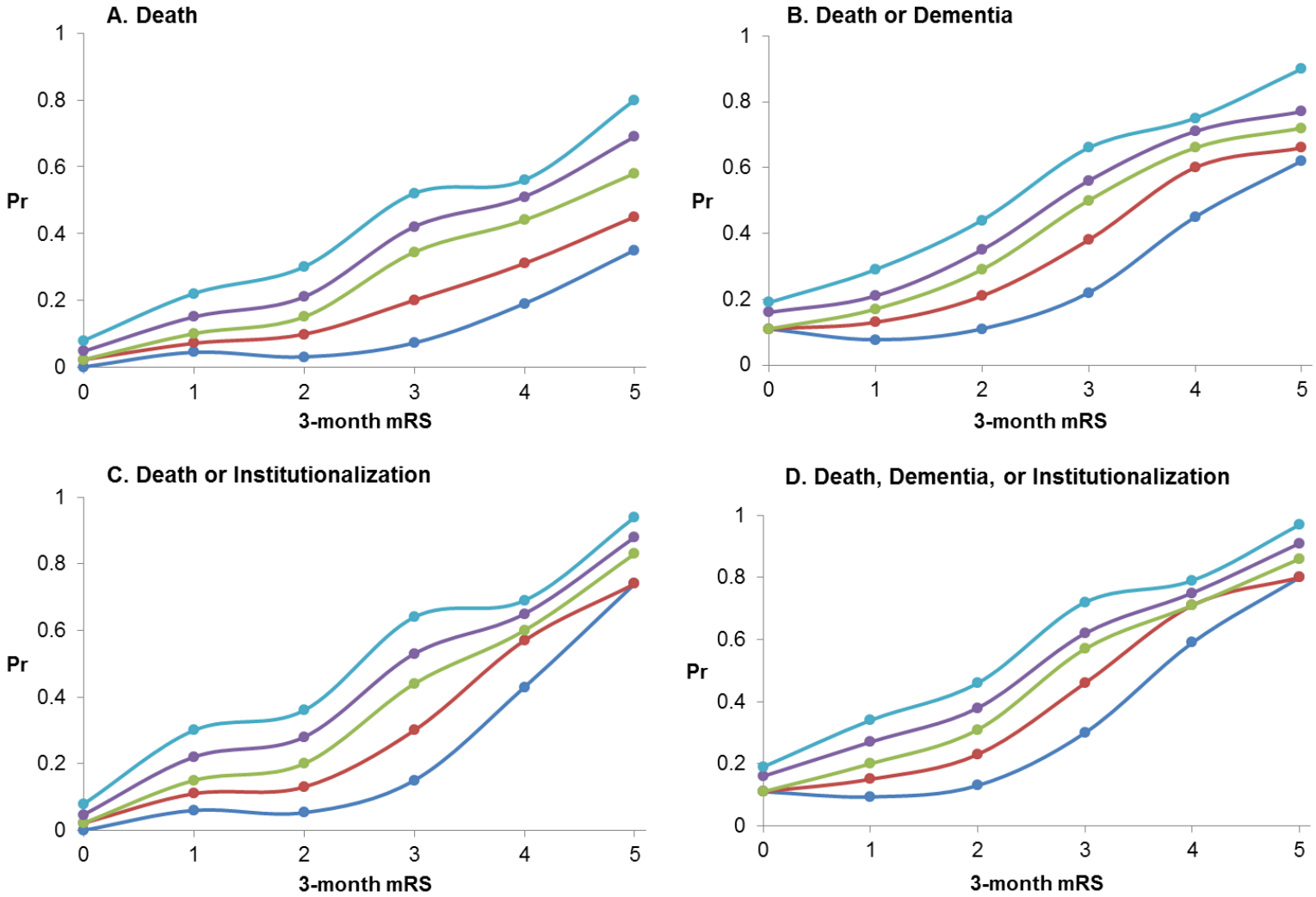
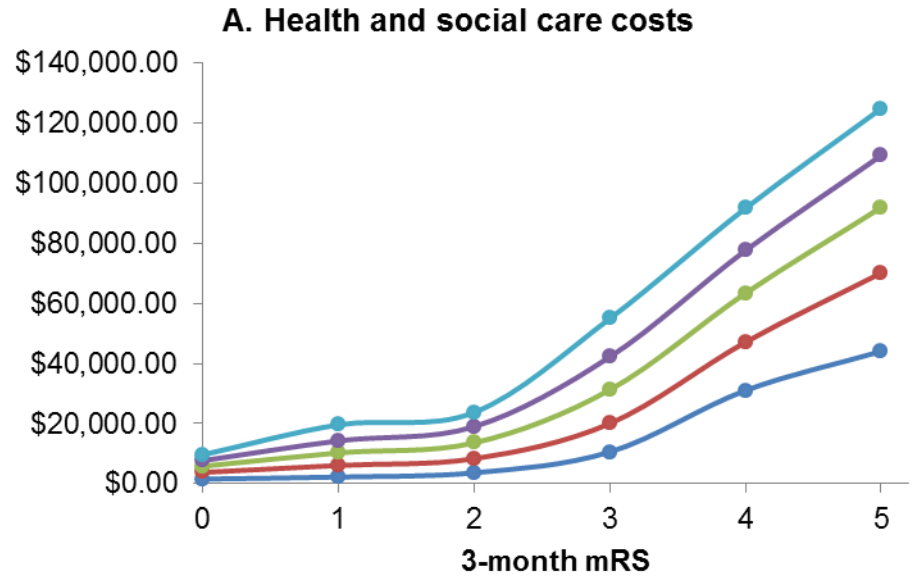


Figure VII. Unadjusted probabilities estimated from logistic regressions for 1-year (dark blue), 2-year (red), 3-year (green), 4-year (purple), and 5-year (light blue) outcomes of (A) death, (B) death or post-stroke dementia, (C) death or post-stroke institutionalization, and (D) death, dementia, or institutionalization for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, restricted to female sex (n=655).



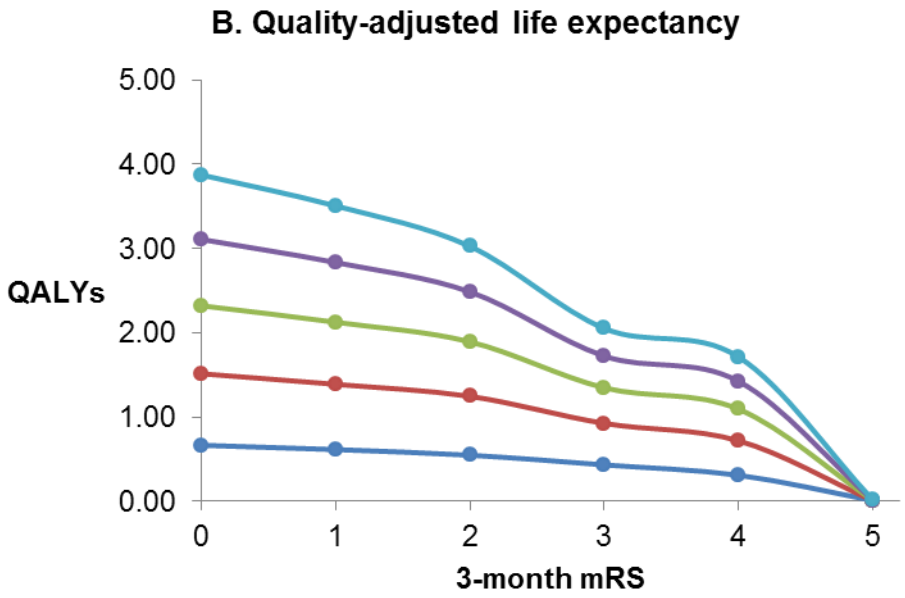


Figure VIII. Estimated (A) 5-year health and social care costs and (B) quality-adjusted life expectancy (in quality-adjusted life-years, QALYs) for 1-year (dark blue), 2-years (red), 3-years (green), 4-years (purple), and 5-years (light blue) post-stroke for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, excluding those with pre-morbid mRS>2 (n=1,171).

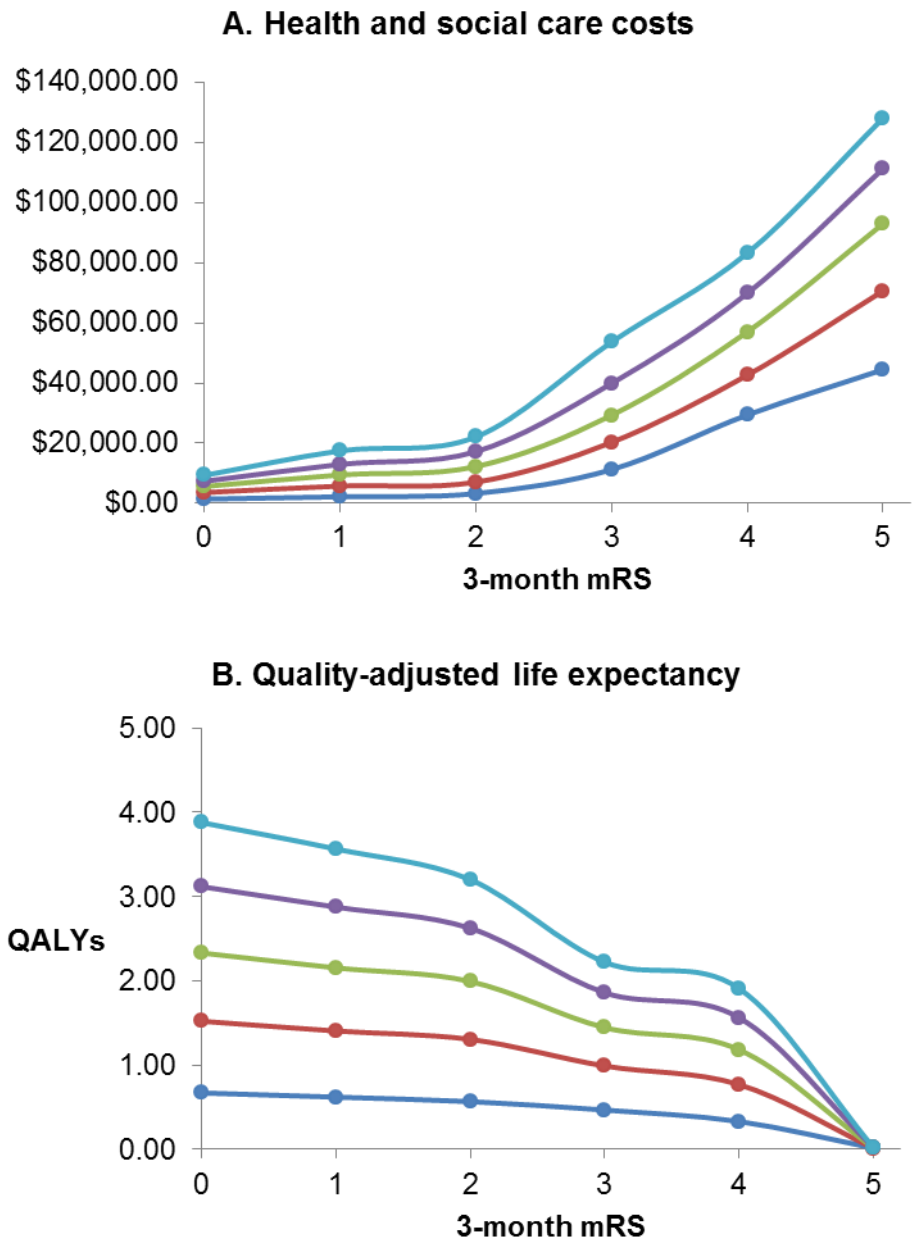


Figure IX. Estimated (A) 5-year health and social care costs and (B) quality-adjusted life expectancy (in quality-adjusted life-years, QALYs) for 1-year (dark blue), 2-years (red), 3-years (green), 4-years (purple), and 5-years (light blue) post-stroke for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, excluding those with pre-morbid mRS>1 (n=984).

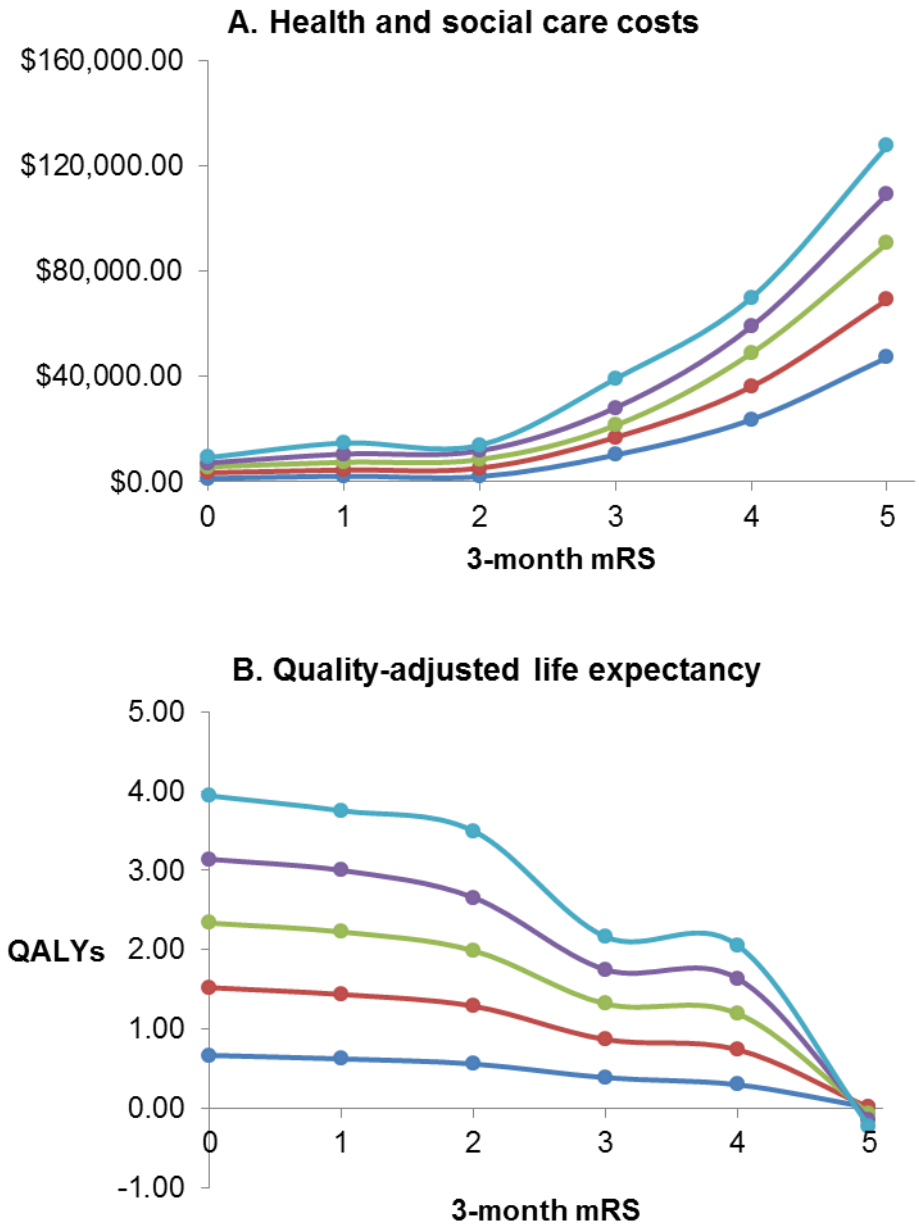


Figure X. Estimated (A) 5-year health and social care costs and (B) quality-adjusted life expectancy (in quality-adjusted life-years, QALYs) for 1-year (dark blue), 2-years (red), 3-years (green), 4-years (purple), and 5-years (light blue) post-stroke for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, restricted to those aged <75 years (n=669).

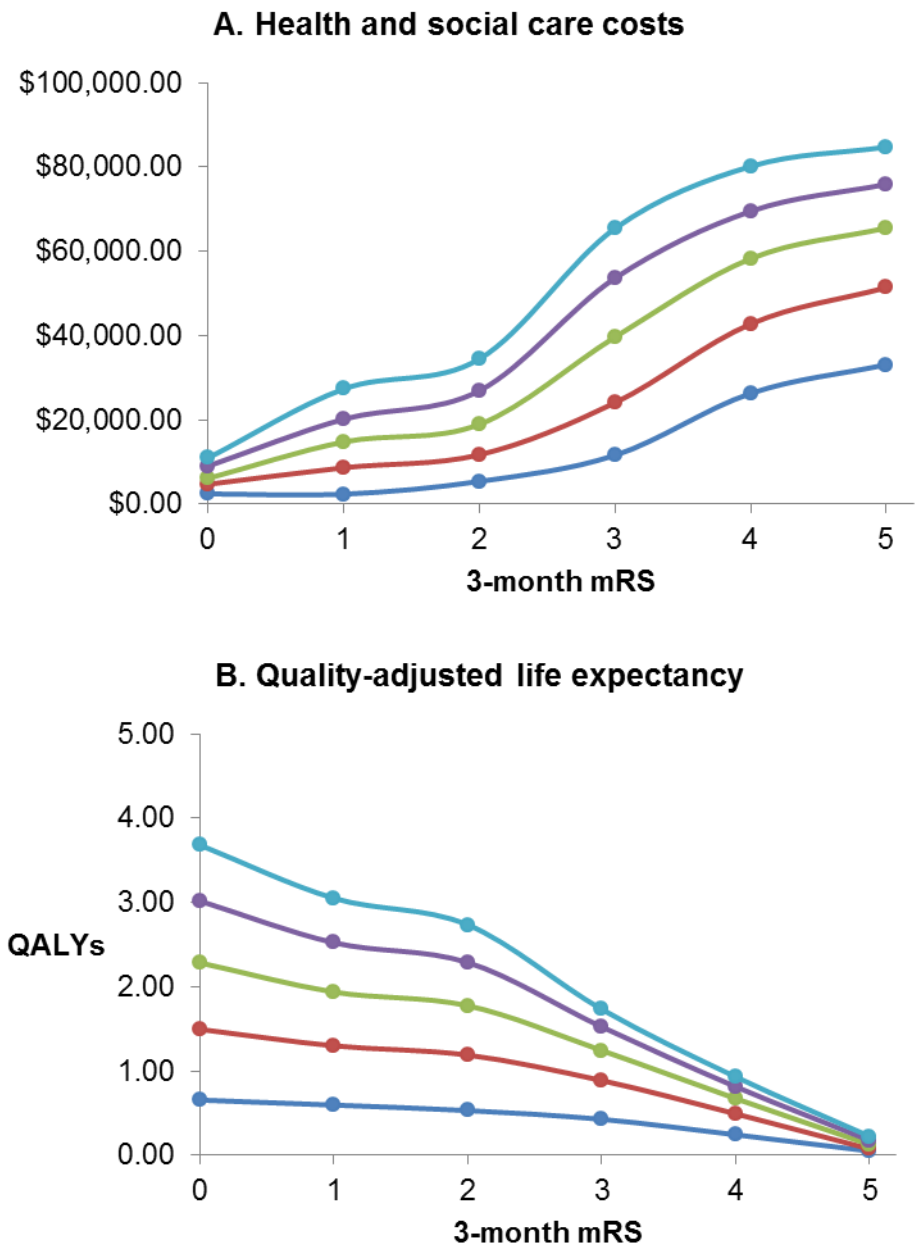


Figure XI. Estimated (A) 5-year health and social care costs and (B) quality-adjusted life expectancy (in quality-adjusted life-years, QALYs) for 1-year (dark blue), 2-years (red), 3-years (green), 4-years (purple), and 5-years (light blue) post-stroke for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, restricted to those aged >75 years (n=733).

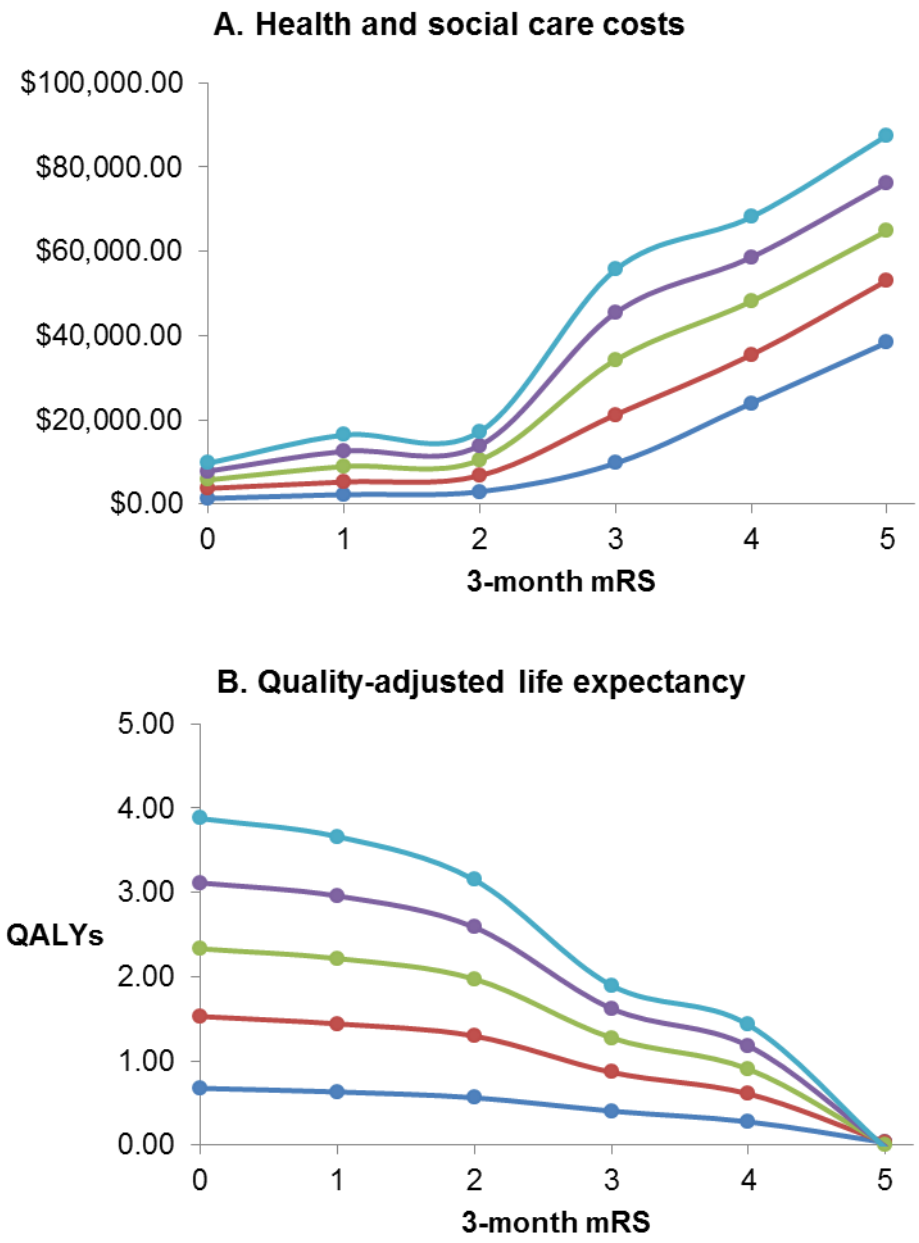


Figure XII. Estimated (A) 5-year health and social care costs and (B) quality-adjusted life expectancy (in quality-adjusted life-years, QALYs) for 1-year (dark blue), 2-years (red), 3-years (green), 4-years (purple), and 5-years (light blue) post-stroke for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, restricted to male sex (n=748).

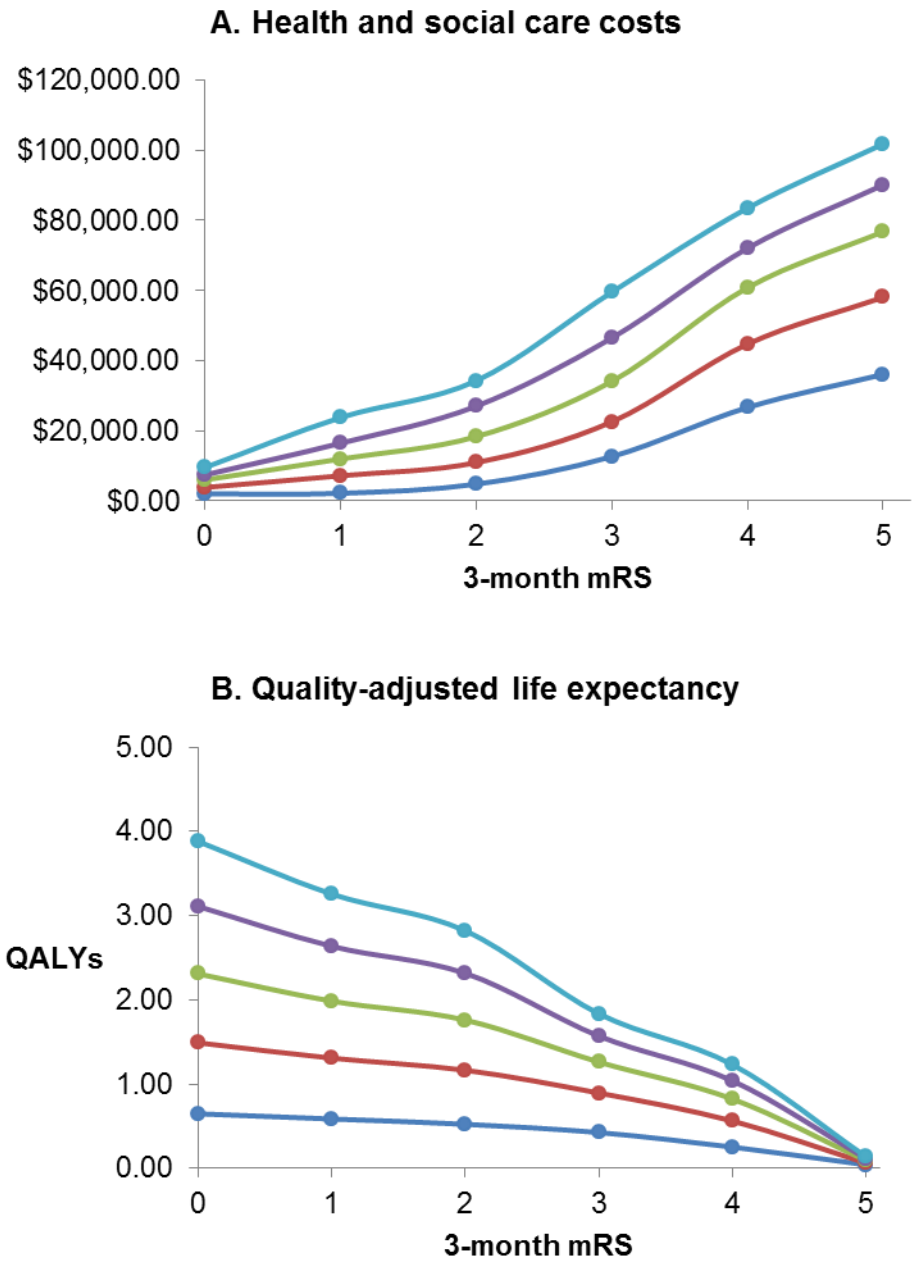


Figure XIII. Estimated (A) 5-year health and social care costs and (B) quality-adjusted life expectancy (in quality-adjusted life-years, QALYs) for 1-year (dark blue), 2-years (red), 3-years (green), 4-years (purple), and 5-years (light blue) post-stroke for 3-month survivors of ischaemic stroke, stratified by 3-month mRS, restricted to female sex (n=655).

CHAPTER 7

Conclusions

7.1 CHAPTER ABSTRACT

In this concluding chapter, I review the key findings presented in the core thesis chapters and discuss potential future work that could be undertaken in these areas, particularly in the context of limitations of my current work. I present some illustrative examples of preliminary work that I have undertaken based on these findings, that involve applying the probability-, cost-, and QALE-based mRS “weights” discussed in the previous chapter to the analysis of published data from ischaemic stroke trials.

I also discuss the potential implications of my thesis findings, particularly regarding ordinal versus dichotomous analysis and the potential use of weighted ordinal analysis, to medical conditions other than stroke, given that ordinal scales like the mRS are used as outcome measures across the breadth of medicine.

Finally, I discuss some enduring uncertainties about outcome measurement in stroke and how it may evolve in the coming years, which may affect the relevance of this thesis.

7.2 KEY THESIS FINDINGS AND FUTURE WORK

This thesis has examined 5-year clinical and health-economic outcomes of ischaemic stroke, and their relationship to short-term post-stroke disability, as captured by the 3-month mRS, using data from the OXVASC study. Below, I will discuss the key findings of each chapter as well as potential future work that could build on them.

Time-course of evolution of disability and cause-specific mortality after ischaemic stroke (Chapter 2)

In the relative absence of reliable up-to-date data on how short-term outcome after ischaemic stroke relates to longer-term disability and/or mortality outcomes – including late recovery, delayed stroke-related deaths, recurrent strokes, and non-stroke deaths – I found that functional outcome at 3-months (assessed using the mRS) strongly predicted 5-year disability and mortality, both in the overall cohort of 3-month survivors and in clinically relevant subgroups of treatable major strokes, atrial fibrillation-related strokes, and lacunar strokes. I demonstrated that more than a quarter of the deaths beyond 3-months were potentially related to residual disability from the index stroke, and that patients were unlikely to show meaningful recovery beyond 1-year. These results reaffirm the use of the 3-month mRS as a primary outcome measure in stroke trials. Although I found that late functional recovery does occur in about 1 in 4 patients beyond 3-months post-stroke, extending clinical trial follow-up to 1-year would likely capture most long-term stroke-related disability. However, my results also indicate that longer-term administrative mortality follow-up has the potential to demonstrate translation of early disability gains into additional reductions in long-term mortality without much erosion by non-stroke-related deaths.

Overall, these findings imply that treatments that reduce acute stroke severity (e.g. thrombolysis and thrombectomy) or that prevent disabling strokes (e.g. anticoagulation for atrial fibrillation) are likely to promote sustained independence and long-term survival. However, future work should seek to conclusively demonstrate this in the setting of randomized clinical trials; this could be accomplished fairly economically using administrative mortality follow-up beyond 1-year in countries like the United Kingdom or Canada that have well-documented central administrative data on deaths through the Department of Public Health or the Canadian Institute of Health Information.[1] Recently, the 3-year mortality follow-up results of IST-3 were published, showing that thrombolysis reduced mortality between 3- and 12-months post-stroke, and that this difference was maintained at 3-years.[2] Similar data could be expected in the near future from thrombectomy trials.

The time-course of late functional recovery beyond 3-months also merits further study. One question that I plan to investigate in the near future is how this late recovery differs by age and stroke severity. The Copenhagen Stroke Study previously demonstrated that the time to maximal recovery in stroke patients depends on index stroke severity and functional disability (on the BI) but high-quality, mRS-specific data is lacking.[3] It would be especially informative for clinical prognostication and rehabilitation planning to examine what proportion of patients in different age groups and categories of stroke severity (per the NIHSS) attain their best mRS at 3-months, 6-months, 1-year, and/or 5-years respectively.

Pre-morbid functional status and apparent sex differences in stroke severity and outcome (Chapter 3)

In Chapter 2, I found that each step up the mRS disability ladder at 3-months is associated with a corresponding jump in 1-year and 5-year death/dependency outcomes, suggesting that comparing the change in mRS in different groups (e.g. men versus women) from pre-stroke to post-stroke may be more clinically-meaningful than the post-stroke mRS in isolation, particularly if the pre-morbid mRS distribution differs in these groups. This led me to examine sex differences in post-stroke outcomes in OXVASC in Chapter 3, comparing not just the post-stroke mRS distribution (at 1-month, 6-months, 1-year, 5-years) but also the change in mRS versus pre-stroke mRS. I found that women were in fact at no higher risk of faring worse post-stroke versus pre-stroke, and that apparent sex differences were explained by differences in age and pre-morbid mRS. Similar results were observed at 1-year and 5-years, and on limiting analyses to those aged ≥65 years. Women also had a lower mortality rate and there was no sex difference in the risk of recurrent stroke. These findings suggest that failure to account for sex differences in pre-morbid handicap likely contributed to the contradictory findings in previous studies.

The finding that women have higher pre-stroke mRS scores than men may reflect differences in comorbidities, but I found that the pre-stroke mRS was higher in women even after adjusting for age and several comorbidities at baseline. Whilst other unmeasured comorbidity-related confounders like frailty may have contributed to this difference, it is may also have been influenced by differences in how men and women rate (or admit) their own symptoms or disability. Inter-observer reliability of the pre-stroke mRS has been found to be limited but comparable with the standard mRS,[4] but one wonders whether variability in both pre- and post-stroke mRS may be influenced by the sex of the rater in relation to the patient. For example, men might be more inclined to rate their functioning more favourably if being interviewed by women. Further studies examining inter-observer variability in pre-stroke and post-stroke mRS assessments by women versus men in patients of either sex would help test this hypothesis.

As presented later in Chapter 6, I also found that males tended to accumulate lower health and social care costs over 5-years of follow-up particularly in lower disability categories (3-month mRS 0-2). Part of this may be due to age differences (men with stroke generally being younger than women) but this may also reflect sex differences in seeking health or social care services. Future work planned with this cohort includes examining age- and pre-morbid disability-adjusted differences in the use of such resources among men and women with different levels of post-stroke disability, stratified not only by mRS but also by other measures of impairment and disability like the RMI and BI. Such data could inform both costing studies as well as education campaigns about the availability and utilization of medical, rehabilitative, and/or social services.

Although the core finding that women do not have worse post-stroke outcomes upon accounting for age and pre-morbid status takes the focus off sex, it may not be entirely appropriate to redirect the focus of apparent differences to age either. As noted previously, whether increased age directly contributes to poorer recovery outcomes remains a controversial topic.[5-9] It is conceivable that apparent differences in post-stroke recovery may be more related to confounding factors like functional and cognitive status at admission and social situation rather than age-related biological differences.[10] Therefore, future studies could seek to further disentangle the relative contributions of age and these other potential factors. Furthermore, this thesis has only examined one of the various demographics-related uncertainties regarding post-stroke recovery and outcome trajectories. Owing to OXVASC being a predominantly White (>95%) cohort, I was unable to examine racial disparities in outcome which are another source of uncertainty. Black patients are reported to have greater stroke severity,[11] higher stroke mortality,[12] and poorer recovery than Whites,[13] but whether such differences actually relate to ethnicity or to confounding factors like access to healthcare services remains to be clearly elucidated. Similar considerations apply for reported socio-economic differences in stroke outcome, which may be confounded by differences in pre-morbid functional status, but could also be related to barriers to accessing health and social care services.[14] I hope to examine apparent socio-economic differences in outcome in subsequent work using a similar approach.

Late functional recovery after lacunar stroke (Chapter 4)

On examining changes in functional status between 3-months and 5-years post-stroke in lacunar versus non-lacunar strokes – using 3 different measures (mRS, RMI, and BI) – I found that lacunar stroke patients were much more likely to demonstrate further functional recovery between 3-months and 1-year post-stroke, even after adjusting for age, sex, and 3-month disability, and upon performing various sensitivity analyses (excluding recurrent events, those with relevant comorbidities, etc). These findings

demonstrate that lacunar strokes have greater potential for late functional recovery from 3-12 months post-stroke, and support the focus of studies of restorative therapies like rTMS and tDCS on this group. However, my findings emphasize that such studies cannot assume that improvements after 3-months are treatment-related, and should therefore be randomized and controlled. Owing to this difference in recovery trajectories, studies of restorative therapies in the general stroke population undertaken between 3-12 months post-stroke should also seek to balance the proportion of patients with lacunar strokes in their treatment and control arms.

In the present work, I did not use any radiological measures of recovery to compare the underlying processes of neuroplasticity in lacunar and non-lacunar strokes over follow-up. Such clinically-correlated neuroradiological data could be particularly helpful in better characterizing time-dependent mechanisms of recovery in lacunar strokes and could help identify potential therapeutic targets. For example, diffusion tensor imaging metrics have emerged as important biomarkers of disease progression and recovery in the setting of small vessel disease and lacunar or subcortical strokes.[15, 16]

Whereas I did not observe a significant difference in post-stroke depression between lacunar and non-lacunar strokes in the OXVASC cohort, I did not have data regarding other psychological symptoms such as anxiety which might also influence rehabilitation and stroke recovery. This is worth exploring in further studies, since a recent analysis of VISTA data reported that lacunar strokes were least associated with both anxiety and depression symptoms compared to other stroke subtypes.[17]

Setting aside the distinction between lacunar and non-lacunar strokes, it is increasingly evident that the burden of various markers of small vessel disease – like white matter hyperintensities, microbleeds, potentially clinically-silent lacunar infarcts, and enlarged perivascular spaces – carries consequences for the risk of recurrent cerebrovascular events as well as cognitive decline.[18, 19] Examining how this burden of small vessel disease (perhaps as captured by the Small Vessel Disease Score)[19] translates into differences in post-stroke functional recovery as well as the capacity for late recovery, could potentially inform clinical prognostication and indicate additional targets for restorative therapies.

Ordinal versus dichotomous analyses of the modified Rankin Scale in the prediction of 5-year outcomes and costs after ischaemic stroke (Chapter 5)

Given the debate about ordinal versus dichotomous analysis of the mRS in stroke trials, I assessed the predictive value of ordinal versus dichotomous representations of the mRS for 5-year post-stroke outcomes (disability, death, costs), and found that ordinal analysis of the

3-month mRS better predicted 5-year disability, mortality, and health and social care costs than the standard dichotomies (0-1/2-6, 0-2/3-6). I also calculated how many patients risk being excluded from trials using dichotomous outcomes due to their higher pre-morbid mRS, and found that exclusion rates were high, particularly for older ages, women, and lower socio-economic strata. The risk of exclusion was especially high with using a 0-1/2-6 dichotomy, as 30% of the cohort (61% aged >85 years) had a pre-morbid mRS>1. These findings indicate that ordinal analysis of the mRS best predicts long-term outcomes after stroke and avoids automatic exclusion of key patient groups.

As in Chapter 3, the findings of Chapter 5 again highlight the important role that pre-morbid disability plays in influencing the perception of stroke outcomes: whereas in Chapter 3 I saw that it contributed to the observation of apparent sex-differences, in Chapter 5 I found that it can lead to different rates of exclusion for different patient groups when dichotomous approaches are used. As discussed previously, these differences in pre-morbid mRS may not just be due to differences in co-morbidities; prior work has highlighted the issue of mRS grading being affected by factors like socio-economic status.[20] But regardless of why these differences in pre-morbid mRS exist, the resultant exclusion of relevant patient segments from clinical trials can extend into practice and influence access to treatment. For example, elderly patients were long considered ineligible for intravenous thrombolysis owing to trial-based contraindications in drug labels (e.g. upper age limit in ECASS trials was 80 years), despite compelling evidence even a decade ago that these patients can attain better outcomes with timely and judicious thrombolysis.[21, 22] That being said, clinical decisions in stroke care are fortunately not informed by randomized controlled trials alone. Registry-based studies like SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) have played a key role in illuminating aspects unstudied in trials, such as outcome predictors to better identify patients suitable for thrombolysis. For example, SITS-MOST data previously indicated that patients with pre-morbid disability (mRS 2-5) had higher 3-month mortality, though this does not mean that they cannot benefit from thrombolysis.[23]

However, if stroke trials start enrolling patients with pre-morbid disability, the comparison of post-stroke mRS outcomes between treatment and control groups could become challenging. With standard ordinal approaches, comparing the “shift” in post-stroke mRS distributions between treatment and control arms is straightforward if all the patients start out at a pre-stroke mRS of 0, but would be misleading if the distribution of pre-morbid disability differs considerably between the treatment and control arms. Pre-morbid mRS could presumably become yet another factor to balance in the randomization process. On the other hand, change in mRS from pre-stroke to post-stroke (“delta mRS") may be a more informative outcome measure in stroke trials that enrol pre-morbidly disabled patients, particularly since there is a rise (albeit a non-linear one) in long-term adverse outcomes with

each step up the mRS ladder. In this regard, future work could compare the predictive value of such a “delta mRS" to the ordinal 3-month mRS for long-term post-stroke outcomes.

In addition, my finding that the ordinal form of the mRS better captures differences in long-term costs than either dichotomy with far less information loss, is in line with the recent recommendations of the ESO Health Economics Working Group, which proposed that health economic information in stroke trials should present costs using the mRS as a complete ordinal scale to preserve relevant information.[24] In the OXVASC cohort, social care costs (primarily institutionalization) contributed to an increasing proportion of 5-year costs with each step up the mRS ladder. However, I underestimated the cost of stroke as I did not examine indirect costs such as home care costs or lost productivity for the patient and family members involved in their care. These indirect costs merit further study to provide a more comprehensive, mRS-stratified valuation of the cost of stroke.

Developing cohort-derived weights to inform ordinal analysis of the modified Rankin Scale in stroke trials (Chapter 6)

Building on the work in Chapter 5, which showed unequal differences between different 3-month mRS grades with respect to death/disability and cost outcomes at 5-years, I examined the relationship between 3-month mRS and 1-year, 2-year, 3-year, 4-year, and 5-year outcomes of death, post-stroke dementia, and/or institutionalization, health/social care costs, and QALE. In both the overall cohort, and in sensitivity analyses stratifying the cohort by age and sex or excluding pre-morbidly disabled patients, I demonstrated that a non-linear (somewhat S-shaped) relationship developed between the 3-month mRS and each of these outcomes over the course of follow-up, with the greatest difference in outcomes generally seen going from mRS 2 to 3, with an additional jump from mRS 4 to 5, and smaller changes across the rest of the scale. These findings indicate that analysing the mRS in stroke trials requires a more nuanced approach than simply choosing between conventional ordinal or dichotomous analyses, and that the ideal approach should reflect the importance of any shifts across the scale (like conventional ordinal analysis) whilst also acknowledging that certain shifts are more clinically meaningful than others (like dichotomous analyses). Weighting the mRS for use in ordinal analysis is an approach that can meet these requirements, and so I derived probability weights for 5-year death, post-stroke dementia, and/or institutionalization outcomes for the 3-month mRS, as well as weights for 5-year cost and QALE outcomes. Despite inherent limitations for generalizability to different trial populations, these clinically meaningful weights could facilitate the adoption of ordinal mRS analysis as the primary outcome measure in stroke trials, and could also be used by clinicians for prognostication and by health economists for cost-effectiveness analyses of stroke therapies.

Overall, a weighted approach to analysing the mRS appears to be promising. Recently, the DAWN (Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo) trial used the utility-weighted mRS as its primary outcome measure, suggesting that such a weighted approach may catch on in the stroke community.[25] Adoption of a weighted scale for clinical use by clinicians and researchers will be facilitated by robust evidence of external validity, i.e., evidence that comparable weights are generated in cohorts independent of the OXVASC population that I used to derive the proposed weights. I have also begun preliminary work applying these mRS weights to the analysis of published trials. For example, I am testing a prognosis-weighted mRS (using estimated probability of 5-year death, dementia, or institutionalization, analysed using the t-test), QALE-weighted mRS, and cost-weighted mRS against the dichotomized mRS (0-2/3-6 and 0-1/2-6, analysed using Fisher extact test) and standard ordinal mRS analyses (Mann Whitney U test) in 42 high-impact trials or meta-analyses of acute stroke treatments. Preliminary results indicate that these weighted mRS analyses provide similar results to standard ordinal analysis and outperform dichotomous mRS analyses, which can miss relevant shifts and can give "false positives" in the setting of bidirectional effects (Figure I, Appendix). Also, as mentioned previously, the mean difference between treatment/control groups provided through this t-test approach can provide a meaningful "effect size" reflecting the predicted long-term difference made by the treatment (Figure II, Appendix). For instance, using the published meta-analysis data on the 3-month mRS distribution for endovascular therapy trials,[26] an average patient in the treatment arm would be predicted to have an 11% lower risk (95%CI 8-14%) of death, institutionalization, or dementia, whilst incurring $13,603 less in health/social-care costs (95%CI $10,196-17,011), and gaining 0.56 additional QALYs (95%CI 0.42-0.71) over 5-years versus a patient in the control arm.

The acute stroke community's recognition of the importance of evaluating the outcome of post-stroke dementia and/or cognitive impairment was reflected in the recent publication of a pre-specified secondary analysis of the REVASCAT (Endovascular Revascularization with Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours) trial, which found that thrombectomy improved trail-making test performance at 1-year post-stroke, especially among patients who attained functional independence (3-month mRS 0-2).[27] Whilst I examined post-stroke dementia as one of the potential adverse outcomes after stroke in relationship to the age/sex-adjusted 3-month mRS in this chapter, future work could investigate how the mRS compares against other known modifiers or predictors of dementia risk, such as blood pressure control,[28]subcortical white matter lesions,[29] enlarged perivascular spaces,[30] or medial temporal lobe atrophy.[31] The METACOHORTS initiative for the study of vascular disease and its contribution to cognitive decline and

neurodegeneration, which includes cohorts from North America, Europe, Australasia, and the Asia Pacific Region, will help advance our understanding of how vascular disease affects brain structure and function, as well as optimize methods for predicting post-stroke dementia outcomes and/or assessing the potential impact of stroke therapies on this outcome.[32] The potential that a new therapy or intervention may directly modify the risk of long-term dementia (or institutionalization or mortality etc.) over and above a reduction in stroke-related disability is an important limitation for my proposed mRS weights, since the weights would then under-estimate treatment benefit. Some potential examples of such treatments include exercise therapy, which appears promising to improve post-stroke cognitive function (but may not necessarily change post-stroke mRS),[33] or intensive blood pressure and lipid control which is being studied in PODCAST (Prevention of Decline in Cognition After Stroke Trial).[34] Dementia is also only one of the many potential long-term neuropsychiatric complications of stroke, and further studies could seek to elucidate the relationship between 3-month mRS and those outcomes. One example is post-stroke clinical depression and anxiety disorders, which can be challenging to study systematically (especially in the acute stage) but which can be disabling.[35]

7.3 RELEVANCE OF FINDINGS TO OTHER MEDICAL CONDITIONS

Although the focus of this thesis has been on ischaemic stroke, my findings, particularly those in Chapters 5 and 6 regarding the analysis of the mRS, carry some broader implications for the analysis of trials in other medical conditions. Ordinal or ordered scales like the mRS are commonly used in medicine, and are a favoured method of assessing functional status and outcome for clinical trials in various specialities. Examples include the Glasgow Outcome Scale (GOS),[36] the New York Heart Association functional class,[37] the Oxford Hip and Knee Scores,[38] and the Functional Independence Measure.[39] The mRS itself has been adopted for use as an outcome measure in over 40 conditions including various neurological, cardiovascular, infectious, and musculoskeletal disorders, in over 4,000 studies (>250 in high-impact journals) since the year 2000 alone (Table I, Appendix). The practice of collapsing ordinal measures into a binary scale for dichotomous analysis is not unique to stroke, and researchers in other fields have also observed that such analyses can result in a loss of information.[40] Although a median split of an ordinal scale is often equated to discarding one-third of the data,[41] the true extent of information loss (particularly with respect to reflecting prognosis) may be very different with different scales or conditions.

It is important to emphasize that just because the ordinal form of the mRS better predicts long-term outcomes in the setting of stroke, one cannot assume that ordinal analysis will be the superior choice for other conditions using the mRS or other ordinal measures. Distinctions among mRS grades may differ in other diseases that use this scale for outcome

analysis, and thus the weights I derived would also directly apply only to the analysis of ischaemic stroke trials. However, my findings regarding ordinal versus dichotomous analyses of the mRS and the derivation of mRS weights for ordinal analysis highlight the methodological value of using long-term prognosis to inform the choice of outcome analysis. In addition to informing trial analyses, such an approach would also examine the predictive validity of these ordinal measures for their respective conditions, a key consideration in choice of measure that often remains unexamined.[42]

For example, the 5-point GOS, typically measured 6-months post-injury, is used as the primary outcome measure in most critical-care trials of traumatic brain injury (TBI), and like the mRS in stroke trials, it has generally been dichotomized as unfavourable (Dead, Vegetative, or Severe Disability) versus favourable outcome (Moderate Disability or Good Recovery) for analysis. As in the stroke literature, TBI researchers have recognized that ordinal analysis of the GOS can substantially increase statistical power.[43] Building on my work with the mRS, one could also compare the predictive value of ordinal versus dichotomous forms of the 6-month GOS in predicting long-term disability, death, care costs, QALE, and/or similar outcomes of interest after TBI, ideally in the setting of a high-quality prospective cohort study. Such GOS-stratified long-term clinical and health-economic data would help demonstrate whether there is a meaningful difference in outcome with each step up the GOS ladder (favouring ordinal analysis), and also inform the derivation of weights if different state transitions are of unequal value. It would also help quantify the extent of information loss with dichotomization. Hypothetically speaking, if the long-term outcome data were to show an obvious jump in adverse outcomes between two particular levels of the GOS (e.g. between Moderate and Severe Disability) and less meaningful differences for the rest of the scale, and the information loss in predicting long-term outcomes is minimal for the dichotomized versus ordinal GOS, then the evidence may actually support the use of simple dichotomous analysis rather than any weighted or conventional ordinal approaches.

Prospective cohort studies of other medical conditions could seek to similarly evaluate the predictive validity of their commonly-used ordinal scales with respect to long-term outcomes, and/or derive prognosis-based weights for these scales as indicated for ordinal analysis.

7.4 ENDURING UNCERTAINTIES IN OUTCOME MEASUREMENT

The research presented in this thesis was undertaken in the present-day context of the 3-month mRS being the favoured outcome measure of acute ischaemic stroke trials. However, as discussed throughout this thesis, the mRS has a number of limitations, and is certainly not favoured by all researchers in the stroke community; for instance, some rehabilitation researchers disapprove of the mRS mixing the technically distinct outcomes of

impairment, disability, and handicap in a single scale.[44] It is entirely plausible that in the coming decades, the stroke community may favour other outcome measures. It is uncertain whether we will continue to favour using simple scales like the mRS in large trials to demonstrate treatment effects, or whether this approach will be superseded by a preference to perform smaller trials using more complicated measures with potentially greater granularity and sensitivity to treatment effects.

The acceptable time-frame for measuring the efficacy of stroke therapies is another important factor that will influence the evolution of outcome measurement in stroke trials. This thesis has generally focused on 1-year to 5-year outcomes after ischaemic stroke, making the assumption that stroke treatments that promote improvements in such long-term outcomes are more favourable than those that just exert short-term effects. If improving these long-term outcomes should be the ultimate goal of stroke therapies, then one may argue that stroke trials should directly measure these outcomes (e.g. 1-year disability/mortality, or 5-year quality-adjusted life expectancy) as their primary outcome measures rather than using shorter-term "surrogate" measures like the 3-month mRS. But of course, there is an upper limit to the time-frame within which any treatment can demonstrate a favourable long-term effect; for instance, it is quite unlikely that any stroke treatment will be able to improve 20-year death/dementia/institutionalization outcomes since nearly all the patients will have met at least one of those endpoints within that time-frame. In this regard, there is a push in the acute stroke community towards even earlier outcome measurement to avoid treatment effects being confounded by early mortality or medical instability at later time points. However, there is also going to be a lower limit to the acceptable time-frame for outcome measurement; for example, assessment at 24 hours may miss crucial later evolution of ischaemic damage such as brain swelling, secondary ischaemia, or haemorrhagic transformation.[45] That being said, outcome measures capturing the early trajectory of stroke severity and neurological recovery like the 24-hour NIHSS, change in NIHSS at 48-hours, or 7-day mRS have been shown to strongly correlate with the 3-month mRS, and may potentially replace it as the primary outcome measure in future trials.[46]

For now, 60 years after Dr. Rankin first proposed his eponymous scale, the mRS appears to have withstood the test of time. Even as outcome measures for stroke trials and treatment options for ischaemic stroke continue to evolve over the coming years, long-term clinical and health economic outcomes like disability, mortality, post-stroke dementia, institutionalization, and care costs are likely to remain relevant in informing our clinical and policy decisions, as well as how we assess the effectiveness of potential therapies.

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7.6 APPENDIX – SUPPLEMENTARY TABLES AND FIGURES FOR CHAPTER 7

Table I. Medical conditions for which the modified Rankin Scale (or related Rankin Scale or Oxford Handicap Scale) has been used as an outcome measure, and their publication in leading journals since 2000.*

Medical condition	Estimated publications	JAMA group (214)	Lancet group (174)	NEJM (87 articles)
Cerebrovascular disorders Stroke, aneurysms, arteriovenous malformations, cavernomas	3,770	X	X	X
Cardiovascular disorders				
Atrial Fibrillation	1,030		X	X
Cardiac arrest	202	X	X	X
Coronary artery bypass (or related surgery)	212		X	X
Heart failure or valvular heart disease (including procedures for aortic stenosis, mitral regurgitation)	201	X		X
Musculoskeletal disorders				
Low back pain	171			
Osteoarthritis, Rheumatoid arthritis	118			
Myopathies: Dermatomyositis, Polymyositis, Mitochondrial, spinal/bulbar muscular atrophy, muscular dystrophy, anti-SRP, hyper-CK-emia, anti-synthetase syndrome	105	X		
Infectious diseases				
Infective endocarditis	108			
HIV/AIDS	99			
Non-stroke CNS disorders				
Traumatic and other acute brain injury	443	X		
Multiple Sclerosis, ADEM, Neuromyelitis Optica	336			
Ataxias (FXTAS, autoimmune, etc)	316			
Parkinson's Disease	307	X	X	
Alzheimer's Disease	294			
Epilepsy, PNES, or Conversion Disorder	269	X		
Subdural hematoma	242		X	
Cerebral venous sinus thrombosis	144			
Infectious meningitis, encephalitis, or encephalomyelitis	128	X	X	X
Coma or herniation	113			
Autoimmune encephalitis: anti-NMDA, anti-GAD, anti-LG1, etc	112	X	X	
Myelopathies: tethered cord, AVFs, epidural hematoma, ossified ligamentum flavum	65			
Gliomas	54			
Huntington's Disease	37			
Normal Pressure Hydrocephalus	35			
Migraine, tension headaches	35			
Dysexecutive syndromes	17			
Progressive Multifocal Leukoencephalopathy	15			
Prion Disease	15		X	
Neurofibromatosis	13			
Adrenoleukodystrophy	4			
Cingulotomy outcomes	1			
Peripheral Nervous System (or Mixed)				
Polyneuropathies: GBS, CIDP, CIAP, CMT, immune-mediated, paraproteinemic, cryoglobulinemic, vasculitis, Sjogren's, paraneoplastic, multifocal motor neuropathy, alcohol/thiamine-deficiency	236		X	X

Amyotrophic Lateral Sclerosis	189			
Myasthenia Gravis	45			
Neuralgic amyotrophy (brachial neuritis)	5			
Other general medical or systemic conditions				
Asthma, COPD	126			
Small-cell lung cancer	79			
Lupus erythematosus	69			
Churg-Strauss syndrome	17			
Ehlers-Danlos syndrome	16			
Lyme Disease	14			
POEMS syndrome	9			

*Each medical condition using/influenced by the mRS was identified by reviewing the titles/abstracts of the first 100 pages of Google Scholar citation results for the two top-cited publications on the Rankin Scale (van Swieten et al 1988, Rankin 1957). Then, the number of publications for each identified disease was estimated using the “search within citing articles” function in Google Scholar for these two publications. There is likely to be some overlap among the publications listed in different categories (e.g. owing to papers that include patients with both rheumatoid arthritis and low back pain).

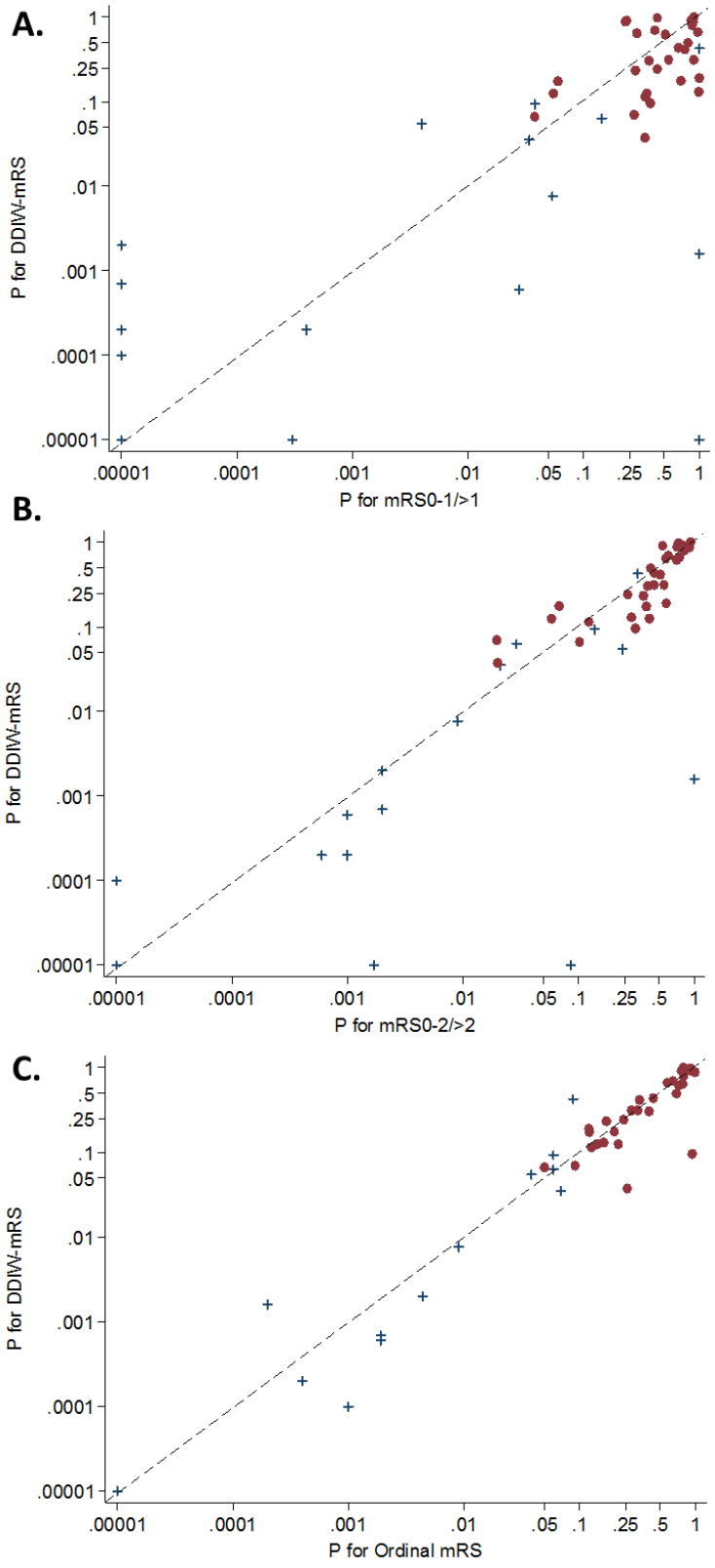


Figure I. Preliminary results comparing P-values obtained from t-tests using probability weights for 5-year death, dementia, or institutionalization for the 3-month mRS (DDIW-mRS), with those obtained from (A) binary analysis of the mRS dichotomized as 0-1 versus 2-6, (B) dichotomized as 0-2 versus 3-6, and (C) standard ordinal analysis (Mann Whitney U test). Results are shown for high impact stroke trials (n=42) published in the New England Journal of Medicine or Lancet journals. Crosses represent trials for therapies like thrombolysis and thrombectomy that are proven to be effective in stroke, whereas dots represent trials for therapies like neuroprotection that are currently thought to be ineffective.

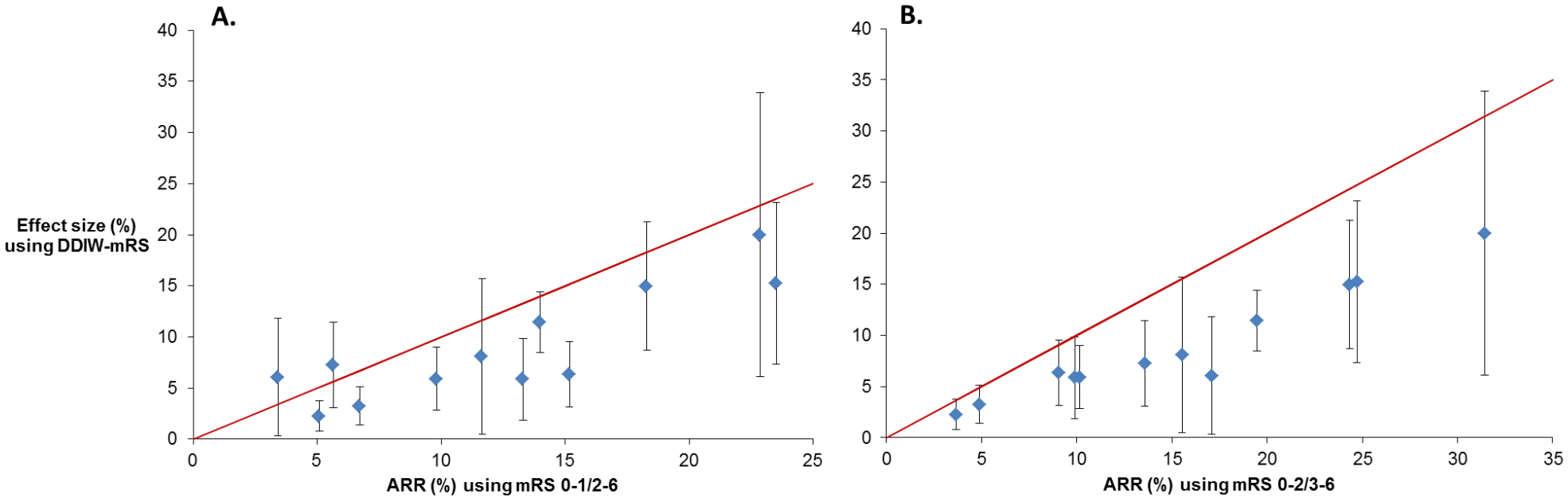


Figure II. Preliminary results comparing the effect sizes (means and 95% confidence intervals) obtained from t-tests using probability weights for 5-year death, dementia, or institutionalization for the 3-month mRS (DDIW-mRS), with the absolute risk reduction (ARR) of "unfavourable outcome" defined as (A) mRS>1 (per 0-1/2-6 dichotomy) and (B) mRS>2 (per 0-2/3-6 dichotomy). Results are shown for high impact trials of established therapies for acute ischaemic stroke (thrombolysis, thrombectomy) published in the New England Journal of Medicine or Lancet journals. The red line is the line of unity (y=x). The effect size for the DDIW-mRS represents the predicted lowering of the probability of 5-year death/institutionalization/dementia in the treatment arm versus the control arm.

OXVASC STUDY FORMS

OXFORD VASCULAR STUDY 1April2016

TIA & STROKE

OREC A:05/Q1604/70

Year 12

Was patient interviewed		Y	N
If NO why not?	Please tick		
1	Refused interview		
2	Aphasic		
3	Too unwell/ multiple medical problems		
4	Dementia (need to record AMTS)		
5	Late ascertainment		
6	Ascertainment after death		
7	Diagnosis uncertain		
9	Unknown		
10	Doesn't speak English		
11	Other: specify		
Was relative interviewed		Y	N

SUBJECT ID NO:

Patient identification label
(check address is current)

Patient contact details	
Telephone	(day)
Telephone (evening)	
Mobile	
Fax number	
Email address 1	
Email address 2	

Next of kin details	
Relationship to patient	
First name	
Surname	
Address 1st line	
Address 2nd line	
City/town	
County	
Postcode	
Country	
Telephone	(day)
Telephone (evening)	
Mobile phone no	
Fax number	
Email address	

Stroke Unit Inpatients who consent to study: Has this patient been referred for Community Stroke Review?	**Y**	**N**
Does patient consent to us sending copies of follow-up letters to Community Stroke Reviewers? (CSR Fax: 01865 713987)	**Y**	**N**

11 digit OXCODE for notification event										

Consultant	

1 Physician
2 Physician with stroke interest
3 Neurologist
4 General surgeon
5 Vascular surgeon
6 Cardiologist
7 Neurosurgeon
9 Other

Name Examiner

GP DETAILS					
Surname					
Location		01 Beaumont Street 03 East Oxford 04 Berinsfield	05 Malthouse 06 Kidlington (Exeter) 07 Wantage	08 Marcham Road 09 Stert Street 10 Kidlington (KYMG) 99 Other (please provide)	Other:
First name or Initials					

Summary Diagnosis		Specify:
S= Stroke T= TIA A= Amaurosis fugax	R= Retinal artery Occlusion M= MI	B= Burden Z= Other (specify)

Is this the first ever in a lifetime (incident) stroke? *	**Y**	**N**	**U**
Is this the first ever in a lifetime (incident) TIA? *	**Y**	**N**	**U**

* Please tick as appropriate

Date of notification event (DD-MM-YY)	

Location of interview	1 JRH inpatient 3 Community hosp	4 Outpatients 5 Home 6 Other (specify) 7 Not interviewed		Specify:
Follow-up plan at 1 month	1 OXVASC TIA clinic 3 Refused follow-up	4 Other (specify) 6 No follow-up 7 Home visits		Specify:
Source of 1st notification	1 GP 2 JRH admission 3 Other Hospital (specify) 4 Other referrals (specify)	5 Health authority search 6 Death 7 Troponin 9 Other (specify)		Specify:

HISTORY OF NOTIFICATION EVENT	Please tick if:	All fields unknown on page 3+4

Narrative history & examination

Did patient have PRANS events?	Y	N	U	Date most recent	OXCODE for PRANS event:
				U	

Details:

Notification event*		What did you think was wrong?
Date DD-MM-YY	**Time** 24 hr clock	
U	: U	

* The event that led to first seeking medical attention

Did notification event occur during hospital stay (while admitted for other reason)?	**Y**	**N**	**U**
Were you alone?	**Y**	**N**	**U**
If you were with someone who was it?	U		
Who called for help?	U		
If you did not call for help at time of event, why not?	U		

Who did you 1st call for help?	1= Medical 2=Non-Medical 9= Unknown		**Date** DD-MM-YY	**Time** 24 hr clock
			Please give date/time for any 1st call *	
1st call for ANY help non-medical or medical				: U
			Please give date/time for 1st medical call	
1st call for MEDICAL help GP/ A&E / 999/ NHS direct				: U

* This could be the same date and time as the first call for medical help (please provide anyway)

Calls for medical attention		**Date** DD-MM-YY	**Time** 24 hr clock
GP by telephone	**Y / N**		:
GP in person	**Y / N**		:
Telephoned 999	**Y / N**		:
Went to A&E in person	**Y / N**		:
Telephoned NHS direct	**Y / N**		:
Went to Oxford Eye Hospital			:
Other (Specify)	**Y / N**		:

Outcome of first call for medical assistance

				Date DD-MM-YY	Time 24 hr clock
If GP referred subject to OXVASC clinic: **Notification by GP to OXVASC**					: U
If subject was not referred to OXVASC: **Admitted to hospital?** (If admitted from A&E, give time seen in A&E as time of admission)	**Y**	**N**	**U**		: U
If admitted to hospital but not referred to OXVASC: **Ascertainment** by OXVASC staff					: U
Assessment by OXVASC staff					: U

HISTORY OF NOTIFICATION EVENT

Duration of symptoms (TIA only)				Hrs:	Mins:
Onset on wakening from sleep?				**Y**	**N**	**U**
Location of event	1 Home 2 Work 3 Leisure (non-sport)	4 Sport 5 Hospital 8 Other (specify) 9 Unknown			Specify:

Was there a further event between notification event and assessment?	Y	N	U

If yes to above please indicate number of events between any of the following:	
	No. events
Between notification event and seeing GP/ other medical opinion (including notification event)	# U
Between seeing GP and notification by GP to OXVASC	# U
Between notification by GP and OXVASC assessment	# U

Were there any events in the month preceding the notification event?	Y	N	U
How many events were there in the month before notification event?	# U		

HISTORY OF NOTIFICATION EVENT

Event	History of events between notification event and assessment		
1	**Notification event itself**		
2		**Event date*:** U	**Time** : U
3		**Event date*:** U	**Time** : U
4		**Event date*:** U	**Time** : U
5		**Event date*:** U	**Time** : U

Use extra piece of paper for event 6 onwards. * DD-MM-YY 24 Hr clock

If admitted as a result of the notification event (use ambulance sheet)

Was subject admitted to hospital? as a direct result of the notification event	Y	N	U

If YES then please answer:

Was subject admitted by ambulance?	Y	N	U

If admitted by ambulance:	**Date** DD-MM-YY	**Time** 24 hr clock
Arrival of emergency service with patient	U	: U
Arrival of emergency service in Hospital *	U	: U

* If not on ambulance sheet use blue admissions

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	ACS						**Cerebral**						**Peripheral**		
	NSTEMI			**STEMI**			**TIA**			**CVA**					
Prior acute events?	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
	Possible*			Possible*			Possible*			Possible*					
# of events	U			U			U			U			U		
Date of most recent	U			U			U			U			U		

* Please circle if it is unclear what type of event it was

MEDICAL HISTORY **PRIOR** TO NOTIFICATION EVENT

Please tick if:	**All No**	**All U**

	Y/N/U
Angina	
Hypertension	
Diabetes Mellitus	
Valvular heart disease	
Intermittent Claudication	
Peripheral vascular intervention	
Atrial fibrillation (diagnosed **before** this TIA/stroke)	
Pacemaker	
Hyper lipidaemia	
Cardiac failure	
	Y/N/U

Treated? **Y** **N** **U**

Diabetes Mellitus

Treatment									
Diet			**Tablets**			**Insulin**			
Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	

Valvular heart disease

Nature: U

Peripheral vascular intervention

Site:

1 Arm
2 Leg
3 Bowel
4 Carotid
5 Abdo aneurysm
6 Thoracic aneurysm
7 Other
8 Uncertain

Type:

Angiogram			**Angioplasty**			**Bypass**			**Amputation**		
Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

U

Atrial fibrillation (diagnosed **before** this TIA/stroke)

1 Current
2 Previous
9 Unknown

Choose from above:

OUTCOME
1=Cardioversion
2=Paroxysmal
3=Persistent
4=Permanent
9=Unknown

Choose from above:

Pacemaker

Type pacemaker

Hyper lipidaemia

Treatment								
Diet			**Statin**			**Other**		
Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Cardiac failure

Treated (loop diuretic)**?** **Y** **N** **U**

OXVASC db: 7

MEDICAL HISTORY **PRIOR** TO NOTIFICATION EVENT - CONTINUED

Please tick if:	**All No**	**All U**

	Y/N/U choose														
Migraine		**With Aura?**			**Prolonged aura (>1hr)**			**Aura type**							
		Y	**N**	**U**	**Y**	**N**	**U**								
Epilepsy															
Cardiac intervention		**Number**	**Angiogram**			**Angioplasty**			**Stent**			**Bypass**			
			Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	
Carotid: Endarterectomy		**Side**													
		Left				**Right**				**Both**					
Carotid: Stent		**Side**													
		Left				**Right**				**Both**					
Diagnosed dementia? (check notes)	Y/N/U	**Type:**				**1: Alzheimer's** **2: Vascular** **3: Mixed** **4: Lewy body**				**5: Other** **9: Dementia of unknown type**					
Ever referred to a memory clinic? (check notes)	Y/N/U	**Which area clinic or consultant?**													
Depression diagnosed? (by a clinician, not self-diagnosed)	Y/N/U	**Age first diagnosed**				**Age at most recent treated episode**									
COAD															
Peptic ulcer disease															
Previous venous thromboses															
End stage renal failure/ dialysis															
Any other past medical history		**Details:** enter U if unknown													

Allergies	Please list all. If no allergies or unknown please enter No or Unknown.

OXVASC db: 8

Have you ever been on OCP?	**Y**	**N**	**U**
Have you ever been on HRT?	**Y**	**N**	**U**
No of years in lifetime on HRT and/or OCP			U

Previous stroke or TIA?

		Y	N	U	3 No. of previous events ALL events prior to notif. Event	1 Date most recent event DD-MM-YYYY Prior to notification event	4 Date 1st event DD-MM-YY Provide date even if same as most recent (number previous events = 1)
Hemispheric stroke carotid	**R**				#		
	L						
Hemispheric TIA carotid	**R**						
	L						
Vertebrobasilar stroke							
Vertebrobasilar TIA							
Stroke unknown territory							
TIA unknown territory							
Amaurosis fugax	**R**						
	L						
Retinal infarction	**R**						
	L						

OXVASC db: 10

MEDICATION AT THE TIME OF THE NOTIFICATION EVENT

Was subject taking medication <u>at the time</u> of the notification event? If YES provide names below			Y	N	U
Drug Category	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od,bd, tds, qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet					
Anticoagulant					
BP lowering *(whether prescribed for hypertension or not- include all diuretics, beta-blockers, alpha-blockers and nitrates)*					
Lipid lowering					
Other (*Don't forget hormonal contraception and HRT)*					
Other additional medication + dose/unit	If all lines above have been used and subject is not taking other medication please enter "No other".				

MEDICATION AT DISCHARGE OR DEATH (inpatients)
PRESCRIPTION GIVEN AT ASCERTAINMENT CLINIC (clinic patients)

Was subject's medication <u>changed</u> following the notification event? If YES provide details below				Y	N	U
Drug Category	**Change** **0**: Unchanged **1**: new drug added **2**: stopped **3**: up dose **4**: down dose **5**: other **9**: unknown	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od,bd, tds, qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet						
Anticoagulant						
BP lowering						
Lipid lowering						
Other						
Other additional medication + dose/unit		If all lines above have been used and subject is not taking other medication please enter "No other".				

FAMILY HISTORY

Patient is adopted	Y	N	U	Twin	Y	N	U
Total number of siblings (inc)				Any vascular history	Y	N	U

Oldest → Youngest

		Dad	Mum	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9	Sib 10	Sib 11	Sib 12
Stroke	Y/N/U														
	Age 1st*														
MI	Y/N/U														
	Age 1st*														
Diabetes	Y/N/U														
	Age 1st*														
Dementia	Y/N/U														
	Age 1st*														

**Age/Sibling: please fill in "U" if unknown*

	Alive/ Dead			Sex		Age at death	Cause of death
Mother	A	D	U			U	U
Father	A	D	U			U	U
Sib1 oldest	A	D	U	M	F	U	U
Sib 2	A	D	U	M	F	U	U
Sib 3	A	D	U	M	F	U	U
Sib 4	A	D	U	M	F	U	U
Sib 5	A	D	U	M	F	U	U
Sib 6	A	D	U	M	F	U	U
Sib 7	A	D	U	M	F	U	U
Sib 8	A	D	U	M	F	U	U
Sib 9	A	D	U	M	F	U	U
Sib 10	A	D	U	M	F	U	U
Sib 11	A	D	U	M	F	U	U
Sib 12 youngest	A	D	U	M	F	U	U

Total number of subject's children ☐ **# Male** ☐ **# Female** ☐

please fill in "U" if unknown

OXVASC db: 11

SMOKING

Have you ever smoked?	**Y**	**N**	**U**
Are you a lifetime non-smoker?	**Y**	**N**	**U**
Smoking oddities (pipes etc)	U		
Are you an ex-smoker?	**Y**	**N**	**U**
If so how long ago did you stop? (< 1 month = current smoker)	**Years**		**Months**
<u>If you have stopped</u>: How many years did you smoke?	# Years: U		
Do you currently smoke?	**Y**	**N**	**U**
How many do you smoke per day?	Number: U		
<u>If you are still smoking</u>: How many years have you smoked?	# Years: U		

OXVASC db: 12

Premorbid modified Rankin

Do you have any symptoms?	**Y**	**N**	**U**
Are you able to look after yourself and carry out normal activities?	**Y**	**N**	**U**
Does anyone else help pay the bills, do the shopping, cleaning etc?	**Y**	**N**	**U**
Do you need someone to help you walk?	**Y**	**N**	**U**
Do you need help to wash yourself?	**Y**	**N**	**U**
Do you need to be lifted in and out of bed?	**Y**	**N**	**U**

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death	Score

OXVASC db: 13

Premorbid Barthel

1. The index should be used as a record of what a patient does, ***not*** a record of what a patient can do. It considers ability not technique, over the last month.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. Someone may use equipment but be independent in doing so e.g. use of a stairlift, hoist, or care of a catheter or stoma.
4. The need for supervision or someone to be on stand-by 'just in case' renders the patient ***not*** independent

	Score	Key
Feeding		0 = unable 1 = needs help cutting, spreading butter, etc, or requires modified diet 2 = independent
Bathing		0 = dependent 1 = independent (or in shower)
Grooming		0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Dressing		0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)
Bowels		0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent
Bladder		0 = incontinent, or catheterised and unable to manage alone 1 = occasional accident 2 = continent
Toilet use		0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)		0 = unable, no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent
Mobility (on level surfaces)		0 = immobile 1 = wheelchair independent, including corners, > 50 metres 2 = walks with help of one person (verbal or physical) > 50 metres 3 = independent (but may use any aid; for example, stick) > 50 metres
Stairs		0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent

BARTHEL SCORE	

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

Place of residence		1 Home 2 Home of relative 3 Home of friend 4 Warden housing 5 Care home 8 Other (specify) 9 Not known	**8-Specify:**
Do you live alone? Y/N/U		**If NO with whom?**	**SPOUSE or:**
Are you a carer*? Y/N/U		*Physical assistance to wash/dress/mobility	
Does anyone assist you at home?		1 Spouse 2 Relative 3 Private carer 4 Community services (specify) 5 No assistance needed 6 Friend or neighbour 9 Not known	**4-Specify:**
Marital status		1 Married 2 Widow 3 Single 4 Separated 5 Partner 9 Not known	
Age left school			
Education		1 Basic 2 Further 3 Higher 9 Not known	
Age left full-time education			
Employment status		1 Working FT 2 Working PT 3 Caring for home 4 Unemployed 5 Unable to work 6 Retired 7 Student 9 Not known	
Age of retirement			
Most recent occupation (spouse's occupation if not employed)		U	
Socioeconomic class		1 **Professional** (Doctors, accountants, engineers) **2 Managerial/technical** (Marketing, sales managers, teachers, journalists 3N **Skilled non-manual** (Clerks, cashiers, retail staff) 3M **Skilled manual** (Carpenters, van/lorry drivers, Joiner) 4 **Partly skilled** (Warehousemen, security guards, machine/tool operators) 5 **Unskilled** (Building/civil engineering labourers, other labourers, cleaners) 6 **Armed forces** 9 **Unknown**	
Ethnic origin		1 White 2 Black Carribean 3 Black African 4 Indian 5 Pakistani 6 Bangladeshi 7 Chinese 8 Other 9 Not known	
Exercise (Clinician judgement on amount of physical activity –age corrected- per week)		1 None 2 Below average 3 Normal 4 Above average 9 Not known	
Alcohol units per week		*Use table below to calculate weekly alcohol units; only the total units is required data.*	

(Sparkling) wine and Champagne			
	ml	10%-units	14% - units
M glass	175	1.75	2.5
L glass	250	2.5	3.5
Bottle		7.5	10.5

Shots (Gin, Rum, Vodka, Whisky, Tequila, Sambuca)		
	ml	Units
Small	25	1
Large	35	1.3
Double	50	2
L double	70	2.8

Lager, Beer and Cider			
	ml	4% - units	9%-units
Bottle	330	1.3	3
Can	440	1.8	4
Pint	568	2.3	5.1

275 ml bottle alcopops	1.4 units
50 ml glass Sherry/ Port	1 Unit

IF USUAL LIVING ARRANGEMENT IS A CARE HOME - turn to next page.

Do you live alone?
Yes ☐ No ☐ If **No**, who do you live with?.....

Does anyone give you any kind of help because of long-term physical or mental ill-health / disability, or problems related to old age?

Yes ☐ No ☐ (If **No**: turn to next page. If Yes, continue below.)

Types of help include: (choose the number for the highest-dependency help received)
1=Personal care, e.g. dressing, bathing, showering, eating, getting in/out of bed, using the toilet
2=Practical household help, e.g. preparing meals, gardening, transportation, shopping, household chores
3=Other e.g. Help with paperwork, such as filling out forms, settling financial or legal matters

Who provides help?	Care provided by the person(s) who lives with you	Not living-in care, e.g. relative, friend, neighbour, charitable organisation (Specify……)	Professional/paid help (Specify care giving agency if known……)
Type of help:	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3 Was help two-handed? Yes ☐ No ☐
How often do you receive this help? (Total for personal, practical and other)		☐ daily ☐ weekly ☐ monthly ☐ Less often	☐ daily ☐ weekly ☐ monthly ☐ Less often
How many times/hours do you receive this help?		If daily: ____ times per day If weekly: ____ hours per week If monthly: ____ hours per month If less often: ____ hours per year	If daily: ____ times per day If weekly: ____ hours per week If monthly: ____ hours per month If less often: ____ hours per year

Do you receive Attendance Allowance/ Disability Living Allowance? No ☐ Yes, lower rate ☐ Yes, higher rate ☐

Do you attend a day centre or luncheon club? No ☐ Yes ☐ Number of days per week____

Do you have respite care? No ☐ Yes ☐ Number of weeks per year ____

Notes:

SLEEP

What is the likelihood of you dozing in the following three situations:

1) Sitting and reading		0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing 9= Unknown
2) Lying down to rest in the afternoon		
3) Sitting and talking to someone		
On average, how many hours of sleep do you get per night?	U	
Do you snore?	Y N U	
Do you snore loudly (louder than talking or loud enough to be heard through a closed door)?	Y N U	
Have you been told that you stop breathing at night?	Y N U	
People tell me that I snore		1= Never 2= Rarely (1-2x / year) 3= Occasionally (4-8x /year) 4= Sometimes (1-2x /month) 5= Often (1-2x /week) 6= Usually (3-5x /week) 7= Always (every night) 8 = I don't know 9 = Unknown C=Already on CPAP for Sleep Apnoea
People tell me that I gasp, choke or snort while I am sleeping		

NUTRITION

How is your appetite?		1= Good 2= Normal 3= Poor 4= Uncertain
Do you have a healthy diet?	Y N U	
On average, how many portions of fish do you eat per week? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= 2 /week 4= ≥ 3/week 9= Unkown
Do you add salt to your food?	Y N U	
Do you drink full fat or low fat dairy milk (cow/goat)?		1= Full fat 2= Low fat (skimmed/ semi-skimmed) 3= No milk consumed 4= No dairy milk consumed 9= Uncertain
On average, how many portions of fresh fruit and vegetables? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= several/ week 4= 1 /day 5= 2-4 /day 6= > 4 /day 9= Unknown

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

MOOD	Do you often feel sad or depressed?	**Y**	**N**	**U**	
DRIVING	Do you drive?	**Y**	**N**	**U**	
HANDEDNESS		**Left**	**Right**	**Both**	**Unknown**
MEMORY	Do you have problems with memory?	**Y**	**N**	**U**	
FALLS	Have you had any falls in the past year?	**None**	**One**	**More than one**	**Unknown**
	Have you ever been referred to a falls clinic?	**Y**	**N**	**U**	
Clinical impression of frailty: "frail" means greater impairment than expected for age in two or more of four domains: cognition, sensory impairment, nutrition, and physical function.					1= Frail 2= Normal 9= Unknown

OXVASC db: 21

AMTS		
Age	**0**	**1**
Time (nearest hour)	**0**	**1**
Give address for later recall: ask patient to repeat it to check they have heard correctly. "42, West Street".		
Year	**0**	**1**
Name of place	**0**	**1**
Recognition of 2 persons (eg doctor, nurse)	**0**	**1**
Date and month of birth	**0**	**1**
Date of 1st World War (either 1914 or 1918)	**0**	**1**
Name of present Monarch	**0**	**1**
Count 20-1 backwards	**0**	**1**
Recall full street address	**0**	**1**
	0= Fail 1= Pass	

If AMTS not done, why not?		
1 Sensory impairment 2 Aphasic 3 Refused 4 Severe dementia	5 Language barrier 6 Too Unwell 7 Other: Specify	

GENERAL EXAMINATION			
	cm*	**inches***	
Collar size			U
Waist measurement			U
Hip measurement			U
Height			U
	kg*	**stone***	
Weight			U

*Data entry instructions: Please take care not to enter inches in cm box, and vice versa. If entering feet/inches or stone/ pounds, do not leave the inches or pounds box blank; fill in with zero if relevant, so that the BMI calculation will happen.

For all patients: 1st HEART RATE and BLOOD PRESSURE post event				
		Date DD-MM-YY	**Time** 24 hr clock	
		U	:	U
Blood pressure 1st BP post event		**Sys**	**Dias**	U
Heart rate 1st HR post event				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Recorded by	P Paramedic G GP A A&E C Clinic O Other N Not recorded U Unknown			

For admitted patients only: TEMP, HEART RATE and BLOOD PRESSURE at admission				
Temp on admission		ºC		U
Admission Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
BP on admission		Sys	Dias	U
Sats/air		**%**		U
BM				U

For all subjects: HEART RATE, RHYTHM and BLOOD PRESSURE at assessment				
BP on assessment		Sys	Dias	U
Heart rate on assessment				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
Any pre-existing neurological disability?		Y	N	U

STROKE	Normal exam		All Unknown	

Prestroke disability	U	**Predicted 30 day Rankin**	U

SYMPTOMS AT ONSET

	Weakness		**Sensory**			**Eyes/vision**		**Other**	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemia nopia**			**Dys phasia**	
Arm					**Mono cular**			**Dys arthria**	
Hand								**Vertigo**	
Leg					**Diplopia**			**Head ache**	

Confusion		1: None 2: Usual for them 3: Worse than usual 4: New 9: Unknown

FINDINGS ON EXAMINATION

Glasgow Coma Scale			
Eyes	**/4**	1 – No eye opening 2 – Eye opening in response to pain	3- Eye opening in response to speech 4- Spontaneous eye opening
Motor	**/6**	1 – No response to pain 2 – Extensor posturing to pain 3 - Flexor response to pain	4 – Withdrawal to pain 5 - Localizing response to pain 6 – Obeys commands
verbal	**/5**	1 – No speech 2 – Incomprehensible speech 3 – Inappropriate speech	4 – Confused conversation 5 – Oriented

	Weakness		**Sensory**			**Eyes/ vision**		**Other**	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemia nopia**			**Dysphasia**	
Arm					**Gaze palsy**			**Dysarthria**	
Hand					**Nystag mus**			**Ataxia**	
Leg								**Neglect**	
								Swallowing problem	

OXVASC db: 23

NIH STROKE SCALE - SCORE ON ASSESSMENT For instructions see separate sheet					Source:	**1:EXAMINED** **2:ESTIMATED FROM NOTES** **3:NOT DONE**		
LOC		LOC questions		LOC commands			Best gaze	
Best visual		Facial Palsy		Right arm			Left arm	
Right leg		Left leg		Limb ataxia			Sensory	
Language		Dysarthria		Neglect			**TOTAL**	

OXVASC db: 23

ABCD^2 score: TIA only

A (Age); 1 point for age ≥60 years ☐

B (Blood pressure) ≥ 140/90 mmHg); 1 point for hypertension at the acute evaluation ☐

C (Clinical features); 2 points for unilateral weakness, 1 for speech disturbance without weakness ☐

D (Symptom Duration); 1 point for 10-59 minutes, 2 points for ≥60 minutes ☐

D (Diabetes); 1 point ☐

Total ☐

OXVASC db: 15

Clinical Syndrome: Stroke only

TACS

PACS

LACS

POCS

PICH

SAH

Uncertain

Clinic patients: provisional TOAST as discussed with PMR

Large vessel

Cardioembolic

Small Vessel

Undetermined

Other

Multiple

Unknown

Form completed and entered by Name: **Signature:** **OXVASC db: 27**

MONTH 1 – CLINIC PATHWAY

PLEASE COMPLETE ALL FIELDS

SUBJECT ID NO:

DATE DD/MM/YYYY**:**

CATEGORY:

Please check previous correspondence and circle <u>one</u>
For Afx please circle TIA

Possible	TIA	STROKE	OTHER: SAH ICH
Probable			
Definite			

Current Smoking		Y	N	U	**Are you driving?**	Y	N	U
BP 1st at start of FU 2nd at end of FU					**Are you in paid employment?**	Y	N	U
Heart rate					**On prescription treatment for depression?**	Y	N	U
Cardiac rhythm on palpation	1= Sinus 2= Atrial Fibrillation 3= Other 4= Regular 5= Irregular				**On treatment for seizures?**	Y	N	U
Rankin (0-6)					**Any seizure since event?**	Y	N	U
Barthel (/20)					**MMSE** (/30)			
Rivermead (/15)					**MOCA** (/30)			
Euroquol (/100)					**Symbol Digit Test Total**			
Can they provide a control?					**GDS** (/15)			

Type of contact		1 Phone call 2 Hospital visit (patient attending clinic) 3 Home visit (visit to patient at home, work, hospital etc.)		
Location of follow up		1 Home 2 Acute hospital 3 Residential home 4 Clinic / OPD 5 In a nursing home 6 In intermediate care e.g. community hospital, OCE	7 In sheltered / warden controlled accommodation 8 Staying with relative (unable to manage return home) 9 Other (specify) e.g. work	<u>Other:</u>
Living arrangements at time of follow up		1 In own home (rented or owned) 2 In relative's home 3 In nursing home 4 In hospital	5 In residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	<u>Other:</u>
Stroke patients who were inpatients only (not TIA): does patient consent to us sending copy of follow-up letter to Community Stroke Reviewers? (CSR Fax: 01865 713987)				**Y** **N**

RECURRENT EVENTS If 'Yes' please complete recurrent event form and enter event on spreadsheet				
Event	Y/N/U	No. events	Date of event DD/MM/YYYY	Comments
Chest pain (requiring admission)			1	
			2	
			3	
TIA (<24h sudden onset focal neurological disturbance)			1	
			2	
			3	
Stroke (>24h)			1	
			2	
Acute PVD event embolus, aneurysm			1	
			2	
CARDIAC PROCEDURE				
Angiogram				
Angioplasty				
Stent				
CABG				
CAROTID PROCEDURE				
Carotid endarterectomy				
PERIPHERAL PROCEDURE				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				
OTHER				
Other procedures			1	
			2	
Hospital admission during which you were confused or muddled			1	
			2	
			3	
Other admissions			1	
			2	
			3	
Bleeding requiring medical attention				

MOCA TESTING

Perform the test in the following order:

1. Naming (animals)
2. Visuospatial/executive
   - Clock
   - Cube
   - Trail test

Then follow the order shown on the sheet

Record the following additional information from the MoCA during testing:

Verbal fluency Number of words beginning with f generated in the first 15 seconds	
Verbal fluency Total number of words beginning with f generated in the whole 60 seconds	
Delayed recall (category cue) Number of words recalled with category cue (if patient does not spontaneously recall all the words)	
Delayed recall (multichoice cue) Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)	
Start and finish time for testing Please record in the boxes on the testing sheet on the following page. Similarly, please record start and finish time for the MMSE at the end of the follow-up.	
Problems with cognitive testing Please record any problems with testing at the end of the MMSE using the boxes provided	

For further information, please see the information sheet (and please refer to this each time you perform the MoCA to ensure consistency of administration).

When conducting the assessment face to face, ask subject to answer <u>all</u> MOCA questions (max score:30).

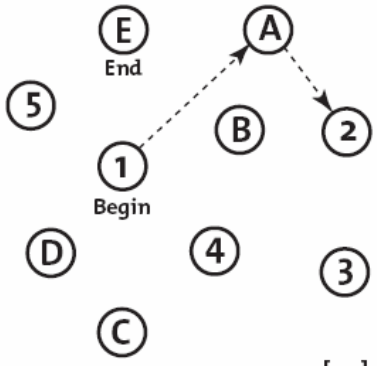
When conducting the assessment over the phone, ask all MOCA items not requiring a visual stimulus (max score: 22). For tapping at the letter A, ask patient to tap on the side of the phone with a pen or pencil. In the database, select “telephone MOCA” from the drop-down box.

MOCA	Full test*	Short test*	Not done
	START TIME:		

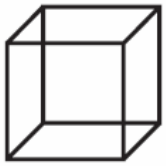
Age finished school:
Any further/higher education: Y / N
Any diploma/degree: Y / N

MONTREAL COGNITIVE ASSESSMENT (MOCA)

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



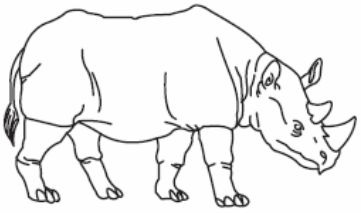
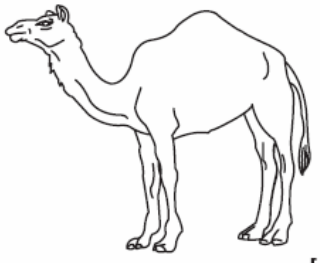
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

PHONE **MEMORY** Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

PHONE **ATTENTION** Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2

__/2

PHONE Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

PHONE Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

__/3

PHONE **LANGUAGE** Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]

__/2

PHONE Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

PHONE **ABSTRACTION** Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

PHONE **DELAYED RECALL**

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

PHONE **ORIENTATION** [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

FINISH TIME:	

MEDICATION

Is subject taking medication? If YES provide names below	Y	N	U

Has blood pressure medication changed since ascertainment?	Name of drug changed	Name of drug changed
	Date of change	Date of change
	Who made change?	Who made change?
	Why change made?	Why change made?

Drug Category	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od,bd, tds, qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet					
Anticoagulant					
BP lowering *(whether prescribed for hypertension or not- include all diuretics, beta-blockers, alpha-blockers and nitrates)*					
Lipid lowering					
Other (*Don't forget hormonal contraception and HRT)*					

Other additional medication + dose/unit, or information on compliance	If all lines above have been used and subject is not taking other medication please enter "No other".

Falls	Have you had any falls since OXVASC ascertainment?	**None**	**One**	**More than one**	**Unknown**
Presyncope	Have you felt light-headed or dizzy since OXVASC ascertainment?	**No**	**Once**	**More than once**	**Unknown**
Any falls (above) caused by presyncope?		Y	N	Uncertain	

RANKIN SCORE

Do you have ***any*** symptoms?	Y	N	U
Are you able to look after yourself and carry out normal activities?	Y	N	U
Does anyone else help pay the bills, do the shopping, cleaning etc? check that this is different since the event	Y	N	U
Do you need someone to help you walk?	Y	N	U
Do you need help to wash yourself?	Y	N	U
Do you need to be lifted in and out of bed?	Y	N	U

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities (those performed at least once a month) 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death	Key differences between scores: ↓ Some symptoms present ↓ Reduced activities. Can be left 1 week Reduced ADLs. Cannot be left 1 week Cannot walk independently. Can be left a few hours/day Cannot be left	**Score**

If there is significant *non-stroke* disability, enter reason in "other comments" box on database.

SIMPLE QUESTIONS

Please ask the patient:

Do you need help with every day activities?							Y	N	U
Following your vascular event	1	6	12	24	36	48	60	months ago	
Have you been left with any problems?							Y	N	U
Have you made a full recovery?							Y	N	U

Other comments

BARTHEL

1. The index should be used as a record of what a patient does, ***not*** a record of what a patient can do. It considers ability not technique, over the last 24-48 hours.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. Someone may use equipment but be independent in doing so e.g. use of a stairlift, hoist, or care of a catheter or stoma.
4. The need for supervision or someone to be on stand-by 'just in case' renders the patient ***not*** independent.

	Key	Score
Feeding	0 = Unable 1 = Needs help cutting, spreading butter, etc, or requires modified diet 2 = Independent	
Bathing	0 = Dependent 1 = Independent (or in shower)	
Grooming	0 = Needs help with personal care 1 = Independent face/hair/teeth/shaving (implements provided)	
Dressing	0 = Dependent 1 = Needs help but can do about half unaided 2 = Independent (including buttons, zips, laces, etc.)	
Bowels	0 = Incontinent (or needs to be given enemas) 1 = Occasional accident 2 = Continent	
Bladder	0 = Incontinent, or catheterised and unable to manage alone 1 = Occasional accident 2 = Continent	
Toilet use	0 = Dependent 1 = Needs some help, but can do something alone 2 = Independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	0 = Unable, no sitting balance 1 = Major help (one or two people, physical), can sit 2 = Minor help (verbal or physical) 3 = Independent	
Mobility (on level surfaces)	0 = Immobile 1 = Wheelchair independent, including corners, > 50 metres 2 = Walks with help of one person (verbal or physical) > 50 metres 3 = Independent (but may use any aid; for example, stick) > 50 metres	
Stairs	0 = Unable 1 = Needs help (verbal, physical, carrying aid) 2 = Independent	

BARTHEL SCORE	

RIVERMEAD MOBILITY INDEX

The patient is asked the following 15 questions and observed (for item 5). A score of 1 is given for each yes answer.

1. Score 1 if they complete the task independently using an aid e.g. climb stairs with stick
2. Score 0 if equipment does the task for them e.g. stairlift, helping hand
3. Help is defined as the assistance of a person.

QUESTION		COMMENT	N = 0 Y = 1	
1	Do you turn over from your back to your side without help?		0	1
2	From lying in bed do you get up to sit on the edge of the bed?		0	1
3	Do you sit on the edge of the bed without holding on for 10 seconds?		0	1
4	Do you stand up (from any chair) in less then 15 sec & stand there for 15 sec (using hands & with aid if necessary)?		0	1
5	Observe standing for 10 sec without any aid or support.		0	1
6	Do you manage to move, e.g. from bed to chair and back, without any help?		0	1
7	Do you walk 10 metres, with an aid or furniture if necessary but with no stand-by help?		0	1
8	Do you manage a flight of stairs without help?		0	1
9	Do you walk around outside, on pavements without help?		0	1
10	Do you walk 10m inside with no calliper, splint or aid and no stand-by help?		0	1
11	If you drop something on the floor, do you manage to walk 5 m, pick it up and walk back?		0	1
12	Do you walk around outside over uneven ground (grass, gravel, dirt, snow etc) without help?		0	1
13	Do you get in/out of the bath or shower unsupervised and wash yourself?		0	1
14	Do you manage to go up and down four steps with no rail, but with using an aid if necassery?		0	1
15	Do you run 10m without limping in 4 seconds? (fast walk is acceptable)		0	1
		TOTAL		

YOUR OWN HEALTH STATE TODAY

By placing a TICK in ONE box in each group below, please indicate which statement best describes your own health state today.

DO NOT TICK MORE THAN ONE BOX IN EACH GROUP

MOBILITY	
I have no problems in walking about	
Or: I have some problems in walking about	
Or: I am confined to bed	

SELF-CARE	
I have no problems with self-care	
Or: I have some problems washing or dressing myself	
Or: I am unable to wash or dress myself	

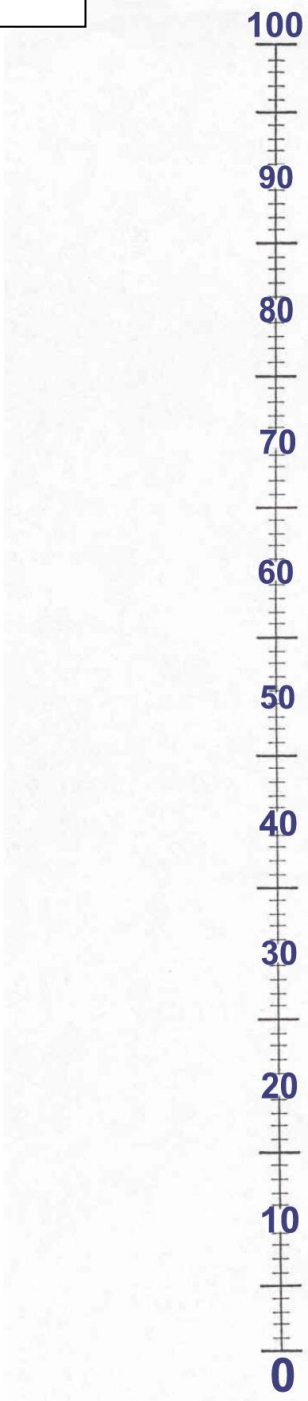
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities	
Or: I have some problems with performing my usual activities	
Or: I am unable to perform my usual activities	

PAIN / DISCOMFORT	
I have no pain or discomfort	
Or: I have moderate pain or discomfort	
Or: I have extreme pain or discomfort	

ANXIETY / DEPRESSION	
I am not anxious or depressed	
Or: I am moderately anxious or depressed	
Or: I am extremely anxious or depressed	

Please could you indicate on this scale, in your opinion, how good or bad your health is today. Please do this by drawing a line from the arrow on the left to whichever point on the scale indicates your health state. The best state you can imagine is 100, the worst state is 0.

Best imaginable health state



Your own health state today ►

Worst imaginable health state

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over **the <u>past week</u>**

1. Are you basically satisfied with your life? … … … … Yes No
2. Have you dropped many of your activities and interests? … Yes No
3. Do you feel that your life is empty? … … … … Yes No
4. Do you often get bored? … … … … … … Yes No
5. Are you in good spirits most of the time? … … … … Yes No
6. Are you afraid that something bad is going to happen to you? Yes No
7. Do you feel happy most of the time? … … … … Yes No
8. Do you often feel helpless? … … … … … Yes No
9. Do you prefer to stay at home, rather than going out & doing things? Yes No
10. Do you feel that you have more problems with memory than most? Yes No
11. Do you think it is wonderful to be alive now? … … … Yes No
12. Do you feel worthless the way you are now? … … … Yes No
13. Do you feel full of energy? … … … … … … Yes No
14. Do you feel that your situation is hopeless? … … … Yes No
15. Do you think that most people are better off than you are? … Yes No

Symbol digit coding task. Look at the key to see which number goes with each symbol. Complete the practice section (up to thick line); interviewer will correct if necessary.
Then complete as many as you can, as accurately as you can, in **90 seconds**.

(	÷	⊢	⌐	⊣	>	+	)	÷
1	2	3	4	5	6	7	8	9

(	⊣	÷	(	⊢	>	÷	⌐	(	>	÷	(	>	(	÷

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MMSE: MINI MENTAL STATE EXAMINATION

START TIME*:*

ORIENTATION TO TIME, What is the…

NOTE: IGNORE the items shown in smaller type (these have already been assessed in the MoCA) and only ask the highlighted questions

	Response		
Year?		0	1
Season?		0	1
Month of the year?		0	1
Day of the week?		0	1
Date?		0	1
	TOTAL		

ORIENTATION TO PLACE*, Where are we now, what is the…

	Response		
County?		0	1
City/town/village		0	1
Street (suburb)		0	1
House name/ no (building name)		0	1
Room of house (ward number/level)		0	1
	TOTAL		

***** Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are …APPLE *[pause]*, **PENNY** *[pause]*, **TABLE** *[pause]*. **Now repeat those words back to me.** [Repeat up to 5 times, but only score on the first trial]

	Response		
APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

**Now keep those words in mind. I am going to ask you to say them again in a few minutes. ***Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION

NOTE: Perform the WORLD task on all subjects
DO NOT USE THIS SCORE IN THE TOTAL MMSE SCORE, INSTEAD USE THE SERIAL 7S SCORE FROM THE MOCA.

Spell the word WORLD forward, then backward, correct forward spelling if misspelled, but score only the backward spelling.

D		L		R		O		W		Score 1 each	

RECALL

What were those three words I asked you to remember? *[Do not offer any hints]*

APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

NAMING*			
What is this? [point to pencil/ pen]		**0**	**1**
What is this? [watch]		**0**	**1**
	TOTAL		

* Alternative common objects (e.g.eyeglasses, chair, keys may be substituted and noted

REPETITION			
Now I am going to ask you to repeat what I say. Ready? "NO IFs ANDs OR BUTs." Now you say that. [repeat up to 5 times, but score only on the first trial]			
NO IFs ANDs OR BUTs		0	1
	TOTAL		

COMPREHENSION			
Listen carefully because I am going to ask you to do something. Take this paper in your right hand *[pause]*, **fold it in half** *[pause]***, and put it on the floor (or table).**			
Take in right hand		0	1
Fold in half		0	1
Put on floor/table		0	1
	TOTAL		

READING			
Please read this and do what it says. [Show the examinee the words on the stimulus form]			
Close your eyes		0	1
	TOTAL		

WRITING		
Please write a sentence. [If examinee does not respond, say: **Write about the weather.**] Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.	0	1

DRAWING		
Please copy this design. [Display the intersecting pentagons on the stimulus form]. Score 1 point if the drawing consists of two 5-sided figures that intersect to from a 4-sided figure.	0	1
FINISH TIME:		
NB Using serial 7s score and NOT WORLD TOTAL/30		

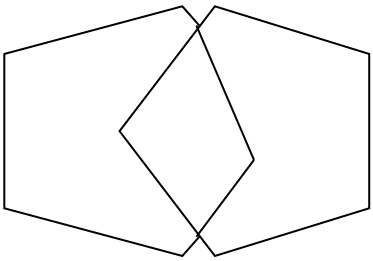
Any problem with testing? ie the MMSE **was done**, but there was a problem that interfered with the test. Indicate the problem.		1 No problem 2 Sensory impairment 3 Dysphasic 4 Residual arm weakness 5 Arthritis/#/tremor	6 Co-existent neurological dis. 7 First language not English 8 Other **9 MMSE not done** IL Illiteracy C Known cognitive impairment
If not done, why not? ie if the MMSE was **not** done, what was the reason?		1 Sensory impairment 2 Aphasic 3 Refused cognitive testing 4 Severe dementia 5 Illiterate	6 Language barrier 7 Unwell 8 Telephone/email FU 9 Other 10 MMSE was done

IQCODE FORM DONE	YES	NO
If not done, please give the reason		

Follow up form completed and entered by

Name: Signature:

CLOSE YOUR EYES



MONTH 3

PLEASE COMPLETE ALL FIELDS

SUBJECT ID NO

CATEGORY:
Please check previous correspondence and circle one

DATE DD/MM/YYYY**:**

Possible			OTHER:
Probable	TIA	STROKE	SAH ICH
Definite			

For Afx please circle TIA

Current Smoking		Y	N	U	**Are you driving?**		Y	N	U
BP 1st at start of FU 2nd at end of FU					**Are you in paid employment?**		Y	N	U
Heart rate					**On prescription treatment for depression?**		Y	N	U
Cardiac rhythm on palpation	1= Sinus 2= Atrial Fibrillation 3= Other 4= Regular 5= Irregular				**On treatment for seizures?**		Y	N	U
Falls	Have you had any falls since your last OXVASC follow-up?				**None**	**One**	**More than one**	**Unknown**	
Presyncope	Have you felt light-headed or dizzy since your last follow-up?				**No**	**Once**	**More than once**	**Unknown**	
Any fall (above) due to presyncope?					Y	N	U		
Rankin (0-6)					**Was 1mn IQCODE form received?** (If no, reissue)			Y	N

Type of contact		1 Phone call 2 Hospital visit (patient attending clinic) 3 Home visit (visit to patient at home, work, hospital etc.)	
Location of follow up		1 Home 2 Acute hospital 3 Residential home 4 Clinic / OPD 5 In a nursing home 6 In intermediate care e.g. community hospital, OCE 7 In sheltered / warden controlled accommodation 8 Staying with relative (unable to manage return home) 9 Other (specify) e.g. work	Other:
Living arrangements at time of follow up		1 In own home (rented or owned) 2 In relative's home 3 In nursing home 4 In hospital 5 In residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	Other:

RECURRENT EVENTS SINCE LAST FOLLOW-UP If 'Yes' please complete recurrent event form and enter event on spreadsheet				
Event	Y/N/U	No. events	Date of event DD/MM/YYYY	Comments
Chest pain (requiring admission)			1	
			2	
			3	
TIA (<24h sudden onset focal neurological disturbance)			1	
			2	
			3	
Stroke (>24h)			1	
			2	
Acute PVD event embolus, aneurysm			1	
			2	
CARDIAC PROCEDURE				
Angiogram				
Angioplasty				
Stent				
CABG				
CAROTID PROCEDURE				
Carotid endarterectomy				
PERIPHERAL PROCEDURE				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				
OTHER				
Other procedures			1	
			2	
Hospital admission during which you were confused or muddled			1	
			2	
			3	
Other admissions			1	
			2	
			3	
Bleeding requiring medical attention				

MEDICATION

Is subject taking medication? If YES provide names below			Y	N	U
Drug Category	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od,bd, tds, qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet					
Anticoagulant					
BP lowering *(whether prescribed for hypertension or not- include all diuretics, beta-blockers, alpha-blockers and nitrates)*					
Lipid lowering					
Other (*Don't forget hormonal contraception and HRT)*					
Other additional medication + dose/unit, or information on compliance	If all lines above have been used and subject is not taking other medication please enter "No other".				
Blood pressure	Name of drug changed		Name of drug changed		

medication changes	Date of change	Date of change
	Who made change?	Who made change?
	Why change made?	Why change made?

RANKIN SCORE

Do you have ***any*** symptoms?	Y	N	U
Are you able to look after yourself and carry out normal activities?	Y	N	U
Does anyone else help pay the bills, do the shopping, cleaning etc? check that this is different since the event	Y	N	U
Do you need someone to help you walk?	Y	N	U
Do you need help to wash yourself?	Y	N	U
Do you need to be lifted in and out of bed?	Y	N	U

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities (those performed at least once a month) 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death	<u>Key differences between scores:</u> ↓ Some symptoms present ↓ Reduced activities. Can be left 1 week Reduced ADLs. Cannot be left 1 week Cannot walk independently. Can be left a few hours/day Cannot be left	**Score**

If there is significant *non-stroke* disability, enter reason in "other comments" box on database.

SIMPLE QUESTIONS

Please ask the patient:

Do you need help with every day activities?										Y	N	U
Following your vascular event	1	3	6	12	18	24	36	48	60	months ago		
Have you been left with any problems?										Y	N	U
Have you made a full recovery?										Y	N	U

Other comments

Follow up form completed and entered by

Name: Signature:

OXFORD VASCULAR STUDY FOLLOW UP

MONTH 6
PLEASE COMPLETE ALL FIELDS

SUBJECT ID NO:

DATE DD/MM/YYYY**:**

CATEGORY:

Please check previous correspondence and circle one

Possible	TIA	STROKE	OTHER: SAH ICH
Probable			
Definite			

For Afx please circle TIA

Current Smoking	Y	N	U	**Are you driving?**	Y	N	U
BP 1st at start of FU 2nd at end of FU	/	/		**Are you in paid employment?**	Y	N	U
Heart rate				**On prescription treatment for depression?**	Y	N	U
Cardiac rhythm on palpation 1= Sinus 2= Atrial Fibrillation 3= Other 4= Regular 5= Irregular				**On treatment for seizures?**	Y	N	U
MOCA (/30)				**Euroqol** (/100)			
Rankin (0-6)				**MMSE** (/30)			
Barthel (/20)				**In Patients: Was 1mn IQCODE form received?** (If no, reissue)	Y	N	U
Rivermead (/15)							

Type of contact		1 Phone call 2 Hospital visit (patient attending clinic) 3 Home visit (visit to patient at home, work, hospital etc.)		
Location of follow up		1 Home 2 Acute hospital 3 Residential home 4 Clinic / OPD 5 In a nursing home 6 In intermediate care e.g. community hospital, OCE	7 In sheltered / warden controlled accommodation 8 Staying with relative (unable to manage return home) 9 Other (specify) e.g. work	Other:
Living arrangements at time of follow up		1 In own home (rented or owned) 2 In relative's home 3 In nursing home 4 In hospital	5 In residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	Other:

Asked if they can provide a control?

RECURRENT EVENTS SINCE LAST FOLLOW-UP If 'Yes' please complete recurrent event form and enter event on spreadsheet				
Event	Y/N/U	No. events	Date of event DD/MM/YYYY	Comments
Chest pain (requiring admission)			1	
			2	
			3	
TIA (<24h sudden onset focal neurological disturbance)			1	
			2	
			3	
Stroke (>24h)			1	
			2	
Acute PVD event embolus, aneurysm			1	
			2	
CARDIAC PROCEDURE				
Angiogram				
Angioplasty				
Stent				
CABG				
CAROTID PROCEDURE				
Carotid endarterectomy				
PERIPHERAL PROCEDURE				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				
OTHER				
Other procedures			1	
			2	
Hospital admission during which you were confused or muddled			1	
			2	
			3	
Other admissions			1	
			2	
			3	
Bleeding requiring medical attention				

Falls	Have you had any falls since your last OXVASC follow-up?	**None**	**One**	**More than one**	**Unknown**
Presyncope	Have you felt light-headed or dizzy since your last follow-up?	**No**	**Once**	**More than once**	**Unknown**
Any falls caused by presyncope?		Y	N	U	

MOCA TESTING

Perform the test in the following order:

3. Naming (animals)
4. Visuospatial/executive
   - Clock
   - Cube
   - Trail test

Then follow the order shown on the sheet

Record the following additional information from the MoCA during testing:

Verbal fluency Number of words beginning with f generated in the first 15 seconds	
Verbal fluency Total number of words beginning with f generated in the whole 60 seconds	
Delayed recall (category cue) Number of words recalled with category cue (if patient does not spontaneously recall all the words)	
Delayed recall (multichoice cue) Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)	
Start and finish time for testing Please record in the boxes on the testing sheet on the following page. Similarly, please record start and finish time for the MMSE at the end of the follow-up.	
Problems with cognitive testing Please record any problems with testing at the end of the MMSE using the boxes provided	

For further information, please see the information sheet (and please refer to this each time you perform the MoCA to ensure consistency of administration).

When conducting the assessment face to face, ask subject to answer <u>all</u> MOCA questions (max score:30).

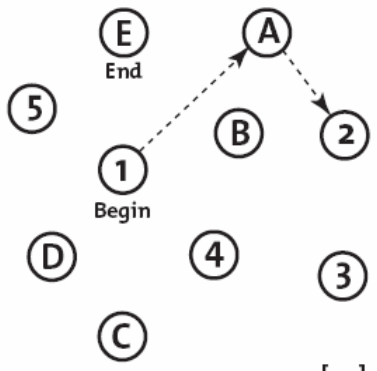
When conducting the assessment over the phone, ask all MOCA items not requiring a visual stimulus (max score: 22). For tapping at the letter A, ask patient to tap on the side of the phone with a pen or pencil. In the database, select “telephone MOCA” from the drop-down box.

MOCA	Full test*	Short test*	Not done
	START TIME:		

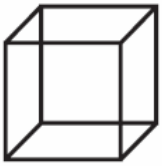
MONTREAL COGNITIVE ASSESSMENT (MOCA)

Age finished school:
Any further/higher education: Y / N
Any diploma/degree: Y / N

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



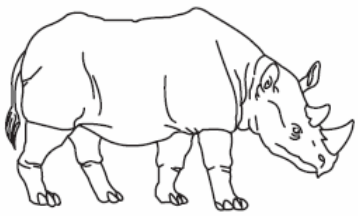
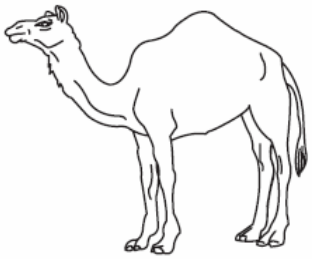
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

PHONE

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

__/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

PHONE

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

PHONE

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

PHONE

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD Version 7.0 www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

	FINISH TIME:	

MEDICATION					
Is subject taking medication? If YES provide names below			Y	N	U
Drug Category	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od,bd, tds, qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet					
Anticoagulant					
BP lowering *(whether prescribed for hypertension or not- include all diuretics, beta-blockers, alpha-blockers and nitrates)*					
Lipid lowering					
Other (*Don't forget hormonal contraception and HRT)*					
Other additional medication + dose/unit, or information on compliance	If all lines above have been used and subject is not taking other medication please enter "No other".				

Blood pressure medication changes	Name of drug changed	Name of drug changed
	Date of change	Date of change
	Who made change?	Who made change?
	Why change made?	Why change made?

IF USUAL LIVING ARRANGEMENT IS A CARE HOME - turn to next page.

Do you live alone?

Yes ☐ No ☐ If **No**, who do you live with?.....

Does anyone give you any kind of help because of long-term physical or mental ill-health / disability, or problems related to old age?

Yes ☐ No ☐ (If **No**: turn to next page. If Yes, continue below.)

Types of help include: (choose the number for the highest-dependency help received)
1=Personal care, e.g. dressing, bathing, showering, eating, getting in/out of bed, using the toilet
2=Practical household help, e.g. preparing meals, gardening, transportation, shopping, household chores
3=Other e.g. Help with paperwork, such as filling out forms, settling financial or legal matters

Who provides help?	Care provided by the person(s) who lives with you	Not living-in care, e.g. relative, friend, neighbour, charitable organisation (Specify……)	Professional/paid help (Specify care giving agency if known……)
Type of help:	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3 Was help two-handed? Yes ☐ No ☐
How often do you receive this help? (Total for personal, practical and other)		☐ daily ☐ weekly ☐ monthly ☐ Less often	☐ daily ☐ weekly ☐ monthly ☐ Less often
How many times/hours do you receive this help?		If daily: ____ times per day If weekly: ____ hours per week If monthly: ____ hours per month If less often: ____ hours per year	If daily: ____ times per day If weekly: ____ hours per week If monthly: ____ hours per month If less often: ____ hours per year

Do you receive Attendance Allowance/ Disability Living Allowance? No ☐ Yes, lower rate ☐ Yes, higher rate ☐

Do you attend a day centre or luncheon club? No ☐ Yes ☐ Number of days per week____

Do you have respite care? No ☐ Yes ☐ Number of weeks per year ____

Notes:

RANKIN SCORE

Do you have ***any*** symptoms?	Y	N	U
Are you able to look after yourself and carry out normal activities?	Y	N	U
Does anyone else help pay the bills, do the shopping, cleaning etc? check that this is different since the event	Y	N	U
Do you need someone to help you walk?	Y	N	U
Do you need help to wash yourself?	Y	N	U
Do you need to be lifted in and out of bed?	Y	N	U

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities (those performed at least once a month) 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death	Key differences between scores: ↓ Some symptoms present ↓ Reduced activities. Can be left 1 week Reduced ADLs. Cannot be left 1 week Cannot walk independently. Can be left a few hours/day Cannot be left	**Score**

If there is significant *non-stroke* disability, enter reason in "other comments" box on database.

SIMPLE QUESTIONS

Please ask the patient:

Do you need help with every day activities?								Y	N	U
Following your vascular event	1	6	12	24	36	48	60	months ago		
Have you been left with any problems?								Y	N	U
Have you made a full recovery?								Y	N	U

Other comments

BARTHEL

5. The index should be used as a record of what a patient <u>does</u>, ***not*** a record of what a patient can do. It considers ability not technique, over the last 24-48 hours.
6. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
7. Someone may use equipment but be independent in doing so e.g. use of a stairlift, hoist, or care of a catheter or stoma.
8. The need for supervision or someone to be on stand-by 'just in case' renders the patient ***not*** independent.

	Key	Score
Feeding	0 = Unable 1 = Needs help cutting, spreading butter, etc, or requires modified diet 2 = Independent	
Bathing	0 = Dependent 1 = Independent (or in shower)	
Grooming	0 = Needs help with personal care 1 = Independent face/hair/teeth/shaving (implements provided)	
Dressing	0 = Dependent 1 = Needs help but can do about half unaided 2 = Independent (including buttons, zips, laces, etc.)	
Bowels	0 = Incontinent (or needs to be given enemas) 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Bladder	0 = Incontinent, or catheterised and unable to manage alone 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Toilet use	0 = Dependent 1 = Needs some help, but can do something alone 2 = Independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	0 = Unable, no sitting balance 1 = Major help (one or two people, physical), can sit 2 = Minor help (verbal or physical) e.g. asst of 1 person 3 = Independent	
Mobility (on level surfaces)	0 = Immobile 1 = Wheelchair independent, including corners, > 50 metres 2 = Walks with help of one person (verbal or physical) > 50 metres 3 = Independent (but may use any aid; for example, stick) > 50 metres	
Stairs	0 = Unable 1 = Needs help (verbal, physical, carrying aid) 2 = Independent	

BARTHEL SCORE	

RIVERMEAD MOBILITY INDEX

The patient is asked the following 15 questions and observed (for item 5). A score of 1 is given for each yes answer.

4. Score 1 if they complete the task independently using an aid e.g. climb stairs with 1 stick
5. Score 0 if equipment does the task for them e.g. stairlift, helping hand
6. Help is defined as the assistance of a person.

QUESTION		COMMENT	N = 0 Y = 1	
1	Do you turn over from your back to your side without help?		0	1
2	From lying in bed do you get up to sit on the edge of the bed?		0	1
3	Do you sit on the edge of the bed without holding on for 10 seconds?		0	1
4	Do you stand up (from any chair) in less then 15 sec & stand there for 15 sec (using hands & with aid if necessary)?		0	1
5	Observe standing for 10 sec without any aid or support.		0	1
6	Do you manage to move, e.g. from bed to chair and back, without any help?		0	1
7	Do you walk 10 metres, with an aid or furniture if necessary but with no stand-by help?		0	1
8	Do you manage a flight of stairs without help?		0	1
9	Do you walk around outside, on pavements without help?		0	1
10	Do you walk 10m inside with no calliper, splint or aid and no stand-by help?		0	1
11	If you drop something on the floor, do you manage to walk 5 m, pick it up and walk back?		0	1
12	Do you walk around outside over uneven ground (grass, gravel, dirt, snow etc) without help?		0	1
13	Do you get in/out of the bath or shower unsupervised and wash yourself?		0	1
14	Do you manage to go up and down four steps with no rail, but with using an aid if necessary?		0	1
15	Do you run 10m without limping in 4 seconds? (fast walk is acceptable)		0	1
		TOTAL		

YOUR OWN HEALTH STATE TODAY

By placing a TICK in ONE box in each group below, please indicate which statement best describes your own health state today.

DO NOT TICK MORE THAN ONE BOX IN EACH GROUP

MOBILITY	
I have no problems in walking about	
Or: I have some problems in walking about	
Or: I am confined to bed	

SELF-CARE	
I have no problems with self-care	
Or: I have some problems washing or dressing myself	
Or: I am unable to wash or dress myself	

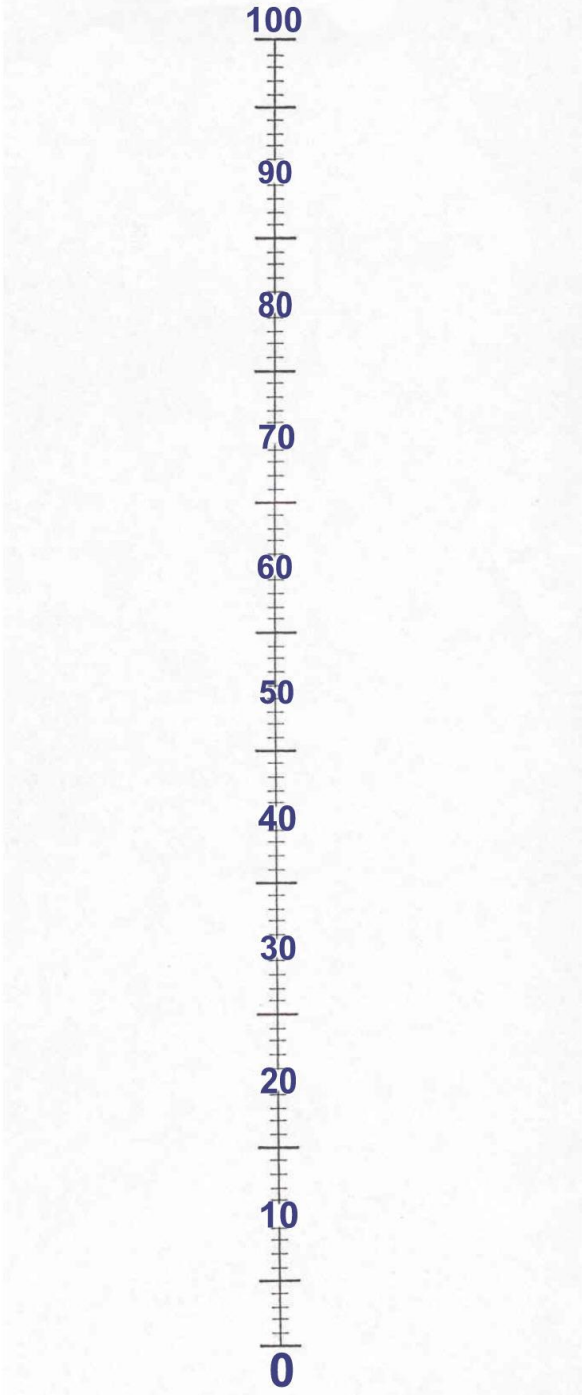
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities	
Or: I have some problems with performing my usual activities	
Or: I am unable to perform my usual activities	

PAIN / DISCOMFORT	
I have no pain or discomfort	
Or: I have moderate pain or discomfort	
Or: I have extreme pain or discomfort	

ANXIETY / DEPRESSION	
I am not anxious or depressed	
Or: I am moderately anxious or depressed	
Or: I am extremely anxious or depressed	

Please could you indicate on this scale, in your opinion, how good or bad your health is today. Please do this by drawing a line from the arrow on the left to whichever point on the scale indicates your health state. The best state you can imagine is 100, the worst state is 0.

Best imaginable health state



Your own health state today ▶

Worst imaginable health state

FATIGUE QUESTIONNAIRE

To be completed if Barthel ≥18/20 and MMSE ≥24/30

Please answer all the questions simply by underlining or circling the answer that you think most nearly applies to you.

We would like to know whether or not you have been having any problems with feeling tired, weak or lacking in energy in the last month. If you have been feeling tired for a long time we want you to compare yourself to how you felt when last well.

1	Do you have problems with tiredness?	Less than usual	No more than usual	More than usual	Much more than usual
2	Do you need to rest more?	Less than usual	No more than usual	More than usual	Much more than usual
3	Do you feel sleepy or drowsy?	Less than usual	No more than usual	More than usual	Much more than usual
4	Do you have problems starting things?	Less than usual	No more than usual	More than usual	Much more than usual
5	Do you lack energy?	Less than usual	No more than usual	More than usual	Much more than usual
6	Do you have less strength in your muscles?	Better than usual	No more than usual	More than usual	Much more than usual
7	Do you feel weak?	Less than usual	No more than usual	More than usual	Much more than usual
8	Do you have difficulty concentrating?	Less than usual	No more than usual	More than usual	Much more than usual
9	Do you make slips of the tongue when speaking?	Less than usual	No more than usual	More than usual	Much more than usual
10	Do you find it more difficult to find the correct word?	Less than usual	No more than usual	More than usual	Much more than usual
11	How is your memory?	Better than usual	No worse than usual	Worse than usual	Much worse than usual

Why do you think you are feeling tired? (Please try to give one reason).

MMSE: MINI MENTAL STATE EXAMINATION

START TIME*:*

ORIENTATION TO TIME, What is the…

NOTE: IGNORE the items shown in smaller type (these have already been assessed in the MoCA) and only ask the highlighted questions

	Response		
Year?		0	1
Season?		0	1
Month of the year?		0	1
Day of the week?		0	1
Date?		0	1
	TOTAL		

ORIENTATION TO PLACE*, Where are we now, what is the…

	Response		
County?		0	1
City/town/village		0	1
Street (suburb)		0	1
House name/ no (building name)		0	1
Room of house (ward number/level)		0	1
	TOTAL		

***** Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are …APPLE *[pause]*, **PENNY** *[pause]*, **TABLE** *[pause]*. **Now repeat those words back to me.** [Repeat up to 5 times, but only score on the first trial]

	Response		
APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

**Now keep those words in mind. I am going to ask you to say them again in a few minutes. ***Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION

NOTE: Perform the WORLD task on all subjects
DO NOT USE THIS SCORE IN THE TOTAL MMSE SCORE, INSTEAD USE THE SERIAL 7S SCORE FROM THE MOCA.

Spell the word WORLD forward, then backward, correct forward spelling if misspelled, but score only the backward spelling.

D		L		R		O		W		Score 1 each	

RECALL

What were those three words I asked you to remember? *[Do not offer any hints]*

APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

NAMING*

What is this? [point to pencil/		**0**	**1**

pen]			
What is this? [watch]		**0**	**1**
	TOTAL		

* Alternative common objects (e.g.eyeglasses, chair, keys may be substituted and noted

REPETITION			
Now I am going to ask you to repeat what I say. Ready? "NO IFs ANDs OR BUTs." Now you say that. [repeat up to 5 times, but score only on the first trial]			
NO IFs ANDs OR BUTs		0	1
	TOTAL		

COMPREHENSION			
Listen carefully because I am going to ask you to do something. Take this paper in your right hand *[pause]*, **fold it in half** *[pause]***, and put it on the floor (or table).**			
Take in right hand		0	1
Fold in half		0	1
Put on floor/table		0	1
	TOTAL		

READING			
Please read this and do what it says. [Show the examinee the words on the stimulus form]			
Close your eyes		0	1
	TOTAL		

WRITING		
Please write a sentence. [If examinee does not respond, say: **Write about the weather.**] Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.	0	1

DRAWING		
Please copy this design. [Display the intersecting pentagons on the stimulus form]. Score 1 point if the drawing consists of two 5-sided figures that intersect to from a 4-sided figure.	0	1

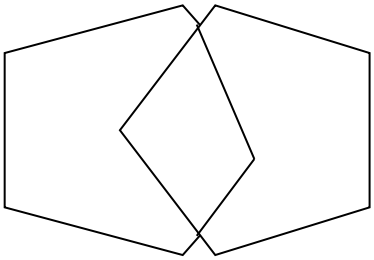
FINISH TIME:	
NB Using serial 7s score and NOT WORLD TOTAL/30	

Any problem with testing? ie the MMSE **was done**, but there was a problem that interfered with the test. Indicate the problem.		1 No problem 2 Sensory impairment 3 Dysphasic 4 Residual arm weakness 5 Arthritis/#/tremor	6 Co-existent neurological dis. 7 First language not English 8 Other 9 MMSE not done IL Illiteracy C Known cognitive impairment
If not done, why not? ie if the MMSE was **not** done, what was the reason?		1 Sensory impairment 2 Aphasic 3 Refused cognitive testing 4 Severe dementia 5 Illiterate	6 Language barrier 7 Unwell 8 Telephone/email FU 9 Other 10 MMSE was done

Follow up form completed and entered by

Name: Signature:

CLOSE YOUR EYES



OXFORD VASCULAR STUDY FOLLOW UP

MONTH 12 / 60*

***Please circle one**

PLEASE COMPLETE ALL FIELDS

SUBJECT ID NO:

DATE DD/MM/YYYY**:**

CATEGORY:

Please check previous correspondence and circle one

Possible	TIA	STROKE	OTHER: SAH ICH
Probable			
Definite			

For Afx please circle TIA

Current Smoking		Y	N	U	**Are you driving?**	Y	N	U
BP 1st at start of FU 2nd at end of FU					**Are you in paid employment?**	Y	N	U
Heart rate					**On treatment for seizures?**	Y	N	U
Cardiac rhythm on palpation	1= Sinus 2= Atrial Fibrillation 3= Other 4= Regular 5= Irregular				**Nottingham ADL** (/66)			
MOCA (/30)					**MMSE (/30)**			
Rankin (0-6)					**New AF?**	Y	N	U
Barthel (/20)					**If Yes, what type?**	Permanent	Paroxysmal	Unknown
Rivermead (/15)					**Date of diagnosis**			
Euroquol (/100)					**Repeat RTest required?**	Y	N	

Type of contact		1 Phone call 2 Hospital visit (patient attending clinic) 3 Home visit (visit to patient at home, work, hospital etc.)		
Location of follow up		1 Home 2 Acute hospital 3 Residential home 4 Clinic / OPD 5 In a nursing home 6 In intermediate care e.g. community hospital, OCE	7 In sheltered / warden controlled accommodation 8 Staying with relative (unable to manage return home) 9 Other (specify) e.g. work	Other:
Living arrangements at time of follow up		1 In own home (rented or owned) 2 In relative's home 3 In nursing home 4 In hospital	5 In residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	Other:

Asked if they can provide a control? ☐

Check for change of address/ phone/ GP ☐

RECURRENT EVENTS SINCE LAST FOLLOW-UP If 'Yes' please complete recurrent event form and enter event on spreadsheet				
Event	Y/N/U	No. events	Date of event DD/MM/YYYY	Comments
Chest pain (requiring admission)			1	
			2	
			3	
TIA (<24h sudden onset focal neurological disturbance)			1	
			2	
			3	
Stroke (>24h)			1	
			2	
Acute PVD event embolus, aneurysm			1	
			2	
CARDIAC PROCEDURE				
Angiogram				
Angioplasty				
Stent				
CABG				
Pacemaker				
CAROTID PROCEDURE				
Carotid endarterectomy				
PERIPHERAL PROCEDURE				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				
OTHER				
Other procedures			1	
			2	
Hospital admission during which you were confused or muddled			1	
			2	
			3	
Other admissions			1	
			2	
			3	
Bleeding requiring medical				

attention				

MEMORY		**Have you/has the patient been more forgetful in the past 12 months to the extent that it has affected your/their daily life?**		**Y**	**N**	**U**	
Ever referred to a memory clinic? (check notes)		Y/N/U	**Which area clinic or consultant?**				
Diagnosed dementia? (check notes)		Y/N/U	**Type:**		**1: Alzheimer's** **2: Vascular** **3: Mixed**	**4: Lewy body** **5: Other** **9: Dementia of unknown type**	
Depression diagnosed since last follow-up? (by a clinician, not self-diagnosed)		Y/N/U	**At 5 years ask year first diagnosed**		**On prescription treatment now?**		Y/N/U
FALLS	**At 1 year ask:**	Have you had any falls since your last OXVASC follow-up?		**None**	**One**	**More than one**	**U**
	At 5 years ask:	Have you had any falls in the past year?					
		Have you ever been referred to a falls clinic?		**Y**	**N**	**U**	
Pre-syncope	**At 1 year ask:**	Have you felt light-headed or dizzy since your last follow-up?		**No**	**Once**	**More than once**	**U**
	At 5 years ask:	Have you felt light-headed or dizzy in the past year?					
Any fall (above) due to presyncope?				**Y**	**N**	**U**	

MOCA TESTING

Perform the test in the following order:

5. Naming (animals)
6. Visuospatial/executive
   - Clock
   - Cube
   - Trail test

Then follow the order shown on the sheet

Record the following additional information from the MoCA during testing:

Verbal fluency Number of words beginning with f generated in the first 15 seconds	
Verbal fluency Total number of words beginning with f generated in the whole 60 seconds	
Delayed recall (category cue) Number of words recalled with category cue (if patient does not spontaneously recall all the words)	
Delayed recall (multichoice cue) Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)	
Start and finish time for testing Please record in the boxes on the testing sheet on the following page. Similarly, please record start and finish time for the MMSE at the end of the follow-up.	
Problems with cognitive testing Please record any problems with testing at the end of the MMSE using the boxes provided	

For further information, please see the information sheet (and please refer to this each time you perform the MoCA to ensure consistency of administration).

When conducting the assessment face to face, ask subject to answer all MOCA questions (max score:30).

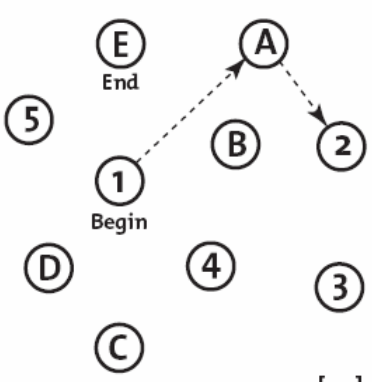
When conducting the assessment over the phone, ask all MOCA items not requiring a visual stimulus (max score: 22). For tapping at the letter A, ask patient to tap on the side of the phone with a pen or pencil. In the database, select “telephone MOCA” from the drop-down box.

MOCA	Full test*	Short test*	Not done
		START TIME:	

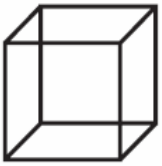
Age finished school:
Any further/higher education: Y / N
Any diploma/degree: Y / N

MONTREAL COGNITIVE ASSESSMENT (MOCA)

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



[ ] [ ]

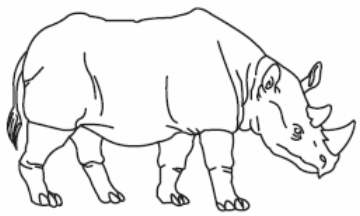
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ]



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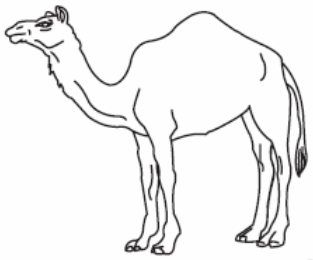


[ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

PHONE

ATTENTION

Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 — __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt — __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] — __/2

PHONE

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) — __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler — __/2

PHONE

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

PHONE

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — __/6

© Z.Nasreddine MD Version 7.0 www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

FINISH TIME:	

MEDICATION					
Is subject taking medication? If YES provide names below			Y	N	U
Drug Category	**Generic Drug Name**	**Dose as prescribed**	**Frequency** (od,bd, tds, qds)	**Total Dose** mg/day	**Other unit?** Please specify
Antiplatelet					
Anticoagulant *(If new, check if for AF)*					
BP lowering *(whether prescribed for hypertension or not- include all diuretics, beta-blockers, alpha-blockers and nitrates)*					
Lipid lowering					
Other (*Don't forget hormonal contraception and HRT)*					
Other additional medication + dose/unit, or information on compliance	If all lines above have been used and subject is not taking other medication please enter "No other".				
Blood pressure medication changes	Name of drug changed		Name of drug changed		
	Date of change		Date of change		
	Who made change?		Who made change?		
	Why change made?		Why change made?		

IF USUAL LIVING ARRANGEMENT IS A CARE HOME - turn to next page.

Do you live alone?

Yes ☐ No ☐ If **No**, who do you live with?.....

Does anyone give you any kind of help because of long-term physical or mental ill-health / disability, or problems related to old age?

Yes ☐ No ☐ (If **No**: turn to next page. If Yes, continue below.)

Types of help include: (choose the number for the highest-dependency help received)
1=Personal care, e.g. dressing, bathing, showering, eating, getting in/out of bed, using the toilet
2=Practical household help, e.g. preparing meals, gardening, transportation, shopping, household chores
3=Other e.g. Help with paperwork, such as filling out forms, settling financial or legal matters

Who provides help?	Care provided by the person(s) who lives with you	Not living-in care, e.g. relative, friend, neighbour, charitable organisation (Specify……)	Professional/paid help (Specify care giving agency if known……)
Type of help:	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3 Was help two-handed? Yes ☐ No ☐
How often do you receive this help? (Total for personal, practical and other)		☐ daily____ times per day ☐ weekly____ hours per week ☐ monthly____ hours per month ☐ Less often____ hours per year	☐ daily____ times per day ☐ weekly____ hours per week ☐ monthly____ hours per month ☐ Less often____ hours per year

Do you receive Attendance Allowance/ Disability Living Allowance? No ☐ Yes, lower rate ☐ Yes, higher rate ☐

Do you attend a day centre or luncheon club? No ☐ Yes ☐ Number of days per week____

Do you have respite care? No ☐ Yes ☐ Number of weeks per year ____

Notes:

RANKIN SCORE

Do you have ***any*** symptoms?	Y	N	U
Are you able to look after yourself and carry out normal activities?	Y	N	U
Does anyone else help pay the bills, do the shopping, cleaning etc? (check that this is different since the event)	Y	N	U
Do you need someone to help you walk?	Y	N	U
Do you need help to wash yourself?	Y	N	U
Do you need to be lifted in and out of bed?	Y	N	U

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities (those performed at least once a month) 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death	Key differences between scores: ↓ Some symptoms present ↓ Reduced activities. Can be left 1 week Reduced ADLs. Cannot be left 1 week Cannot walk independently. Can be left a few hours/day Cannot be left	**Score**

If there is significant *non-stroke* disability, enter reason in "other comments" box
on database.

SIMPLE QUESTIONS

Please ask the patient:

Do you need help with every day activities?								Y	N	U
Following your vascular event	1	6	12	24	36	48	60	months ago		
Have you been left with any problems?								Y	N	U
Have you made a full recovery?								Y	N	U

Other comments

BARTHEL

9. The index should be used as a record of what a patient does, ***not*** a record of what a patient can do. It considers ability not technique, over the last 24-48 hours.
10. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
11. Someone may use equipment but be independent in doing so e.g. use of a stairlift, hoist, or care of a catheter or stoma.
12. The need for supervision or someone to be on stand-by 'just in case' renders the patient ***not*** independent.

	Key	Score
Feeding	0 = Unable 1 = Needs help cutting, spreading butter, etc, or requires modified diet 2 = Independent	
Bathing	0 = Dependent 1 = Independent (or in shower)	
Grooming	0 = Needs help with personal care 1 = Independent face/hair/teeth/shaving (implements provided)	
Dressing	0 = Dependent 1 = Needs help but can do about half unaided 2 = Independent (including buttons, zips, laces, etc.)	
Bowels	0 = Incontinent (or needs to be given enemas) 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Bladder	0 = Incontinent, or catheterised and unable to manage alone 1 = Occasional accident (i.e. >1 in last week) 2 = Continent	
Toilet use	0 = Dependent 1 = Needs some help, but can do something alone 2 = Independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	0 = Unable, no sitting balance 1 = Major help (one or two people, physical), can sit 2 = Minor help (verbal or physical) e.g. asst of 1 person 3 = Independent	
Mobility (on level surfaces)	0 = Immobile 1 = Wheelchair independent, including corners, > 50 metres 2 = Walks with help of one person (verbal or physical) > 50 metres 3 = Independent (but may use any aid; for example, stick) > 50 metres	
Stairs	0 = Unable 1 = Needs help (verbal, physical, carrying aid) 2 = Independent	

BARTHEL SCORE	

RIVERMEAD MOBILITY INDEX

The patient is asked the following 15 questions and observed (for item 5). A score of 1 is given for each yes answer.

7. Score 1 if they complete the task independently using an aid e.g. climb stairs with 1 stick
8. Score 0 if equipment does the task for them e.g. stairlift, helping hand
9. Help is defined as the assistance of a person.

QUESTION		COMMENT	N = 0 Y = 1	
1	Do you turn over from your back to your side without help?		0	1
2	From lying in bed do you get up to sit on the edge of the bed?		0	1
3	Do you sit on the edge of the bed without holding on for 10 seconds?		0	1
4	Do you stand up (from any chair) in less then 15 sec & stand there for 15 sec (using hands & with aid if necessary)?		0	1
5	Observe standing for 10 sec without any aid or support.		0	1
6	Do you manage to move, e.g. from bed to chair and back, without any help?		0	1
7	Do you walk 10 metres, with an aid or furniture if necessary but with no stand-by help?		0	1
8	Do you manage a flight of stairs without help?		0	1
9	Do you walk around outside, on pavements without help?		0	1
10	Do you walk 10m inside with no calliper, splint or aid and no stand-by help?		0	1
11	If you drop something on the floor, do you manage to walk 5 m, pick it up and walk back?		0	1
12	Do you walk around outside over uneven ground (grass, gravel, dirt, snow etc) without help?		0	1
13	Do you get in/out of the bath or shower unsupervised and wash yourself?		0	1
14	Do you manage to go up and down four steps with no rail, but with using an aid if necessary?		0	1
15	Do you run 10m without limping in 4 seconds? (fast walk is acceptable)		0	1
		TOTAL		

YOUR OWN HEALTH STATE TODAY

By placing a TICK in ONE box in each group below, please indicate which statement best describes your own health state today.

DO NOT TICK MORE THAN ONE BOX IN EACH GROUP

MOBILITY	
I have no problems in walking about	
Or: I have some problems in walking about	
Or: I am confined to bed	

SELF-CARE	
I have no problems with self-care	
Or: I have some problems washing or dressing myself	
Or: I am unable to wash or dress myself	

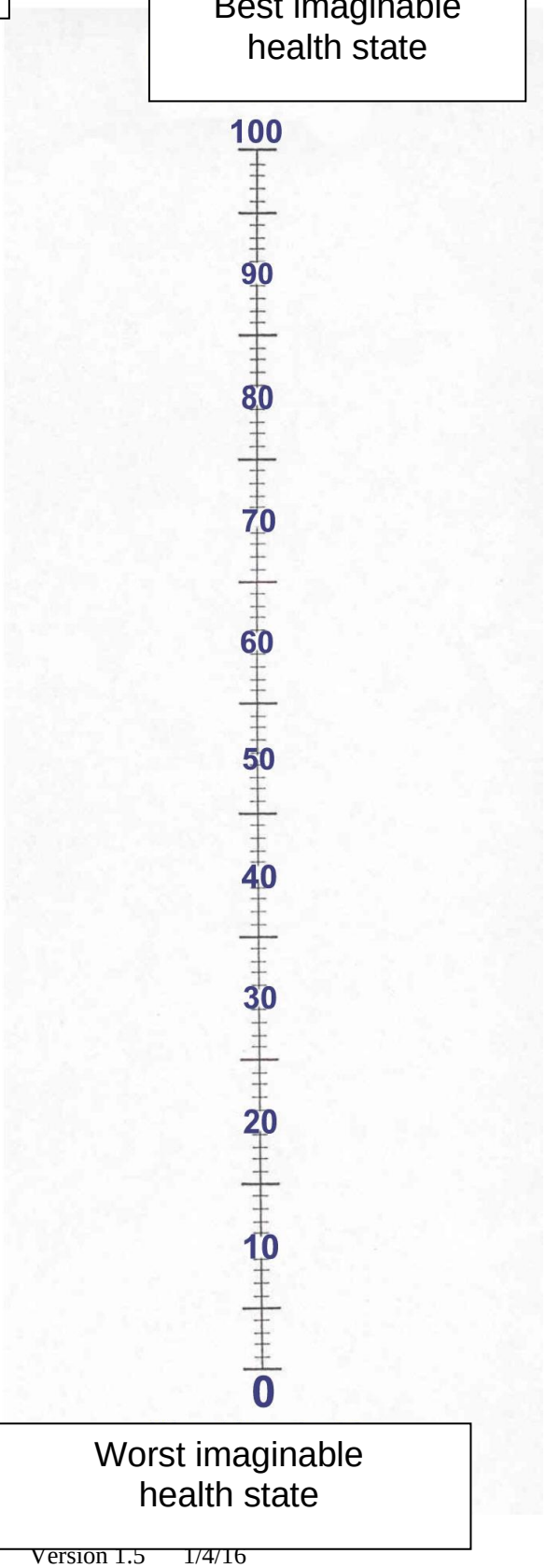
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities	
Or: I have some problems with performing my usual activities	
Or: I am unable to perform my usual activities	

PAIN / DISCOMFORT	
I have no pain or discomfort	
Or: I have moderate pain or discomfort	
Or: I have extreme pain or discomfort	

ANXIETY / DEPRESSION	
I am not anxious or depressed	
Or: I am moderately anxious or depressed	
Or: I am extremely anxious or depressed	

Please could you indicate on this scale, in your opinion, how good or bad your health is today. Please do this by drawing a line from the box on the left to whichever point on the scale indicates your health state. The best state you can imagine is 100, the worst state is 0.

Best imaginable health state



Your own health state today ►

Worst imaginable health state

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over the past week

1. Are you basically satisfied with your life?	Yes	No
2. Have you dropped many of your activities and interests?	Yes	No
3. Do you feel that your life is empty?	Yes	No
4. Do you often get bored?	Yes	No
5. Are you in good spirits most of the time?	Yes	No
6. Are you afraid that something bad is going to happen to you?	Yes	No
7. Do you feel happy most of the time?	Yes	No
8. Do you often feel helpless?	Yes	No
9. Do you prefer to stay at home, rather than going out and doing new things?	Yes	No
10. Do you feel that you have more problems with memory than most?	Yes	No
11. Do you feel it's wonderful to be alive?	Yes	No
12. Do you feel pretty worthless the way you are now?	Yes	No
13.. Do you feel full of energy?	Yes	No
14. Do you feel that your situation is hopeless?	Yes	No
15. Do you think that most people are better off than you?	Yes	No

NOTTINGHAM EXTENDED ADL INDEX

Please answer all the questions by placing a TICK in the box under the answer that you think most nearly applies to you.

Where appropriate use relative/carer input as well as self-reported answers.

DO YOU?	Not at all (0)	With help (1)	On your own with difficulty (2)	On your own easily (3)
Walk around outside?				
Climb stairs?				
Get in and out of a car?				
Walk over uneven ground?				
Cross roads?				
Travel on public transport?				
Manage to feed yourself?				
Manage to make yourself a hot drink?				
Take hot drinks from one room to another?				
Do the washing up?				
Make yourself a hot snack?				
Manage your own money when you are out?				
Wash small items of clothing?				
Do your own housework?				
Do your own shopping?				
Do a full clothes wash?				
Read newspapers or books?				
Use the telephone?				
Write letters?				
Go out socially?				
Manage your own garden?				
Drive a car?				
Total / 66				

MMSE: MINI MENTAL STATE EXAMINATION

START TIME*:*

ORIENTATION TO TIME, What is the…

NOTE: IGNORE the items shown in smaller type (these have already been assessed in the MoCA) and only ask the highlighted questions

	Response		
Year?		0	1
Season?		0	1
Month of the year?		0	1
Day of the week?		0	1
Date?		0	1
	TOTAL		

ORIENTATION TO PLACE*, Where are we now, what is the…

	Response		
County?		0	1
City/town/village		0	1
Street (suburb)		0	1
House name/ no (building name)		0	1
Room of house (ward number/level)		0	1
	TOTAL		

***** Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are …APPLE *[pause]*, **PENNY** *[pause]*, **TABLE** *[pause]*. **Now repeat those words back to me.** [Repeat up to 5 times, but only score on the first trial]

	Response		
APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

**Now keep those words in mind. I am going to ask you to say them again in a few minutes. ***Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION

NOTE: Perform the WORLD task on all subjects
DO NOT USE THIS SCORE IN THE TOTAL MMSE SCORE, INSTEAD USE THE SERIAL 7S SCORE FROM THE MOCA.

Spell the word WORLD forward, then backward, correct forward spelling if misspelled, but score only the backward spelling.

D		L		R		O		W		Score 1 each	

RECALL

What were those three words I asked you to remember? *[Do not offer any hints]*

APPLE		0	1
PENNY		0	1
TABLE		0	1
	TOTAL		

NAMING*

What is this? [point to pencil/ pen]		**0**	**1**
What is this? [watch]		**0**	**1**
	TOTAL		

* Alternative common objects (e.g.eyeglasses, chair, keys may be substituted and noted

REPETITION			
Now I am going to ask you to repeat what I say. Ready? "NO IFs ANDs OR BUTs." Now you say that. [repeat up to 5 times, but score only on the first trial]			
NO IFs ANDs OR BUTs		0	1
	TOTAL		

COMPREHENSION			
Listen carefully because I am going to ask you to do something. Take this paper in your right hand *[pause]*, **fold it in half** *[pause]***, and put it on the floor (or table).**			
Take in right hand		0	1
Fold in half		0	1
Put on floor/table		0	1
	TOTAL		

READING			
Please read this and do what it says. [Show the examinee the words on the stimulus form]			
Close your eyes		0	1
	TOTAL		

WRITING		
Please write a sentence. [If examinee does not respond, say: **Write about the weather.**] Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.	0	1

DRAWING		
Please copy this design. [Display the intersecting pentagons on the stimulus form]. Score 1 point if the drawing consists of two 5-sided figures that intersect to from a 4-sided figure.	0	1

FINISH TIME:	
NB Using serial 7s score and NOT WORLD TOTAL/30	

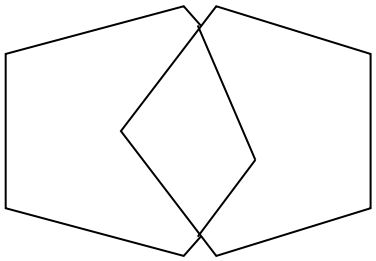
Any problem with testing? ie the MMSE/MoCA **was done**, but there was a problem that interfered with the test. Indicate the problem.		1 No problem 2 Sensory impairment 3 Dysphasic 4 Residual arm weakness 5 Arthritis/#/tremor	6 Co-existent neurological dis. 7 First language not English 8 Other 9 MMSE not done IL Illiteracy C Known cognitive impairment
If not done, why not? ie if the MMSE/MoCA was **not** done, what was the reason?		1 Sensory impairment 2 Aphasic 3 Refused cognitive testing 4 Severe dementia 5 Illiterate	6 Language barrier 7 Unwell 8 Telephone/email FU 9 Other 10 MMSE was done

IQCODE FORM DONE (60 and 120 months only)	YES	NO
If not done, please give the reason		

Follow up form completed and entered by

Name: Signature:

CLOSE YOUR EYES



OXFORD VASCULAR STUDY **Phone FOLLOW UP**

MONTH 1 / 3 / 6 / 12 / 60 /120 *

***Please circle one**

PLEASE COMPLETE ALL FIELDS

SUBJECT ID NO:

DATE DD/MM/YYYY**:**

CATEGORY:

Please check previous correspondence and circle one

Possible	TIA	STROKE	OTHER: SAH ICH
Probable			
Definite			

For Afx please circle TIA

Current Smoking	Y	N	U	**Are you driving?**	Y	N	U
MOCA (/12)				**Are you in paid employment?**	Y	N	U
Rankin (0-6)				**On prescription treatment for depression?**	Y	N	U
Barthel (/20)				**On treatment for seizures?**	Y	N	U
Rivermead (/15)				**Falls/presyncope**	Y	N	U
Euroquol (/100)				**If 'yes' please give date and details:**			
Nottingham ADL (/66) (12 & 60 month only)							
Known dementia?	Y/N/U			**Type:** **1: Alzheimer's** **2: Vascular** **3: Mixed** **4: Lewy body** **5: Other** **9: Dementia of unknown type**			

PLEASE COMPLETE THE FOLLOWING AND **ENTER ON THE DATABASE:**

Type of contact		1 Phone call 2 Hospital visit (patient attending clinic) 3 Home visit (visit to patient at home, work, hospital etc.)		
Location of follow up		1 Home 2 Acute hospital 3 Residential home 4 Clinic / OPD 5 In a nursing home 6 In intermediate care e.g. community hospital, OCE	7 In sheltered / warden controlled accommodation 8 Staying with relative (unable to manage return home) 9 Other (specify) e.g. work	Other:
Living arrangements at time of follow up		1 In own home (rented or owned) 2 In relative's home 3 In nursing home 4 In hospital	5 In residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	Other:

RECURRENT EVENTS SINCE LAST FOLLOW-UP If 'Yes' please complete recurrent event form and enter event on spreadsheet				
Event	Y/N/U	No. events	Date of event DD/MM/YYYY	Comments
Chest pain (requiring admission)			1	
			2	
			3	
TIA (<24h sudden onset focal neurological disturbance)			1	
			2	
			3	
Stroke (>24h)			1	
			2	
Acute PVD event embolus, aneurysm			1	
			2	
CARDIAC PROCEDURE				
Angiogram				
Angioplasty				
Stent				
CABG				
CAROTID PROCEDURE				
Carotid endarterectomy				
PERIPHERAL PROCEDURE				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				
OTHER				
Other procedures			1	
			2	
Hospital admission during which you were confused or muddled			1	
			2	
			3	
Other admissions			1	
			2	
Bleeding requiring medical attention				

MOCA	Full test*	Short test*	Not done
		START TIME:	

Age finished school:
Any further/higher education: Y / N
Any diploma/degree: Y / N

MONTREAL COGNITIVE ASSESSMENT (MOCA)

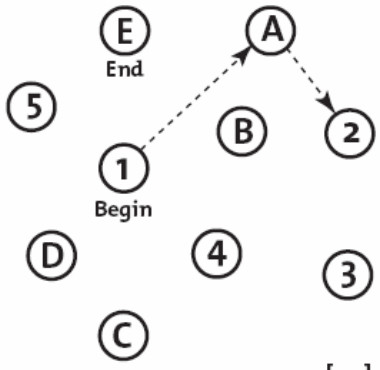
PHONE

PHONE

PHONE

PHONE

VISUOSPATIAL / EXECUTIVE



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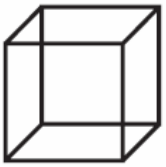


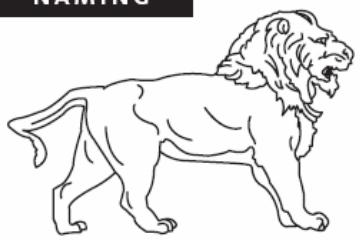
[ ] [ ]

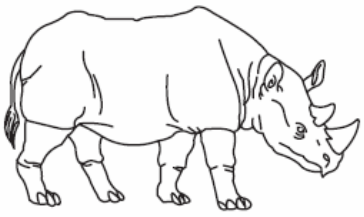
Draw CLOCK (Ten past eleven) (3 points)

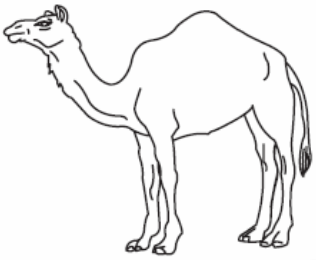
[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

NAMING







[ ] [ ] [ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED
		[ ]	[ ]	[ ]	[ ]	[ ]
Optional	Category cue					
	Multiple choice cue					

Points for UNCUED recall only

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

	FINISH TIME:	

When conducting the assessment over the phone, ask all MOCA items not requiring a visual stimulus (max score: 22). For tapping at the letter A, ask patient to tap on the side of the phone with a pen or pencil.

In the database, select "telephone MOCA" from the drop-down box.
For the MMSE, please select "telephone/email follow up" in the "Reason why MMSE not done" box

PLEASE FILL IN THE FOLLOWING **MANDATORY** COGNITIVE FIELDS ON THE DATABASE

Verbal fluency Number of words beginning with f generated in the first 15 seconds	
Verbal fluency Total number of words beginning with f generated in the whole 60 seconds	
Delayed recall (category cue) Number of words recalled with category cue (if patient does not spontaneously recall all the words)	
Delayed recall (multichoice cue) Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)	
Start and finish time for testing Please record in the boxes on the testing sheet	
Problems with cognitive testing Please record any problems with testing below	

Any problem with testing? ie the MoCA **was done**, but there was a problem that interfered with the test. Indicate the problem.		1 No problem 2 Sensory impairment 3 Dysphasic 4 Residual arm weakness 5 Arthritis/#/tremor	6 Co-existent neurological dis. 7 First language not English 8 Other 9 MMSE not done IL Illiteracy C Known cognitive impairment

For patients who are unable to do the telephone MOCA, eg those in care homes or in whom information has to be obtained from an informant (eg spouse, nurse), PLEASE ENQUIRE ABOUT THE PATIENT'S COGNITIVE FUNCTION AND DETAIL BELOW:

If there is significant *non-stroke* disability, enter reason in "other comments" box on database.

Follow up form completed and entered by
Name: Signature: