

BMJ Open Secondary prevention and cognitive function after stroke: a study protocol for a 5-year follow-up of the ASPIRE-S cohort

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ABSTRACT

Introduction: Cognitive impairment is common following stroke and can increase disability and levels of dependency of patients, potentially leading to greater burden on carers and the healthcare system. Effective cardiovascular risk factor control through secondary preventive medications may reduce the risk of cognitive decline. However, adherence to medications is often poor and can be adversely affected by cognitive deficits. Suboptimal medication adherence negatively impacts secondary prevention targets, increasing the risk of recurrent stroke and further cognitive decline. The aim of this study is to profile cognitive function and secondary prevention, including adherence to secondary preventive medications and healthcare usage, 5 years post-stroke. The prospective associations between cognition, cardiovascular risk factors, adherence to secondary preventive medications, and rates of recurrent stroke or other cardiovascular events will also be explored.

Methods and analysis: This is a 5-year follow-up of a prospective study of the Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) cohort of patients with stroke. This cohort will have a detailed assessment of cognitive function, adherence to secondary preventive medications and cardiovascular risk factor control.

Ethics and dissemination: Ethical approval for this study was granted by the Research Ethics Committees at Beaumont Hospital, Dublin and Connolly Hospital, Dublin, Mater Misericordiae University Hospital, Dublin, and the Royal College of Surgeons in Ireland. Findings will be disseminated through presentations and peer-reviewed publications.

and poorer quality of life, and can increase disability and levels of dependency, potentially leading to a greater burden on carers and the healthcare system.^{3 4} While there is evidence to support early rehabilitation interventions post-stroke, less is known about the reduction of longer term stroke-related disability.⁵ The chronic phase of stroke accounts for a considerable proportion of the total costs of stroke care, with measures to improve long-term outcomes potentially having a substantial impact on the economic burden of stroke.⁶

Cardiovascular risk factor management and secondary prevention

Several risk factors, including hypertension, dyslipidaemia, diabetes, obesity and smoking, are associated with both cardiovascular disease and cognitive impairment. A study of 355 patients with stroke aged over 75 years reported that the presence of three or more cardiovascular risk factors increased the risk of dementia during a mean follow-up of 3.8 years.⁷ Secondary preventive treatment, including antihypertensive and anticoagulant medications, has been associated with a reduced risk of cognitive impairment 6 months post-stroke.² Similarly, the use of anticoagulant, antiplatelet and antihypertensive medications was associated with a reduced risk of cognitive impairment up to 7 years post-stroke in a sample of patients with stroke from the South London Stroke Register.⁸ Targeting cardiovascular risk factors may reduce both the risk of recurrent vascular events and the risk of cognitive decline.^{2 7 9} Secondary prevention and rehabilitation are thus essential to maximising health and well-being post-stroke, particularly as recurrent strokes account for up to 50% of all strokes, indicating unsuccessful



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INTRODUCTION

Stroke is one of the leading causes of death and disability worldwide,¹ with over half of patients exhibiting signs of cognitive impairment 6 months post-stroke.² Deficits in cognitive function are associated with poor functional outcomes, increased vulnerability

secondary prevention.¹⁰ However, there are limited longer term follow-up data on patients with stroke, and a lack of information regarding the adequacy of longer term post-stroke secondary prevention.^{11 12} The Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) study found a high prevalence of cognitive impairment and cardiovascular risk factors at 6 months post-stroke.^{2 4 11} While three-quarters of the sample were on antihypertensive therapy, almost two-thirds had blood pressure above the recommended target of 140/90 mm Hg. Similarly, while 95% of patients were on lipid-lowering medications, only approximately three-quarters had total cholesterol or low-density lipoprotein (LDL) cholesterol at European guideline targets.¹¹

Medication adherence

Effective secondary stroke prevention is contingent on consistent adherence to prescribed secondary preventive medications.¹³ Non-adherence is associated with adverse outcomes, including rehospitalisation, recurring vascular events and death, as well as increased costs of care.^{14 15} However, medication adherence is often poor, with up to 50% of patients discontinuing secondary preventive medications 2 years post-stroke.¹⁶ A recent systematic review reported an estimated rate of non-adherence to secondary preventive medications among stroke survivors of 30.9% (95% CI 26.8% to 35.3%).¹⁷ A number of factors were found to be related to non-adherence in individual studies, including disability, reduced cognitive function, polypharmacy and concerns about treatment.¹⁷ However, this review also noted substantial heterogeneity in the inclusion criteria and definitions and measurements of adherence, with several studies excluding patients with stroke with evidence of cognitive impairment.

Medication adherence and cognitive function

Adherence to medication regimens requires a number of cognitive skills that are affected by cognitive impairment, including instructions for medication taking and accessing and scheduling medications.¹⁸ Suboptimal adherence, in turn, adversely impacts secondary prevention targets, increasing the risk of recurrent stroke and further cognitive decline.² However, there is a scarcity of data on longer term treatment continuation and adherence rates in patients with stroke, with several studies of adherence either not including cognitive assessments, or focusing exclusively on adherence to antithrombotic medications by patients with stroke and atrial fibrillation.^{11 13 19–22} Further, previous studies of stroke outcomes are limited by relatively short follow-ups and small sample sizes, and may not reflect contemporary outcomes or treatments.²³

Thus, while secondary prevention may be related to a reduced risk of cognitive impairment in patients with stroke, few studies have examined the association between adherence to secondary preventive medications

and cognitive impairment, and it is unclear whether sub-optimal adherence affects the risk of later cognitive impairment. Further, there are little data available at present regarding the use of healthcare resources, outcomes and costs post-stroke, or how these may be impacted by cognitive impairment or inadequate secondary prevention.²⁴ The identification of medication adherence patterns, factors associated with adherence, and the impact on clinical and cognitive outcomes can inform the development of policies and interventions focused on improving medication management.²⁵ Given the growing health, social and economic burden of cognitive impairment and dementia, longer term follow-up studies are needed to test these associations over extended periods of time.^{3 20}

Aims and objectives

The aim of this study is to profile cognitive function and secondary prevention, including healthcare usage and adherence to secondary preventive medications, at 5 years post-stroke. Specifically, the objectives are:

- ▶ To provide a detailed description of cognitive function and secondary prevention, including medication adherence at 5 years post-stroke;
- ▶ To investigate risk factor management, including blood pressure and cholesterol control 5 years post-stroke;
- ▶ To ascertain rates of recurrent stroke, other cardiovascular events and death in the 5 years post-stroke;
- ▶ To explore the prospective associations between cognition, cardiovascular risk factors and adherence to secondary preventive medications from 6 months to 5 years post-stroke;
- ▶ To explore levels of agreement between self-reported medication adherence assessed using a validated scale, pill counts and adherence estimates using pharmacy prescription refill data, in this cohort of patients with stroke;
- ▶ To explore longer term stroke rehabilitation and healthcare usage, and their associations with cognition and secondary prevention 5 years post-stroke;
- ▶ To examine the longer term costs of stroke, in terms of healthcare usage and quality of life, and their association with cognition and secondary prevention 5 years post-stroke.

A secondary aim is to explore carer well-being and the reciprocal associations between changes in cognitive function of patients with stroke and emotional distress and vulnerability in carers or family members.⁴

METHODS AND ANALYSIS

Study design

This is a 5-year follow-up of a prospective observational study of the ASPIRE-S cohort of patients with stroke.^{2 4 11} The ASPIRE-S study recruited patients with acute stroke in 2011–2012. A total of 256 patients and their family members or carers were last followed up at

6 months post-stroke. This cohort will be followed up again, 5 years post-stroke (2016–2017), with a comprehensive assessment of clinical and cognitive measures. A detailed health assessment will be conducted, including cognitive function, adherence to secondary prevention and cardiovascular risk factor control. Data will be collected using a combination of clinical and laboratory measurements using standard data collection forms, interviewer and self-completion questionnaires.

Sample size

All participants from the original study will be eligible to participate. On the basis of an estimated rate of attrition of 30% (including death and other loss to follow-up), it is anticipated that c. 180 patients and their family members or carers will be reassessed.

Outcomes

Cardiovascular risk factor control

Secondary prevention will be assessed using a number of clinical measures as part of a health assessment, including height and weight, blood pressure, pulse, anticoagulation, blood analysis and breath analysis (table 1). Analysis of serum total cholesterol, calculated LDL cholesterol and blood glucose will be carried out on all participants. Diabetic patients will also have glycated haemoglobin assessed.

Secondary preventive medications

Reported medications at the time of follow-up will be recorded as part of the interviewer-administered patient

questionnaire, and confirmed with prescription refill data where possible.

Medication adherence

There is no consensus on the best measure to define medication adherence.¹⁴ Combining prescription refill data with self-reported measures of adherence is considered essential to capturing the full extent to which patients are (non-)adherent.¹⁵ Thus, adherence to secondary preventive medications will be assessed using a number of methods:

Prescription refills

Participants who are eligible for the General Medical Services (GMS) scheme will be asked for permission to access records of monthly dispensed medications from the Irish Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) database. Access to the GMS scheme, which provides free general practitioner (GP) and hospital visits, and prescription medications at minimal cost, is means-tested for persons aged <70 years, with a substantially higher income threshold for the over 70 s,²⁶ such that over 90% of those over 70 in Ireland are included in the scheme. As a result, members of the scheme are representative of the Irish population of over-70 s, but this is not the case for those aged under 70, where women and those in lower socio-economic groups are over-represented. The HSE-PCRS pharmacy claims database provides details on monthly dispensed medications for each individual in the scheme.²⁶ Prescription refills provide an objective estimate of medication adherence, circumventing the problem of incorrect self-reporting of medication adherence.^{14 16 25 27} Prescription refills can be used to calculate metrics such as the proportion of days covered—the sum of the days supplied for medications within each medication class, divided by the number of days in the study period.^{14 15} This method has been adopted by another recent study on adherence to secondary preventive medications post-stroke.²¹

Self-reported medication adherence

Self-reported medication adherence will be assessed using the Medication Adherence Report Scale (MARS-5),²⁸ a five-point scale that assesses both intentional and unintentional non-adherence. The eight-item Morisky Medication Adherence Scale (MMAS),²⁹ which assesses a number of medication-taking behaviours, will also be included.

Pill counts

The research team will conduct pill counts of the remaining tablets in each medication or blister pack, to assess to what extent patients have taken medications as prescribed. In addition to providing a more comprehensive account of medication-taking, the use of several methods to estimate adherence will allow exploration of the levels of agreement between self-reported

Table 1 Clinical measures to be collected as part of a health assessment

Clinical measure	Details
Blood pressure	Three measurements will be taken with the average of the last two readings used for analysis. Twenty-four-hour BP monitoring will also be performed where possible.
Pulse	Where the pulse is found to be irregular, an ECG will be arranged to confirm atrial fibrillation.
Anticoagulation	Record of the last three INR measurements to assess the safety of anticoagulation medication, where relevant
Blood analysis	To assess serum total cholesterol, HDL cholesterol and calculated LDL cholesterol, glucose and HbA1c
Weight and height	To assess BMI
Breath analysis	Carbon monoxide monitoring to confirm non-smoking status in former smokers

BMI, body mass index; BP, blood pressure; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; INR, international normalised ratio; LDL, low-density lipoprotein.

medication adherence, pill counts and adherence estimates using pharmacy prescription refill data, which has not previously been reported for patients with stroke.

Stroke recurrence and other cardiovascular events

In order to ascertain stroke recurrence or other cardiovascular events, participants will be asked if they have experienced a stroke or other cardiovascular event since the last assessment. Stroke and other cardiovascular event occurrence will also be ascertained from participants' hospital medical notes, based on recording of diagnosis or other mention in the record.

Cognitive function

Cognitive function will be assessed using a number of standardised, validated instruments, including the Montreal Cognitive Assessment (MoCA),³⁰ the National Institute of Neurological Disorders and Stroke (NINDS) 30 min test battery,³¹ and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)³² (table 2).

Rehabilitation and healthcare usage

A number of questions on use of physiotherapy, occupational therapy, psychology, and speech and language therapy in the past 12 months, and the perceived need for these services, will be included in the patient assessment. Questions on healthcare usage, adapted from The Irish Longitudinal Study on Ageing,⁴⁴ will also be included. These questions will assess use of GP and nursing services, inpatient and outpatient hospital care, use of mental health services, home help and home

care, and meals-on-wheels in the past 12 months. In addition, the Timed Up and Go test, a performance-orientated mobility assessment tool used to identify individuals at increased risk of falls,³³ and a number of questions on falls adapted from the Irish Longitudinal Study on Ageing, will be included.

Covariates

A range of demographic information, including age, education, occupational status, marital status and living arrangements, will be collected as part of the patient and family member/carer assessments. The patient assessment will also include questions relating to lifelong learning, social participation and current smoking. Potential barriers to medication adherence will be explored using the Beliefs about Medicines Questionnaire (BMQ),²⁸ which assesses concerns and perceived necessity of medications. Beliefs of patients with stroke about medicines have been reported to be associated with non-adherence, with non-adherent patients scoring lower on the positive beliefs dimensions of the BMQ (necessity and benefit) and higher on negative beliefs (concern, overuse and harm).³⁴

The Frenchay Aphasia Screening Test (FAST)³⁵ will be used to screen for communication problems that may affect performance on cognitive assessments. Quality of life and health and well-being status will be assessed using the ICEpop CAPability measure for Older people (ICECAP-O),³⁶ the EQ-5D³⁷ and the Stroke Specific Quality of Life Scale (SSQOL).³⁸ Finally, the Nottingham Extended Activities of Daily Living Scale,³⁹ which assesses activities that may be important to patients with stroke who have been discharged home, and the Vulnerable Elders Scale (VES),⁴⁰ a simple function-based tool for identifying older persons who may be at risk of health deterioration, will be included.

Family member and carer assessments

In addition to the patient assessment, family members or carers will be asked to complete a family member or carer assessment. This assessment will involve a self-completion questionnaire that includes the IQCODE³² and the Neuropsychiatric Inventory, Questionnaire Version (NPI-Q) from the NINDS test battery, as well as a number of questions regarding the extent to which patients receive assistance with taking medications. The use of informant report in addition to patient assessments will facilitate triangulation of measures of cognition and increase the validity of the findings. Furthermore, informant report is important in cases where patients receive help from carers with medication taking, as there is a lack of data on factors affecting medication adherence in patients relying on others for medication management.⁴¹

The family member and carer assessment will also include a measure of anxiety (the Hospital Anxiety and Depression Scale—Anxiety (HADS-A))⁴² and depression (the Centre for Epidemiologic Studies Depression Scale (CES-D)),⁴³ and vulnerability (VES).⁴⁰ These measures

Table 2 Cognitive assessments

Assessment	Details
Patient MoCA ³⁰	A rapid screening instrument for global cognitive function, which has exhibited good sensitivity and specificity for mild cognitive impairment
NINDS 30 min test protocol ³¹	A 30 min neuropsychological assessment battery that includes: <ul style="list-style-type: none"> ▶ Semantic fluency (Animal Naming) ▶ Phonemic fluency (Controlled Oral Word Association Test) ▶ Digit Symbol-Coding ▶ Verbal Learning Test ▶ Centre for Epidemiologic Studies —Depression Scale NPI-Q ▶ Trail Making Test
Carer/family member IQCODE ³²	An informant-reported assessment of cognitive function

IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MoCA, Montreal Cognitive Assessment; NINDS, National Institute of Neurological Disorders and Stroke; NPI-Q, Neuropsychiatric Inventory, Questionnaire Version.

were included in the original ASPIRE-S study, which reported substantial levels of anxious and depressive symptoms among carers, linked to anxiety, depressive symptoms and cognitive impairment in the patients with stroke.⁴ By repeating the measures of emotional distress and vulnerability included in the original ASPIRE-S study, we will be able to consider carer well-being over time, and explore the associations between changes in cognitive impairment in patients with stroke and emotional distress and vulnerability in carers or family members.

Follow-up procedure

Each potential participant's consultant physician will be contacted to request permission to contact patients and their GPs. Efforts will be made to identify deceased participants prior to contact being made, using, for example, hospital and GP records, as well as a widely used website of death notifications (RIP.ie). Participants will be sent a study information pack by post, containing a cover letter, patient and family member/carer information leaflets, and a stamped addressed postcard that can be returned by participants wishing to opt out of the study. The cover letter will advise patients and family members that they will be contacted by phone by the research team to discuss their participation in the study, unless they return the postcard or inform their consultant that they do not wish to be contacted.

Participants will then be contacted by phone to discuss the study and to ascertain their interest in participating in the follow-up. If participants agree, a meeting will be arranged with two members of the research team, in the participants' own home, at a hospital or another location convenient to participants, and written consent will be obtained. In cases where significant cognitive deficits are suspected, either by the patient's GP or members of the research team conducting the follow-up phone calls, contact will be made with the patient's family member or carer, who will be requested to be present at the time of interview. The research team will attempt to carry out individual interviews with all patients. Assisted self-interviews, in which the participant can answer most of the questions but requires some help from a family member or carer, may also be used. This procedure has been used by follow-up waves of the Irish Longitudinal Study on Ageing.⁴⁴ If a participant is unable to complete an interview (cognitively or physically), the family member or carer will still be eligible to complete the family member/carer assessment.

Data analysis

Data will be analysed and reported using descriptive statistics, including means and SDs for normally distributed data, medians and IQRs for non-normally distributed data, and frequencies and percentages, as appropriate. Adjusted associations between medication (non-)adherence, (uncontrolled) cardiovascular risk factors and cognitive function will be assessed using multivariate

regression models. The predicted sample size of 180 and an estimated prevalence of cognitive impairment of 50% will permit the inclusion of ~9 variables in multivariate analyses.⁴⁵ Covariates that are associated with each outcome at the $p < 0.10$ level will be included in multivariate models. Agreement between measures of medication adherence will be assessed using the κ statistic.²⁶

ETHICS AND DISSEMINATION

Treatment of study participants

Participants will continue to receive standard care throughout the study period from their hospital consultant or GP. If participants become distressed or otherwise unwell during the interview or health assessment, the interview or assessment will be terminated immediately, and the interviewer will call back within 24 hours to see how the participant is. The family member/carer and GP or consultant will be informed that the patient became upset during the course of the interview and, if appropriate, that the patient would like to talk to a member of the medical team. Although potential harm is expected to be minimal, some participants may experience temporary and localised discomfort, mild pain or bruising as a result of venepuncture or blood pressure assessment.

Dissemination

Findings from this study will be disseminated through presentations in academic fora and to relevant policy-maker, practitioner and stakeholder audiences, and through peer-reviewed publications.

LIMITATIONS

This study has a number of limitations, including the reliance on self-report or carer report to ascertain usage of healthcare services. Unfortunately, owing to the complex system of public/private healthcare provision in Ireland, and the lack of universal patient identifiers, there is currently no alternative method available to collect this information. While every effort will be made to follow-up all patients still alive from the original study, patients with more severe cognitive decline may be more likely to be lost to follow-up, which could lead to an underestimation of the prevalence of cognitive impairment in this cohort. Since this is a follow-up study, the sample size will be based on the availability of participants, rather than a statistical power calculation. It is possible that the analyses for some associations of interest will be underpowered. While we will aim to assess and adjust for a number of known confounders, owing to the observational nature of this study, there may be other unknown or unmeasured confounding factors. However, given the fact that longer term follow-up studies of patients with stroke are relatively rare, and no such studies exist in Ireland, recalling this cohort provides a unique opportunity to explore longer term secondary prevention and cognitive function in patients with stroke.

CONCLUSION

Given the potential public health burden of cognitive impairment after stroke, identification of modifiable risk and protective factors to avert or delay cognitive decline is paramount. Delaying cognitive impairment could allow many individuals to reach the end of their natural lifespan before crossing the threshold for dementia.⁴⁶ While effective vascular risk factor management through secondary prevention may reduce the burden of post-stroke cognitive impairment,^{2 7 8} there is a lack of data on longer term treatment continuation and adherence rates in patients with stroke. Similarly, there are currently no Irish data on the costs of cognitive impairment or inadequate secondary prevention post-stroke. This study will provide valuable information on the trajectories of cognitive impairment, medication adherence and cardiovascular risk factors post-stroke, and will indicate how cognitive function and secondary prevention are related to each other, as well as to stroke or other cardiovascular event recurrence and healthcare usage, over time. These findings can help inform future health policy and service planning regarding the longer term management of patients with stroke.

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Contributors DR, DW, KB, EG, EC, ED, ML and AH conceived and designed the study. DR drafted and edited the manuscript. DW, KB, EG, EC, ED, ML and AH critically revised the manuscript. All authors approved the final draft.

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Ethics approval This study was approved by the Research Ethics Committees at Beaumont Hospital (ref. 16/26), Connolly Hospital Blanchardstown (28/11/2016) and the Royal College of Surgeons in Ireland (REC 1355).

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