PLOS ONE

RESEARCH ARTICLE

Cognitive impairment and medication adherence post-stroke: A five-year follow-up of the ASPIRE-S cohort

Daniela Rohde[1]*, Eva Gaynor[2], Margaret Large[3], Lisa Mellon[1], Kathleen Bennett[1], David J. Williams[4], Linda Brewer[4], Patricia Hall[3], Elizabeth Callaly[5], Eamon Dolan[6], Anne Hickey[1]

1 Division of Population Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland, **2** Department of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland, **3** Clinical Research Centre, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland, **4** Geriatric and Stroke Medicine, Royal College of Surgeons in Ireland and Beaumont Hospital, Dublin, Ireland, **5** Geriatric Medicine, Mater Misericordiae University Hospital, Dublin, Ireland, **6** Geriatric Medicine, Connolly Hospital, Dublin, Ireland

* danielamrohde@rcsi.ie

OPEN ACCESS

Citation: Rohde D, Gaynor E, Large M, Mellon L, Bennett K, Williams DJ, et al. (2019) Cognitive impairment and medication adherence post-stroke: A five-year follow-up of the ASPIRE-S cohort. PLoS ONE 14(10): e0223997. https://doi.org/10.1371/journal.pone.0223997

Editor: Anthony Pak-Hin Kong, University of Central Florida, UNITED STATES

Received: June 1, 2019

Accepted: October 2, 2019

Published: October 17, 2019

Data Availability Statement: Data are available upon request. Data are not publicly available due to ethical restrictions, as they contain potentially identifying and sensitive patient information. Ethical approval for this study, and patient informed consent, was provided on the basis that data would not be shared publicly. Data access requests may be sent to the study principal investigators Prof David Williams (david.williams@rcsi.ie) and Prof Anne Hickey (ahickey@rcsi.ie) and the Research Ethics Committee at the Royal College of Surgeons

Abstract

Background

Control of vascular risk factors is essential for secondary stroke prevention. However, adherence to secondary prevention medications is often suboptimal, and may be affected by cognitive impairment. Few studies to date have examined associations between cognitive impairment and medication adherence post-stroke, and none have considered whether adherence to secondary prevention medications might affect subsequent cognitive function. The aim of this study was to explore prospective associations between cognitive impairment and medication non-adherence post-stroke.

Methods

A five-year follow-up of 108 stroke survivors from the Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) prospective observational cohort study. Cognitive function was assessed using the Montreal Cognitive Assessment at 6 months, and a neuropsychological test battery at 5 years. Adherence to antihypertensive, antithrombotic and lipid-lowering medications was assessed using prescription refill data.

Results

The prevalence of cognitive impairment at five years was 35.6%. The prevalence of non-adherence ranged from 15.1% for lipid-lowering agents to 30.2% for antithrombotics. There were no statistically significant associations between medication non-adherence in the first year post-stroke and cognitive impairment at 5 years, nor between cognitive impairment at 6 months and non-adherence at 5 years. Stroke survivors with cognitive impairment were significantly more likely to report receiving help with taking medications [OR (95% CI): 4.84 (1.17, 20.07)].

in Ireland (recadmin@rcsi.ie), for researchers who meet the criteria for access to confidential data.

Funding: This work was supported by the Health Research Board (www.hrb.ie) [grant numbers SPHeRE2013/1, 1404/7400, and RL-15-1579 (to KB)], and the Irish Heart Foundation (www.irishheart.ie) [grant number 1296829 toEG]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: DW has served in the past as an advisory board member for Boehringer Ingelheim, Daiichi Sankyo, Bristol Myers Squibb, and Bayer, and has received personal fees for this outside the submitted work. DW received a speaker honorarium for Boehringer Ingelheim and has received personal fees for this outside the submitted work. All other authors report no conflicting interests. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

Conclusions

This is the first study to explore the potential impact of non-adherence to secondary prevention medications on cognitive impairment in stroke survivors. Findings highlight the role of family members and caregivers in assisting stroke survivors with medication administration, particularly in the context of deficits in cognitive function. Involving family members and caregivers may be a legitimate and cost-effective strategy to improve medication adherence in stroke survivors.

Introduction

Cognitive impairment is common post-stroke and can increase levels of disability and dependency, leading to a greater burden on caregivers and the healthcare system [1–4]. Approximately 10% of stroke survivors experience dementia [5], with an estimated 38% experiencing cognitive impairment that does not meet the criteria for dementia within 12 months post-stroke [6]. Cognitive impairment adversely impacts independence in activities of daily living and may affect the ability to adhere to medications to control secondary risk factors [7–9]. Vascular risk factors, including hypertension, dyslipidemia, and atrial fibrillation, are associated with an increased risk of cognitive impairment [8, 10, 11], while adequate risk factor control could significantly reduce this risk [12]. However, adherence to medications to control these risk factors is frequently sub-optimal [13].

Few studies to date have examined associations between cognitive impairment and medication adherence post-stroke, with a recent systematic review finding no association between cognitive impairment and adherence when all studies were pooled, although heterogeneity was significant and overall evidence quality was poor [14]. Given the variety of assessments of both medication adherence and cognitive impairment, it is difficult to compare findings across studies. Further, all studies to date have examined cognitive impairment as a predictor of medication non-adherence; whether adherence to secondary prevention medications might affect subsequent cognitive impairment remains unexplored [14]. Medication adherence consists of three distinct phases: initiation, implementation or persistence, and discontinuation or non-persistence [15], but which phase of adherence is being assessed is often not adequately reported. This study focused on the implementation phase of adherence, and assessed adherence using both self-report and prescription refill data in an attempt to better capture medication (non)adherence [16]. The main aims of this study were: 1) to explore the prospective association between cognitive impairment at six months and adherence to secondary prevention medications at five years post-stroke, and 2) to explore the prospective association between medication non-adherence at 12 months and cognitive impairment at five years post-stroke.

Materials and methods

Study design

This study involved a five-year follow-up of the Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) observational cohort study, which recruited acute ischemic stroke survivors in hospital and followed them up in the community six months later [17, 18]. The design and methods of this five-year follow-up have been described previously [19, 20].

Participants

All stroke survivors who were alive at five years were eligible to participate. Of 256 participants assessed at six months post-stroke, 63 (24.6%) died within five years, 57 (22.3%) opted out and 29 (11.3%) were not contactable, leaving 108 stroke survivors assessed at five years post-stroke (2016–2017) (Fig 1). The mean follow-up was 5.1 years (SD 0.4) from the index stroke event.

Data collection and analysis

Data were collected using a combination of face-to-face assessments either in participants' own homes or one of the participating hospitals, and self-completion questionnaires.

Cognitive assessments. Global cognitive function was assessed at six months and five years post-stroke using the Montreal Cognitive Assessment (MoCA), a 30-point screening tool that assesses several cognitive domains [21]. Concerns have been raised over the lack of specificity of the original cut-off (<26), with some authors recommending more conservative cut-offs (e.g., <24) [22–24].

In addition to the MoCA, cognitive impairment at five years was assessed using the National Institute of Neurological Disorders and Stroke (NINDS) 30-minute test battery [25], including Digit Symbol Coding (DSC) from the Wechsler Adult Intelligence Scale [26], Verbal and Letter Fluency from the Delis-Kaplan Executive Function System [27], Hopkins Verbal Learning Test (HVLT) [28], and Trail Making Test parts A and B (TMT-A, TMT-B) [29]. Raw test scores for each task were transformed into z-scores according to published age-, and where available, education-adjusted normative means and standard deviations [26, 27, 30, 31]. For each cognitive assessment, a composite z-score was calculated using equal weights; for example for TMT: 0.5*TMTA+ 0.5*TMTB [32]. A composite executive function z-score was then created using equal weights consisting of the composite TMT A/B, verbal/letter fluency and DSC. For patients who did not have all assessments available, the composite used z-scores

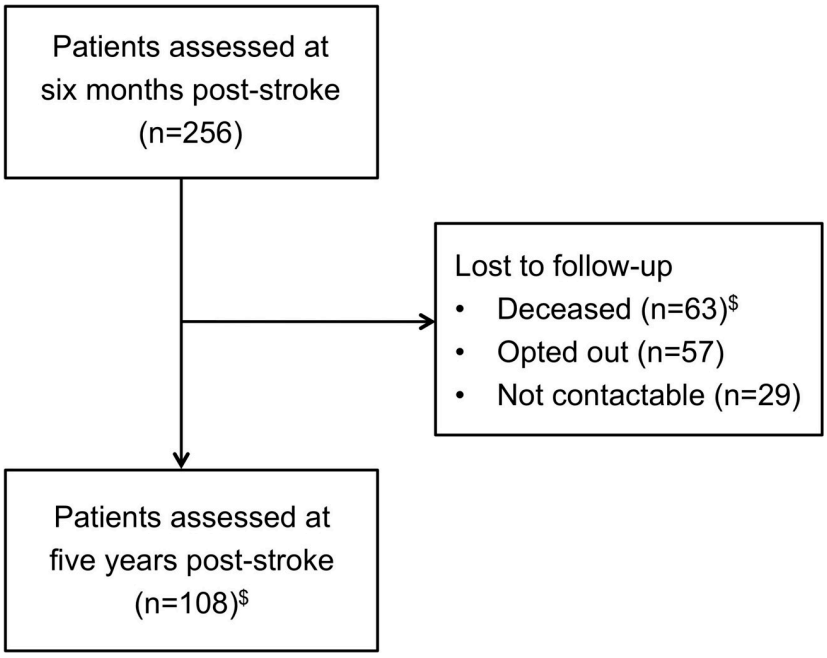

Fig 1. Flowchart of ASPIRE-S stroke survivors. $One participant was followed up at five years, but subsequently died before the end of the study period.

https://doi.org/10.1371/journal.pone.0223997.g001

from the completed assessments, e.g., category and letter fluency for patients who were visually impaired or unable to use a pen to complete TMT or DSC. Memory was assessed using HVLT total recall score. Patients were classified as cognitively impaired if they had evidence of impairment in at least one of the two domains according to scores 1.5SD below norms [31, 33, 34]. 102 of 108 stroke survivors followed up at five years completed the NINDS neuropsychological test battery; 6 participants were unable or unwilling to complete the assessments due to fatigue or severe cognitive, language, or functional impairments.

Medication adherence. Self-reported adherence at six months and five years post-stroke was assessed using the Medication Adherence Rating Scale (MARS-5) [35]. The MARS-5 consists of 5 items relating to medication-taking behaviour, including forgetting to take medications, or altering, skipping or missing doses. Respondents rate their own use of medications according to each item on a scale from 1 (very often) to 5 (never). Responses are summed to provide a total score, with higher scores indicating better self-reported adherence. Due to a ceiling effect, we used a cut-off of <25 to identify non-adherence [36, 37].

For stroke survivors with available data, medication adherence in the year following stroke was assessed using prescription refills. Data was extracted from the Irish Health Service Executive Primary Care Reimbursement Services (HSE-PCRS) pharmacy claims database. This database contains all monthly-dispensed medications for each individual eligible for the General Medical Services (GMS) reimbursement scheme, which includes access to free healthcare and a small co-payment for medicines. Further details of the HSE-PCRS are available elsewhere [19, 38]. We considered medications commonly used for secondary prevention of ischemic stroke, categorized according to three therapeutic groups: antihypertensives, antithrombotics (anticoagulant/antiplatelet), and lipid lowering medications [39, 40]. We assessed medication adherence according to the proportion of days covered (PDC) for the 12 months following the stroke event: the total number of days of medications supplied within each therapeutic class, divided by 365 [16]. A cut-off of $<80\%$ is commonly used to identify non-adherence in populations with cardiovascular disease and stroke, and was applied in this study [16, 41]. Medication adherence at five years post-stroke according to prescription refills was calculated in the same way, by considering the 12 months prior to the five-year follow-up assessment. Prescription refill data was available for 53 stroke survivors at five years. Missing data was due to participants' ineligibility for the GMS scheme, or failure to provide the necessary information to allow linkage between the HSE-PCRS and the ASPIRE-S databases.

Covariates. Stroke severity was assessed using the Scandinavian Stroke Scale [42]. TOAST (Trial of Org 10172 in Acute Stroke Treatment) [43] and Bamford [44] classifications of the index stroke event were collected as part of the original ASPIRE-S study. Functional disability at 6 months post-stroke was assessed using the modified Rankin Scale (mRS) [45] with a cut-off of ≥ 3 to identify stroke survivors with moderate to severe functional disability [46]. Depressive symptoms at five years were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), with a cut-off of ≥ 16 to identify depressive symptoms [47]. The Frenchay Aphasia Screening Test (short form) (FAST) [48] was used at both six months and five years post-stroke to screen for communication difficulties that may affect performance on cognitive assessments. Clinical measures collected at both six month and five years post-stroke included blood pressure, lipid profiles, fasting glucose levels, weight, history of stroke/TIA, history of heart disease, history of carotid stenosis and presence of atrial fibrillation. Vascular risk factors were classified according to European secondary prevention targets [49]. Given the number of vascular risk factors, the Essen Stroke Risk Score (ESRS), a 10-point scale designed to predict 1-year risk of recurrent stroke and cardiovascular events [50–52], was calculated and included in multivariate analyses. Medication self-administration was ascertained by a single question asking stroke survivors whether they received help with medication taking.

Ethical considerations. All procedures performed in this study were in accordance with ethical standards of the institutional research committees and with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all individual participants included in the study. This study followed the UK Medical Research Council (MRC) guidelines for research involving adults who cannot consent [53], and the Irish National Consent Policy [54]. According to both guidelines, every potential participant should be presumed to have the capacity to make decisions about participation in research, unless there is sufficient reason to question this presumption. The policies suggest that the possibility of incapacity and the need to formally assess capacity should be considered only if, having been given all appropriate help and support, an individual is unable to communicate a clear and consistent choice, or is obviously unable to understand and use the information and choices provided. If the person was deemed, either by their general practitioner, their family member or carer, or the member of the research team conducting the study, to lack the capacity to consent, agreement to include them in the study was sought from a relative or carer [53]. If the relative or carer advised that the person in question would not want to take part in the study, that person was not recruited. In addition, participants who indicated any unwillingness or objection to participation in the study were not recruited [53]. This procedure was approved by the research ethics committees at Beaumont Hospital (REC number: 16/26), Mater Misericordiae University Hospital (REC number: 1/378/1855), Connolly Hospital Blanchardstown (REC number: 28/11/2016), and the Royal College of Surgeons in Ireland (REC number: 1355).

Data analysis

Descriptive statistics are presented using frequencies and percentages. Univariate associations between demographic and clinical variables and cognitive impairment/medication adherence were explored using chi-square and t-tests as appropriate. Associations between cognitive impairment and medication adherence were explored using logistic regression models, adjusted for age, sex, and stroke severity and Essen stroke risk score. Odds ratios (OR) and 95% confidence intervals (CI) are reported. To maximize available data, pairwise deletion of missing data was used. Sensitivity analyses were conducted excluding stroke survivors with possible aphasia. Agreement between medication non-adherence according to prescription refills and self-report was assessed using the kappa statistic. We evaluated the predictive values of MoCA cut-offs (<26 and <24) for cognitive impairment according to the NINDS battery using a receiver operating characteristic (ROC) curve analysis [55]. Data were analyzed using Stata version 13.0 [56].

Results

Demographic, cognitive and medication adherence profiles of stroke survivors at five years post-stroke are presented in Table 1. Thirty-six stroke survivors (35.6%) had evidence of cognitive impairment at five years according to the NINDS battery. When survivors with probable aphasia were excluded, 28.3% had evidence of cognitive impairment. For cognitive and medication adherence profiles of stroke survivors at five years post-stroke according to sex, please see S1 Table in the Supporting Information. At five years post-stroke, MoCA scores <26 had a sensitivity of 94.4% and specificity of 56.9% for cognitive impairment according to the more detailed NINDS test battery in our sample (AUROC 0.757), while the cut-off of <24 substantially increased specificity (78.1%), with a sensitivity of 88.2% (AUROC 0.832).

Table 2 displays the demographic and clinical profile of ASPIRE-S stroke survivors by cognitive status according to the NINDS 30-minute test battery at five years post-stroke. Older age, impaired fasting glucose, history of carotid stenosis, previous or recurrent stroke/TIA and higher Essen Stroke Risk Score at five years were associated with significantly increased

Table 1. Demographic, cognitive, and medication adherence profiles of stroke survivors at five years post-stroke.

Demographics		**N (%)**
Sex (n = 108)	Male	73 (67.6)
	Female	35 (32.4)
Marital status (n = 101)	Married/cohabiting	65 (64.4)
	Single/widowed/divorced	36 (35.6)
Living arrangements (n = 100)	Living alone	26 (26.0)
	Living with others	71 (71.0)
	Nursing home resident	3 (3.0)
Occupational status (n = 94)	Working full-time or part-time	18 (19.2)
	Not working	76 (80.9)
Education (n = 98)	Primary school	31 (31.6)
	Secondary school	42 (42.9)
	Third level	25 (25.5)
Cognitive impairment		**Impaired N (%)**
Memory (n = 100)	HVLT total recall	23 (23.0)
Executive function (n = 102)	Semantic fluency	22 (21.6)
	Letter fluency	28 (27.5)
	Digit symbol coding (n = 96)	31 (32.3)
	Trail Making Test–A (n = 93)	14 (15.1)
	Trail Making Test–B (n = 92)	23 (25.0)
	Composite executive function	24 (23.8)
Impaired in both NINDS domains (n = 102)		11 (10.8)
Impaired in at least one NINDS domain (n = 102)		36 (35.6)
MoCA <24 (n = 101)		46 (45.5)
Medication adherence		**Non-adherent N (%)**
Prescription refills (PDC<80%) (n = 53)	Lipid modifiers	8 (15.1%)
	Antithrombotics	16 (30.2%)
	Antihypertensives	12 (22.6%)
Self-report (MARS) (n = 95)		51 (53.7%)

NINDS: National Institute of Neurological Disorders and Stroke. MoCA: Montreal Cognitive Assessment. MARS: Medication Adherence Report Scale.

https://doi.org/10.1371/journal.pone.0223997.t001

likelihood of cognitive impairment at five years post-stroke. For demographic and clinical profiles of ASPIRE-S stroke survivors by medication adherence status at five years post-stroke, please see S2 Table in the Supporting Information. Stroke survivors with evidence of cognitive impairment at five years were also significantly more likely to receive help with taking medications [aOR (95% CI): 4.84 (1.17, 20.07)] (Table 3).

Non-adherence at five years according to prescription refills ranged from 15.1% for lipid lowering agents to 30.2% for antithrombotic medications. Poor self-reported adherence was noted in 53.7% of stroke survivors (Table 1). Agreement between self-report and prescription refills was poor: 56.3% for antithrombotic medications (kappa 0.125), 54.2% for lipid modifying medications (kappa 0.083), and 52.1% for antihypertensive medications (kappa 0.042). A higher proportion of adherent stroke survivors reported that they received help with taking medications than did non-adherent individuals, although these results were not statistically significant (Table 3).

Table 2. Demographic and clinical profile of ASPIRE-S stroke survivors at six months post-stroke by cognitive status (NINDS) at five years.

Demographics, index stroke characteristics and clinical risk factors at five years		Not impaired	Cognitive impairment	*p*
		N (%)		
Demographics @ 5 years	Age (Mean, SD)	66.2 (12.3)	73.2 (11.9)	.006**
	Male	47 (71.2)	22 (61.1)	.297
	Married (vs. not married)	45 (71.4)	17 (50.0)	.036*
TOAST classification	Large artery artherosclerosis	10 (15.2)	8 (22.2)	.364
	Cardioembolism	20 (30.3)	15 (41.7)	
	Small vessel occlusion	11 (16.7)	4 (11.1)	
	Other	25 (37.9)	9 (25.0)	
Bamford classification	Total anterior circulation stroke	4 (6.1)	2 (5.6)	.901
	Partial anterior circulation stroke	22 (33.3)	15 (41.7)	
	Posterior circulation syndrome	21 (31.8)	9 (25.0)	
	Lacunar syndrome	18 (27.3)	9 (25.0)	
	Unclassifiable	1 (1.5)	1 (2.8)	
Stroke severity	Moderate or severe	9 (13.6)	5 (13.9)	.972
Disability @ 6 months	Moderate or severe	9 (13.6)	5 (13.9)	.972
Vascular risk factors @ 5 years	Hypertension	42 (63.6)	25 (69.4)	.555
	Elevated total cholesterol	20 (30.3)	9 (25.7)	.628
	Impaired fasting glucose	8 (12.1)	10 (29.4)	.033*
	Overweight/obese	50 (76.9)	24 (70.6)	.491
	Smoker	12 (18.2)	4 (11.1)	.348
	History of alcohol abuse	14 (21.2)	10 (27.8)	.455
	Previous or recurrent stroke/TIA	12 (18.2)	15 (41.7)	.010*
	History of heart disease	20 (30.3)	14 (38.9)	.379
	History of carotid stenosis	8 (12.1)	10 (27.8)	.047*
	History of atrial fibrillation	28 (42.4)	14 (38.9)	.729
	Essen Stroke Risk Score (M, SD)	2.4 (1.3)	3.4 (1.7)	< .001***
Depression @ 5 years	Depressive symptoms	13 (20.6)	13 (38.2)	.062

*$p < .05$,
**$p < .01$,
***$p < .001$.

https://doi.org/10.1371/journal.pone.0223997.t002

Medication non-adherence and cognitive impairment

There were no statistically significant associations between non-adherence to any of the three medications in the first year and cognitive impairment at five years (Table 4). The exclusion of 7 individuals with probable aphasia did not greatly change these effect estimates. Similarly, there were no statistically significant associations between cognitive impairment at six months and non-adherence to lipid modifiers or antihypertensive medications at five years (Table 5). Cognitive impairment at six months post-stroke was associated with significantly reduced likelihood of non-adherence to antithrombotic medications at five years post-stroke [OR (95% CI): 0.14 (0.02, 0.90)]; however, when 3 stroke survivors with probable aphasia were excluded, this association was no longer statistically significant [OR (95% CI): 0.16 (0.02, 1.12)]. Stroke survivors with cognitive impairment at six months were 5 times more likely to report receiving help with medication taking at five years [OR (95% CI): 5.19 (1.21, 22.22)] (Table 3).

Table 3. Adjusted Odds ratios (95% CIs) for help received with taking medications at 5 years and cognitive impairment and medication adherence.

			Self-administers N (%)	Receives help N (%)	aOR (95% CI)	*p*
Cognitive impairment	At 5 years (NINDS)	Not impaired	54 (88.5)	7 (11.5)	4.84 (1.17, 20.07)*	.030
		Impaired	21 (61.8)	13 (38.2)		
	At 6 months (MoCA)	Not impaired	60 (92.3)	5 (7.7)	5.19 (1.21, 22.22)*	.027
		Impaired	14 (53.9)	12 (46.2)		
Medication adherence at 5 years	Lipid modifiers (refills)	Adherent	28 (70.0)	12 (30.0)	1.39 (0.15, 12.54)	.767
		Non-adherent	6 (75.0)	2 (25.0)		
	Antithrombotics (refills)	Adherent	24 (68.6)	11 (31.4)	0.57 (0.10, 3.16)	.516
		Non-adherent	10 (76.9)	3 (23.1)		
	Antihypertensives (refills)	Adherent	26 (66.7)	13 (33.3)	0.36 (0.03, 4.08)	.410
		Non-adherent	8 (88.9)	1 (11.1)		
	MARS (self-report)	Adherent	32 (72.7)	12 (27.3)	0.66 (0.18, 2.42)	.533
		Non-adherent	44 (86.3)	7 (13.7)		

*$p < .05$. aOR adjusted for age, sex, stroke severity

https://doi.org/10.1371/journal.pone.0223997.t003

Discussion

This study found no statistically significant associations between cognitive impairment assessed at six months post-stroke and medication non-adherence at five years, which is in line with the findings from a recent meta-analysis [14]. Previous research on the association between cognitive impairment and medication adherence in stroke survivors has considered cognitive impairment as one of a range of potential predictors of poor adherence, with discordant findings [14]. This is, to our knowledge, the first study to explore the potential impact of non-adherence to secondary prevention medications on subsequent cognitive impairment in stroke survivors. There were no statistically significant associations between non-adherence to antihypertensives or lipid lowering agents in the first year post-stroke and cognitive impairment at five years. While cognitive impairment at six months post-stroke was associated with significantly reduced likelihood of non-adherence to antithrombotic medications at five years, this association was no longer statistically significant when stroke survivors with evidence of aphasia were excluded.

These effect estimates suggest that stroke survivors with cognitive impairment at six months post-stroke may be more likely to have good adherence to medications at five years, although

Table 4. Adjusted ORs (95% CI) for medication non-adherence at 6 months and cognitive impairment at 5 years.

Non-adherence at 6 months		Cognitive impairment at 5 years aOR (95% CI)[a]							
		Including stroke survivors with probable aphasia				excluding stroke survivors with probable aphasia (n = 7)			
		NINDS	*p*	MoCA	*p*	NINDS	*p*	MoCA	*p*
Prescription refills (PDC<80%)	Lipid modifiers	3.31 (0.35, 31.46)	.298	1.67 (0.17, 16.64)	.664	3.53 (0.34, 37.14)	.293	2.99 (0.21, 42.05)	.416
	Antihypertensives	0.57 (0.07, 4.34)	.583	0.69 (0.09, 5.28)	.718	0.25 (0.02, 3.34)	.298	0.38 (0.04, 3.64)	.402
	Antithrombotics	0.93 (0.19, 4.62)	.928	1.41 (0.23, 8.79)	.713	0.99 (0.16, 6.11)	.995	1.46 (0.20, 10.78)	.713
Self-report	MARS	1.12 (0.45, 2.75)	.814	0.62 (0.57, 1.54)	.307	1.62 (0.57, 4.62)	.366	0.81 (0.30, 2.15)	.666

[a]adjusted for age, sex, stroke severity, Essen stroke risk score.

https://doi.org/10.1371/journal.pone.0223997.t004

Table 5. Adjusted ORs (95% CI) for cognitive impairment at 6 months and medication non-adherence at 5 years.

Cognitive impairment at six months post-stroke (MoCA<24)	Non-adherence at five years post-stroke aOR (95% CI)				
	Including stroke survivors with probable aphasia			Excluding stroke survivors with probable aphasia (n = 3)	
	Prescription refills		*p*	Prescription refills	*p*
	Lipid modifiers [a]	0.09 (0.01, 1.67)	.104	0.09 (0.01, 1.88)	.121
	Antihypertensives [b]	0.38 (0.07, 2.25)	.289	0.48 (0.08, 3.03)	.436
	Antithrombotics [a]	0.14 (0.02, 0.90)	.038*	0.16 (0.02, 1.12)	.064
	Self-report		*p*	Self-report	*p*
	MARS	0.78 (0.27, 2.25)	.644	0.80 (0.26, 2.48)	.702

[a]adjusted for age, sex, stroke severity, Essen stroke risk score.

[b]due to collinearity with stroke severity, this model is adjusted for age, sex, Essen stroke risk score only.

*$p < .05$.

https://doi.org/10.1371/journal.pone.0223997.t005

this is speculative as results were not statistically significant and should be interpreted with caution. A larger, adequately powered study would be needed to further explore this potential finding. It is important to note that stroke survivors with evidence of cognitive impairment were significantly more likely to report receiving help with taking medications, which might explain the direction of these effects. Our findings highlight the important role of family members and caregivers in assisting stroke survivors with medication administration [57], particularly in the context of cognitive impairment [58, 59].

We found that 35.6% of stroke survivors at five years had evidence of cognitive impairment according to a neuropsychological test battery, while 45.5% were categorized as impaired according to the MoCA. Previous research has reported evidence of cognitive impairment according to the MoCA in 84% of stroke survivors at 4 years [60] and in 61% of stroke survivors at 10 years post-stroke [61]. Differences in these estimates may be explained by the use of different cut-offs; using the originally recommended cut off of <26 on the MoCA, the prevalence of cognitive impairment at five years post-stroke in our sample was 62.9%. While the MoCA was designed as a screening tool, the NINDS battery may present a more robust estimate of cognitive impairment, which is in line with the reported prevalence of cognitive impairment of 38% at 12 months post-stroke according to a recent meta-analysis [6].

Previous estimates of medication adherence have been heterogeneous, with a meta-analysis of stroke survivors reporting a pooled rate of non-adherence of 30.9% [13]. One of the difficulties in medication adherence research is the absence of a gold standard measure and the related problem of the wide range of definitions and measures used, which make comparisons between studies difficult [62]. We found poor levels of agreement between self-reported and prescription refill adherence, which is in contrast to a recent study of Iranian stroke survivors [63]. However, that study considered the MARS as a continuous variable and excluded patients with moderate to severe levels of cognitive impairment [63]. Using a cut-off of <25 to identify poor self-reported adherence in our study may have led to an overestimate of non-adherence. A cut-off of <24 would classify 23.2% of our sample as non-adherent, which although more in line with the prescription refill estimates, would not have improved levels of agreement between the two measures of adherence. As self-report measures can be affected by social desirability and recall biases, which could be especially problematic in the context of cognitive impairment [16], we used the higher cut-off. However, objective assessments of adherence are

likely to be more appropriate in stroke populations, which are characterized by higher levels of cognitive impairment and complex medication regimens.

A fifth of our sample reported receiving help with medication taking. A recent UK survey reported that more than half of stroke survivors living in the community were receiving some help with taking medications, including help with collecting and filling prescriptions and opening pill boxes [57]. Our single question may not have captured all of the ways in which stroke survivors may receive assistance with taking medications, which might explain these differences. Given the prevalence of non-adherence to secondary prevention medications after stroke, interventions to improve adherence have the potential to significantly improve stroke outcomes. However, a number of systematic reviews have noted that interventions to improve adherence in stroke survivors have generally lacked effectiveness [40, 62]. An important point to consider when developing and testing interventions is the extent to which family members or caregivers assist with medication taking, as a sizeable proportion of stroke survivors receive some assistance, particularly where there is cognitive impairment. Caregiver-related factors, including caregiver self-efficacy, cognitive functioning, and health knowledge, may also be associated with medication adherence [64]. Involving both stroke survivors and family members or caregivers could therefore improve the effectiveness of interventions to increase medication adherence.

Strengths and limitations

This study has a number of strengths, including the length of follow-up, the use of prescription refill data as an objective measure of adherence and a neuropsychological test battery as a more robust assessment of cognitive impairment. Prescription refills present an efficient and objective method for calculating medication adherence estimates that are comparable to electronic measures, and may be more reliable than patient self-report [38, 41]. The majority of previous studies reporting on the association between cognitive impairment and medication adherence in stroke have not included information on whether medications were self-administered, and our results highlight the importance of considering help received with medication taking, particularly in the context of cognitive impairment.

There were a number of limitations. We previously reported that stroke survivors with cognitive impairment at six months post-stroke were more likely to have died within the follow-up period [20]. Additionally, stroke survivors who were lost to the 5-year ASPIRE-S follow-up were more likely to be older, female, and to have evidence of cognitive impairment and moderate to severe disability at 6 months post-stroke [9], suggesting that the prevalence of cognitive impairment reported here is likely to be underestimated. This reflects longitudinal stroke studies internationally, which have similarly suggested that rates of poor outcomes may be underestimated in longer-term follow-ups, as those with more severe strokes die or are lost to follow-up [55, 65]. Although efforts were made to follow-up every individual from the original study still alive at five years, those with more severe cognitive impairments and dementia are likely to be under-represented. The associations between cognitive impairment and outcomes reported here are therefore also likely to be underestimated. Given that only three of the ASPIRE-S stroke survivors who were followed up at five years post-stroke were living in long-term care facilities, nursing home residents are also likely to be under-represented in the ASPIRE-S follow-up study.

We were unable to include help with medication taking in multivariate models due to small numbers and issues with collinearity. The sample size limited the number of potential confounders that could be included in multivariate models and led to a lack of statistical power for detecting statistically significant associations between cognitive impairment and medication

adherence. Therefore, this study could not provide a definitive answer on whether or not cognitive impairment is associated with adherence to secondary prevention medications in stroke survivors. Future research should examine associations between cognitive impairment and medication adherence in stroke survivors using a larger sample and longer follow-up period.

Prescription refill data were available for half of our sample. The GMS reimbursement scheme comprises 40% of the population of Ireland; however, owing to the scheme's eligibility criteria, older adults and those who are socially disadvantaged are over-represented. While over 90% of those aged over 70 are entitled to the scheme, less than 50% of the population under 70 years is eligible [38]. In our sample, 51 of the stroke survivors followed up at five years were under 70 years of age; therefore, medication adherence estimates based on prescription refill data may not be generalizable to younger patients or those from higher socioeconomic groups.

Conclusion

This study found no statistically significant associations between cognitive impairment and medication adherence post-stroke. Given the difficulties in synthesizing medication adherence research, there is a need to standardize assessment and reporting of medication adherence, ideally using objective methods. Stroke survivors with evidence of cognitive impairment are significantly more likely to receive help with medication taking, which should be taken into account in future studies of medication adherence post-stroke. Involving family members and caregivers may be a legitimate and cost-effective strategy to improve medication adherence in stroke survivors.

Supporting information

S1 Table. Cognitive impairment, medication adherence, and depressive symptoms at five years post-stroke by sex.
(DOCX)

S2 Table. Demographic and clinical profiles of ASPIRE-S stroke survivors by medication adherence status at five years post-stroke.
(DOCX)

S3 Table. STROBE checklist.
(DOC)

Acknowledgments

The authors would like to thank all participants for taking part in this research.

Author Contributions

Conceptualization: Daniela Rohde, Lisa Mellon, Kathleen Bennett, David J. Williams, Anne Hickey.

Data curation: Daniela Rohde, Eva Gaynor, Lisa Mellon, Kathleen Bennett, Linda Brewer, Patricia Hall.

Formal analysis: Daniela Rohde, Kathleen Bennett.

Funding acquisition: Eva Gaynor, Kathleen Bennett, Anne Hickey.

Investigation: Daniela Rohde, Eva Gaynor, Margaret Large, Lisa Mellon, Linda Brewer, Patricia Hall, Eamon Dolan, Anne Hickey.

Methodology: Daniela Rohde, Lisa Mellon, Kathleen Bennett, Linda Brewer, Anne Hickey.

Project administration: Daniela Rohde, Eva Gaynor, Margaret Large, Lisa Mellon, Linda Brewer, Patricia Hall, Elizabeth Callaly, Eamon Dolan.

Resources: Daniela Rohde, David J. Williams, Elizabeth Callaly, Eamon Dolan, Anne Hickey.

Supervision: Kathleen Bennett, David J. Williams, Anne Hickey.

Writing – original draft: Daniela Rohde.

Writing – review & editing: Daniela Rohde, Eva Gaynor, Margaret Large, Lisa Mellon, Kathleen Bennett, David J. Williams, Linda Brewer, Patricia Hall, Elizabeth Callaly, Eamon Dolan, Anne Hickey.

References

1. Brainin M, Tuomilehto J, Heiss WD, Bornstein NM, Bath PM, Teuschl Y, et al. Post-stroke cognitive decline: an update and perspectives for clinical research. Eur J Neurol. 2015; 22(2):229–38, e13-6. Epub 2014/12/11. https://doi.org/10.1111/ene.12626 PMID: 25492161.
2. Atteih S, Mellon L, Hall P, Brewer L, Horgan F, Williams D, et al. Implications of stroke for caregiver outcomes: findings from the ASPIRE-S study. International journal of stroke: official journal of the International Stroke Society. 2015; 10(6):918–23. Epub 2015/06/11. https://doi.org/10.1111/ijs.12535 PMID: 26061711.
3. Black CM, Ritchie CW, Khandker RK, Wood R, Jones E, Hu X, et al. Non-professional caregiver burden is associated with the severity of patients' cognitive impairment. PloS one. 2018; 13(12):e0204110. Epub 2018/12/07. https://doi.org/10.1371/journal.pone.0204110 PMID: 30521532; PubMed Central PMCID: PMC6283568 following competing interests. Christopher M. Black, Rezaul K. Khandker, Xiaohan Hu, Baishali M. Ambegaonkar, are all current or previous employees of Merck & Co who funded the research. Robert Wood and Eddie Jones are employees of Adelphi Real World which was paid by Merck for conducting the research. Craig W. Ritchie, received consultancy fees from Merck. This does not alter our adherence to PLOS ONE policies on sharing data and materials.
4. Blomgren C, Samuelsson H, Blomstrand C, Jern C, Jood K, Claesson L. Long-term performance of instrumental activities of daily living in young and middle-aged stroke survivors-Impact of cognitive dysfunction, emotional problems and fatigue. PloS one. 2019; 14(5):e0216822. Epub 2019/05/17. https://doi.org/10.1371/journal.pone.0216822 PMID: 31095631.
5. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. The Lancet Neurology. 2009; 8(11):1006–18. Epub 2009/09/29. https://doi.org/10.1016/S1474-4422(09)70236-4 PMID: 19782001.
6. Sexton E, McLoughlin A, Merriman NA, Donnelly NA, Rohde D, Wren M-A, et al. Systematic review and meta-analysis of the prevelance of Cognitive Impairment No Dementia (CIND) in the first year post-stroke. European Stroke Journal. 2019. https://doi.org/10.1177/2396987318825484 PMID: 31259264
7. Institute of Medicine. Cognitive aging: Progress in understanding and opportunities for action. Washington DC: The National Academies Press, 2015.
8. Ligthart SA, Moll van Charante EP, Van Gool WA, Richard E. Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review. Vascular health and risk management. 2010; 6:775–85. Epub 2010/09/23. https://doi.org/10.2147/vhrm.s7343 PMID: 20859546; PubMed Central PMCID: PMC2941788.
9. Rohde D, Gaynor E, Large M, Mellon L, Hall P, Brewer L, et al. The impact of cognitive impairment on poststroke outcomes: A 5-year follow-up. Journal of geriatric psychiatry and neurology. 2019. https://doi.org/10.1177/0891988719853044 PMID: 31167593
10. Unverzagt FW, McClure LA, Wadley VG, Jenny NS, Go RC, Cushman M, et al. Vascular risk factors and cognitive impairment in a stroke-free cohort. Neurology. 2011; 77(19):1729–36. Epub 2011/11/10. https://doi.org/10.1212/WNL.0b013e318236ef23 PMID: 22067959; PubMed Central PMCID: PMC3208949.
11. Peng M, Chen G, Tang KL, Quan H, Smith EE, Faris P, et al. Blood pressure at age 60–65 versus age 70–75 and vascular dementia: a population based observational study. BMC Geriatr. 2017; 17(1):252.

Epub 2017/10/29. https://doi.org/10.1186/s12877-017-0649-3 PMID: 29078750; PubMed Central PMCID: PMC5658926.

12. Douiri A, McKevitt C, Emmett ES, Rudd AG, Wolfe CD. Long-term effects of secondary prevention on cognitive function in stroke patients. Circulation. 2013; 128(12):1341–8. Epub 2013/08/13. https://doi.org/10.1161/CIRCULATIONAHA.113.002236 PMID: 23935013.

13. Al AlShaikh S, Quinn T, Dunn W, Walters M, Dawson J. Predictive factors of non-adherence to secondary preventative medication after stroke or transient ischaemic attack: A systematic review and meta-analyses. European Stroke Journal. 2016; 1(2):65–75. https://doi.org/10.1177/2396987316647187 PMID: 29900404

14. Rohde D, Merriman NA, Doyle F, Bennett K, Williams D, Hickey A. Does cognitive impairment impact adherence? A systematic review and meta-analysis of the association between cognitive impairment and medication non-adherence in stroke. PloS one. 2017; 12(12):e0189339. Epub 2017/12/09. https://doi.org/10.1371/journal.pone.0189339 PMID: 29220386; PubMed Central PMCID: PMC5722379.

15. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. British journal of clinical pharmacology. 2012; 73 (5):691–705. Epub 2012/04/11. https://doi.org/10.1111/j.1365-2125.2012.04167.x PMID: 22486599; PubMed Central PMCID: PMC3403197.

16. Kronish IM, Ye S. Adherence to cardiovascular medications: lessons learned and future directions. Prog Cardiovasc Dis. 2013; 55(6):590–600. Epub 2013/04/30. https://doi.org/10.1016/j.pcad.2013.02.001 PMID: 23621969; PubMed Central PMCID: PMC3639439.

17. Brewer L, Mellon L, Hall P, Dolan E, Horgan F, Shelley E, et al. Secondary prevention after ischaemic stroke: the ASPIRE-S study. BMC neurology. 2015; 15:216. Epub 2015/10/27. https://doi.org/10.1186/s12883-015-0466-2 PMID: 26492943; PubMed Central PMCID: PMC4619229.

18. Mellon L, Brewer L, Hall P, Horgan F, Williams D, Hickey A, et al. Cognitive impairment six months after ischaemic stroke: A profile from the ASPIRE-S study. BMC Neurology. 2015; 15(31).

19. Rohde D, Williams D, Gaynor E, Bennett K, Dolan E, Callaly E, et al. Secondary prevention and cognitive function after stroke: a study protocol for a 5-year follow-up of the ASPIRE-S cohort. BMJ open. 2017; 7(3):e014819. Epub 2017/03/30. https://doi.org/10.1136/bmjopen-2016-014819 PMID: 28348196.

20. Gaynor E, Rohde D, Large M, Mellon L, Hall P, Brewer L, et al. Cognitive Impairment, Vulnerability, and Mortality Post Ischemic Stroke: A Five-Year Follow-Up of the Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) Cohort. Journal of Stroke and Cerebrovascular Diseases. 2018; 27(9):2466–73. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.05.002 PMID: 29803601

21. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53(4):695–9. Epub 2005/04/09. https://doi.org/10.1111/j.1532-5415.2005.53221.x PMID: 15817019.

22. Waldron-Perrine B, Axelrod BN. Determining an appropriate cutting score for indication of impairment on the Montreal Cognitive Assessment. Int J Geriatr Psychiatry. 2012; 27(11):1189–94. Epub 2012/01/10. https://doi.org/10.1002/gps.3768 PMID: 22228412.

23. Coen RF, Cahill R, Lawlor BA. Things to watch out for when using the Montreal cognitive assessment (MoCA). Int J Geriatr Psychiatry. 2011; 26(1):107–8. Epub 2010/12/16. https://doi.org/10.1002/gps.2471 PMID: 21157857.

24. Luis CA, Keegan AP, Mullan M. Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US. Int J Geriatr Psychiatry. 2009; 24(2):197–202. https://doi.org/10.1002/gps.2101 PMID: 18850670

25. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke. 2006; 37(9):2220–41. Epub 2006/08/19. https://doi.org/10.1161/01.STR.0000237236.88823.47 PMID: 16917086.

26. Wechsler D. Wechsler Adult Intelligence Scale (WAIS-III). 3rd ed. San Antonio, TX:: Harcourt Assessment; 1997.

27. Delis DC, Kaplan E, Kramer JH. The Delis- Kaplan Executive Function System. San Antonio: The Psychological Corporation; 2001.

28. Brandt J. The hopkins verbal learning test: Development of a new memory test with six equivalent forms. Clinical Neuropsychologist. 1991; 5(2):125–42. https://doi.org/10.1080/13854049108403297

29. Reitan RM. Validity of the Trail Making Test as an Indicator of Organic Brain Damage. Perceptual and Motor Skills. 1958; 8(3):271–6. https://doi.org/10.2466/pms.1958.8.3.271

30. Hester RL, Kinsella GJ, Ong B, Turner M. Hopkins Verbal Learning Test: Normative data for older Australian adults. Australian Psychologist. 2004; 39(3):251–5.

31. Nakling AE, Aarsland D, Næss H, Wollschlaeger D, Fladby T, Hofstad H, et al. Cognitive Deficits in Chronic Stroke Patients: Neuropsychological Assessment, Depression, and Self-Reports. Dementia and Geriatric Cognitive Disorders Extra. 2017; 7(2):283–96. https://doi.org/10.1159/000478851 PMID: 29033974

32. Harrison JE, Lophaven S, Olsen CK. Which Cognitive Domains are Improved by Treatment with Vortioxetine? The international journal of neuropsychopharmacology. 2016; 19(10):pyw054. Epub 2016/05/28. https://doi.org/10.1093/ijnp/pyw054 PMID: 27231256; PubMed Central PMCID: PMC5091828.

33. Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MoCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and stroke. Stroke. 2012; 43(2):464–9. Epub 2011/12/14. https://doi.org/10.1161/STROKEAHA.111.633586 PMID: 22156700.

34. Barbay M, Taillia H, Nedelec-Ciceri C, Bompaire F, Bonnin C, Varvat J, et al. Prevalence of Poststroke Neurocognitive Disorders Using National Institute of Neurological Disorders and Stroke-Canadian Stroke Network, VASCOG Criteria (Vascular Behavioral and Cognitive Disorders), and Optimized Criteria of Cognitive Deficit. Stroke. 2018; 49(5):1141–7. Epub 2018/04/13. https://doi.org/10.1161/STROKEAHA.117.018889 PMID: 29643258.

35. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology & health. 1999; 14(1):1–24. https://doi.org/10.1080/08870449908407311

36. Lee CS, Tan JHM, Sankari U, Koh YLE, Tan NC. Assessing oral medication adherence among patients with type 2 diabetes mellitus treated with polytherapy in a developed Asian community: a cross-sectional study. BMJ open. 2017; 7(9):e016317. Epub 2017/09/16. https://doi.org/10.1136/bmjopen-2017-016317 PMID: 28912194; PubMed Central PMCID: PMC5640112.

37. Brewer L. Profile of cardiovascular risk factors at six months post ischaemic stroke in Dublin: the ASPIRE-S study. Dublin, Ireland: Royal College of Surgeons in Ireland; 2014.

38. Sinnott SJ, Bennett K, Cahir C. Pharmacoepidemiology resources in Ireland-an introduction to pharmacy claims data. Eur J Clin Pharmacol. 2017; 73(11):1449–55. Epub 2017/08/19. https://doi.org/10.1007/s00228-017-2310-7 PMID: 28819675; PubMed Central PMCID: PMC5662670.

39. Rohde D, Hickey A, Williams D, Bennett K. Cognitive impairment and cardiovascular medication use: Results from wave 1 of The Irish Longitudinal Study on Ageing. Cardiovascular therapeutics. 2017; 35 (6). Epub 2017/08/25. https://doi.org/10.1111/1755-5922.12300 PMID: 28836733.

40. Al AlShaikh S, Quinn T, Dunn W, Walters M, Dawson J. Multimodal Interventions to Enhance Adherence to Secondary Preventive Medication after Stroke: A Systematic Review and Meta-Analyses. Cardiovascular therapeutics. 2016; 34(2):85–93. Epub 2016/01/29. https://doi.org/10.1111/1755-5922.12176 PMID: 26820710.

41. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009; 119(23):3028–35. Epub 2009/06/17. https://doi.org/10.1161/CIRCULATIONAHA.108.768986 PMID: 19528344.

42. Lindenstrøm E, Boysen G, Waage CL, à Rogvi Hansen B, Würtzen Nielsen P. Reliability of Scandinavian Neurological Stroke Scale. Cerebrovascular diseases (Basel, Switzerland). 1991; 1(2):103–7. https://doi.org/10.1159/000108825

43. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993; 24(1):35–41. https://doi.org/10.1161/01.str.24.1.35 PMID: 7678184

44. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet (London, England). 1991; 337(8756):1521–6. Epub 1991/06/22. https://doi.org/10.1016/0140-6736(91)93206-o PMID: 1675378.

45. Bonita R, Beaglehole R. Recovery of motor function after stroke. Stroke. 1988; 19(12):1497–500. Epub 1988/12/01. https://doi.org/10.1161/01.str.19.12.1497 PMID: 3201508.

46. Narasimhalu K, Ang S, De Silva DA, Wong MC, Chang HM, Chia KS, et al. The prognostic effects of poststroke cognitive impairment no dementia and domain-specific cognitive impairments in nondisabled ischemic stroke patients. Stroke. 2011; 42(4):883–8. Epub 2011/02/19. https://doi.org/10.1161/STROKEAHA.110.594671 PMID: 21330625.

47. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psychol Meas. 1977; 1(3):385–401.

48. Enderby PM, Wood VA, Wade DT, Hewer RL. The Frenchay Aphasia Screening Test: a short, simple test for aphasia appropriate for non-specialists. International rehabilitation medicine. 1987; 8(4):166–70. Epub 1987/01/01. PMID: 2440825.

49. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal. 2016; 37(29):2315–81. Epub 2016/05/26. https://doi.org/10.1093/eurheartj/ehw106 PMID: 27222591; PubMed Central PMCID: PMC4986030.

50. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet (London, England). 1996; 348(9038):1329–39. Epub 1996/11/16. https://doi.org/10.1016/s0140-6736(96)09457-3 PMID: 8918275.

51. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. Journal of the neurological sciences. 1996; 143(1–2):1–13. Epub 1996/11/01. https://doi.org/10.1016/s0022-510x(96)00308-5 PMID: 8981292.

52. Weimar C, Diener HC, Alberts MJ, Steg PG, Bhatt DL, Wilson PW, et al. The Essen stroke risk score predicts recurrent cardiovascular events: a validation within the REduction of Atherothrombosis for Continued Health (REACH) registry. Stroke. 2009; 40(2):350–4. Epub 2008/11/22. https://doi.org/10.1161/STROKEAHA.108.521419 PMID: 19023098.

53. Medical Research Council. MRC Ethics Guide 2007: Medical research involving adults who cannot consent. London: Medical Research Council, 2007.

54. Health Service Executive National Consent Advisory Group. National Consent Policy. Dublin: Health Service Executive; 2013 [accessed 15th March 2016]. Available from: http://www.hse.ie/eng/about/Who/qualityandpatientsafety/National_Consent_Policy/National%20Consent%20PolicyMay14.pdf.

55. Lim JS, Oh MS, Lee JH, Jung S, Kim C, Jang MU, et al. Prediction of post-stroke dementia using NINDS-CSN 5-minute neuropsychology protocol in acute stroke. International psychogeriatrics. 2017; 29(5):777–84. Epub 2017/01/26. https://doi.org/10.1017/S1041610216002520 PMID: 28120733.

56. StataCorp. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP., 2013.

57. Jamison J, Ayerbe L, Di Tanna GL, Sutton S, Mant J, De Simoni A. Evaluating practical support stroke survivors get with medicines and unmet needs in primary care: a survey. BMJ open. 2018; 8(3): e019874. Epub 2018/03/13. https://doi.org/10.1136/bmjopen-2017-019874 PMID: 29526835; PubMed Central PMCID: PMC5855212.

58. Smith D, Lovell J, Weller C, Kennedy B, Winbolt M, Young C, et al. A systematic review of medication non-adherence in persons with dementia or cognitive impairment. PloS one. 2017; 12(2):e0170651. Epub 2017/02/07. https://doi.org/10.1371/journal.pone.0170651 PMID: 28166234; PubMed Central PMCID: PMC5293218.

59. Aston L, Hilton A, Moutela T, Shaw R, Maidment I. Exploring the evidence base for how people with dementia and their informal carers manage their medication in the community: a mixed studies review. BMC Geriatr. 2017; 17(1):242. Epub 2017/10/20. https://doi.org/10.1186/s12877-017-0638-6 PMID: 29047339; PubMed Central PMCID: PMC5648510.

60. Mahon S, Parmar P, Barker-Collo S, Krishnamurthi R, Jones K, Theadom A, et al. Determinants, Prevalence, and Trajectory of Long-Term Post-Stroke Cognitive Impairment: Results from a 4-Year Follow-Up of the ARCOS-IV Study. Neuroepidemiology. 2017; 49(3–4):129–34. https://doi.org/10.1159/000484606 PMID: 29145207

61. Delavaran H, Jönsson AC, Lövkvist H, Iwarsson S, Elmståhl S, Norrving B, et al. Cognitive function in stroke survivors: A 10-year follow-up study. Acta Neurologica Scandinavica. 2017; 136(3):187–94. https://doi.org/10.1111/ane.12709 PMID: 27804110

62. Wessol JL, Russell CL, Cheng AL. A Systematic Review of Randomized Controlled Trials of Medication Adherence Interventions in Adult Stroke Survivors. The Journal of neuroscience nursing: journal of the American Association of Neuroscience Nurses. 2017; 49(2):120–33. Epub 2017/02/25. https://doi.org/10.1097/jnn.0000000000000266 PMID: 28234660.

63. Lin CY, Ou HT, Nikoobakht M, Brostrom A, Arestedt K, Pakpour AH. Validation of the 5-Item Medication Adherence Report Scale in Older Stroke Patients in Iran. J Cardiovasc Nurs. 2018; 33(6):536–43. Epub 2018/04/13. https://doi.org/10.1097/JCN.0000000000000488 PMID: 29649015.

64. El-Saifi N, Moyle W, Jones C, Alston-Knox C. Determinants of medication adherence in older people with dementia from the caregivers' perspective. International psychogeriatrics. 2019; 31(3):331–9. Epub 2018/05/11. https://doi.org/10.1017/S1041610218000583 PMID: 29747719

65. Wolfe CD, Crichton SL, Heuschmann PU, McKevitt CJ, Toschke AM, Grieve AP, et al. Estimates of outcomes up to ten years after stroke: analysis from the prospective South London Stroke Register. PLoS medicine. 2011; 8(5):e1001033. Epub 2011/05/26. https://doi.org/10.1371/journal.pmed.1001033 PMID: 21610863; PubMed Central PMCID: PMC3096613.