Patterns of Antidepressant therapy and Clinical Outcomes among Ischemic Stroke Survivors

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Statistical Analysis Plan

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Statistical Analysis Plan

Working Title:	Patterns of Antidepressant therapy and Clinical Outcomes among Ischemic Stroke Survivors
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I. Primary Objectives

1. To estimate the patterns of antidepressant (AD) prescription at hospital discharge among a population of non-contraindicated stroke patients.
2. To estimate the associations between antidepressant use (any vs. none) and outcomes (home time, all-cause mortality, stroke readmissions, cardiovascular readmissions, and depression-related hospitalizations following discharge).
3. Repeat analyses for patients with SSRI information (SSRI vs. other AD).
4. To examine associations between AD and outcomes in subgroups based on age (80/90), sex, race (white/non-white), NIH stroke scale (<16/≥16), and history of depression.
5. To estimate patterns of AD prescription (AD vs none and SSRI vs other AD) at hospital discharge among prospectively enrolled PROSPER patients with ischemic stroke discharge
6. To examine associations between antidepressant use (any vs.none) and patient reported outcomes following ischemic stroke discharge
7. To examine associations between types of antidepressant used (SSRI vs. other AD) and patient reported outcomes.

Study Population	***N Patients***	***N Sites***	***% Remained***
1. Starting Population: All PROSPER (GWTG-Stroke linked to CMS*) patients enrolled in a fully-participating GWTG hospital with a final clinical diagnosis of acute ischemic stroke in year 2014	104,423	1,436	
2. Exclusions:			
1) Patients FFS ineligible	-5,582	-2	94.7%
2) Patients discharged before April 2014	-23,467	-15	76.3%
3) Patients left AMA/discharge disposition UTD/missing	-255	-0	99.7%
4) Patients transferred out	-1,486	-4	98.0%
5) In-hospital deaths	-4,148	-2	94.4%
6) Discharge AD not documented (historic and new)	-31,801	-383	54.2%
7) Patients with AD contraindications	-8,507	-7	77.4%
	=29,177	=1,023	
3. Final Study Population: 29,177 patients from 1,023 hospitals Study period: Apr 1, 2014 – Dec 31, 2014			

* Linkage to CMS implies that patients are at age of 65 or older, linked with first admission

Table. New AD variable by historic AD variable check in the IS study population.

Antidepressant Medication(s) At Discharge (New)	Antidepressant Medication(s) At Discharge (Historic)			
	Missing	1= Yes	2 = No/ND	Total
. = Missing	0 0 0 0	6075 20.82 27.23 99.72	16234 55.64 72.77 99.71	22309 76.46
1 = Yes, SSRI	1063 3.64 99.16 15.63	9 0.03 0.84 0.15	0 0 0 0	1072 3.67

Antidepressant Medication(s) At Discharge (New)	Antidepressant Medication(s) At Discharge (Historic)			
	Missing	1= Yes	2 = No/ND	Total
2 = Yes, any other antidepressant class	438 1.50 98.21 6.44	8 0.03 1.79 0.13	0 0 0 0	446 1.53
3 = No/ND	5302 18.17 99.10 77.94	0 0 0 0	48 0.16 0.90 0.29	5350 18.34
Total	6803 23.32	6092 20.88	16282 55.80	29177 100

Color code: AD Yes patients, AD No patients

II. Variables

1. Primary exposure variable

Any antidepressant prescription at hospital discharge (yes vs. no, derived from a combination of historic and revised antidepressant variables)

- Historic AD variable: AD Yes / AD No
- New AD variable: Yes, SSRI / Yes, other AD class

SSRI (selective serotonin reuptake inhibitors) are defined as any of the following: Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac), Paroxetine (Paxil, Pexeva), Sertraline (Zoloft). Other antidepressant therapy will be defined as all other non-SSRI antidepressants. SSRI analyses will be limited to patients with complete data on the new AD variable.

AD	Frequency	Percent
Yes	7,593	26.02
No	21,584	73.98
Total	29,177	100

SSRI	Frequency	Percent
Yes, SSRI	1,072	70.62
Yes, other AD	446	29.38
Total	1,518	100

Variable	Level	Overall (N=29177)		AD YES (N=7593)		AD NO (N=21584)		P-value+
History of depression	Yes	4341	14.88	3309	43.58	1032	4.78	<.0001
	No	24836	85.12	4284	56.42	20552	95.22	
AD prior to admission	Yes	6432	22.28	5678	75.57	754	3.53	<.0001
	No	22437	77.72	1836	24.43	20601	96.47	
	Missing	308	1.06	79	1.04	229	1.06	

Variable	Level	Overall (N=1518)		SSRI YES (N=1072)		SSRI NO (N=446)		P-value+
History of depression	Yes	667	43.94	474	44.22	193	43.27	0.7361
	No	851	56.06	598	55.78	253	56.73	
AD prior to admission	Yes	1125	74.75	800	75.33	325	73.36	0.4238
	No	380	25.25	262	24.67	118	26.64	
	Missing	13	0.86	10	0.93	3	0.67	

2. Other variables

Demographics:	Age, race, gender, insurance status, medical history (depression, stroke, TIA, DM, CAD, AF, HF, HTN, PVD, smoking)
Presentation variables:	EMS transport, ambulatory status, initial NIHSS, prior antidepressant use
In-hospital variables:	Dysphagia screening, DVT prophylaxis, t-PA, t-PA date/time, VTE interventions, documented DVT/PE, antithrombotics by day 2
Discharge variables:	Discharge disposition, ambulatory status at discharge, ICD-9 discharge diagnosis, Antiplatelet/anticoagulant/HTN/AD meds, stroke education, smoking cessation, assessment for rehabilitation services
Hospital variables:	Primary stroke center; comprehensive stroke center, teaching status, hospital bed size, rural location, region, annual volume of IS admissions

3. Outcomes/Endpoints

Primary:
- Home-time: Total number of days spent alive and outside of a hospital, skilled nursing facility, or inpatient rehabilitation facility since discharge

Secondary:
- All-cause mortality: Ascertained on the basis of the death date recorded in the denominator/vital status file.
- All-cause readmission: Readmission date will be ascertained from the inpatient institutional file.
- Stroke/TIA readmission: Readmission date will be ascertained from the inpatient institutional file and determined by ICD-9-CM principal diagnoses code of 430, 431, 432.x-435.x, and 436 on the inpatient claim. Ischemic stroke and hemorrhagic stroke will be analyzed separately.
- Cardiovascular readmission: CV Readmission date will be ascertained from the inpatient institutional file and determined by DRG 104–112, 115–118, 121–145, 479, 514–518, 525–527, 535, 536, and 547–558 on the inpatient claim.
- Non-cardiovascular readmission: All readmissions not meeting CV readmission criteria.
- Depression related readmission: Completed suicide, suicide attempt or major depressive episode (major depressive disorder [296.2, 296.3, 296.5, 298.0, or 311], completed suicide/suicide attempt [E950-E959*], suicide ideation [V62.84], or suicide tendencies [300.9])

  *Given the potential for under-capture of completed suicides and suicide attempts, depression-related admission outcomes will be considered exploratory (reference: http://www.mini-sentinel.org/work_products/HealthOutcomes/MS_HOI_SuicideReport.pdf)

III. Analysis Tasks

1. Objective 1

Aim: To describe patient and hospital characteristics in the study population by discharge AD.

Analysis: Patient characteristics including demographics, medical history, initial vital signs, lab results and hospital characteristics will be described for the study population by discharge AD use. Categorical variables will be presented as proportions, and continuous variables will be presented as mean (standard deviation). We will compare the respective distributions of baseline characteristics among patients receiving 1) Any AD vs. no AD, and 2) SSRI vs. non-SSRI. Differences between groups will be evaluated using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables.

Output: Table 1 (patient baseline table)

Table 1A. Baseline characteristics of GWTG-Stroke-CMS patients by discharge AD use.

Variables	AD at Discharge	No AD at Discharge	Standardized differences, %	P-value*

Table 1B. Baseline characteristics of GWTG-Stroke-CMS patients by discharge AD type.

Variables	SSRI at Discharge	Other AD at Discharge	Standardized differences, %	P-value*

(Detailed table entries on next page)

Table 1. Baseline characteristics of GWTG-Stroke-CMS patients* overall and by discharge AD.

Variables	AD at Discharge	No AD at Discharge	StdDiff, %	P-value*
Demographics				
Age, year, mean (SD)				
Gender: Female				
Race/Ethnicity				
Medical History				
Depression				
Atrial Fibrillation				
Stroke/TIA				
CAD/MI				
Carotid Stenosis				
Diabetes Mellitus				
PVD				
Hypertension				
Smoker				
Dyslipidemia				
Heart Failure				
Medications prior to admission				
Antidepressants				
Anti-hypertensives				
Cholesterol-reducers				
Diabetic medications				
Presentation				
EMS transport				
Initial NIHSS				
Onset to arrival times (Prehospital delay)				
<2 hours				
2-4 hours				
>4 hours				
Symptoms resolved at time of presentation				
Ambulatory status on admission				
Labs				
Body Mass Index, mean (SD)				
Systolic blood pressure, mean (SD)				
Hemoglobin A1C, mean (SD)				
LDL-C, mean (SD)				
Hospital characteristics				
Teaching status				
Rural location				
Region				
Primary Stroke Centers				
Comprehensive Stroke Centers				
Hospital size, mean (SD)				
Annual IS admission volume, mean (SD)				

All numbers presented are proportions of patient in the study population, unless specified otherwise.
* P-values from chi-squared tests for independence for categorical variables and Wilcoxon rank sum tests for continuous variables

2. Objective 2

Aim: To estimate the associations between antidepressant use (any vs. none) and outcomes (home time, all-cause mortality, all-cause readmission recurrent stroke [ischemic, hemorrhagic], cardiovascular rehospitalization, and depression-related hospitalization [suicidality or major depressive episode] following discharge).

Analysis: Because patients who receive AD may differ from those who do not on important baseline and clinical characteristics that may affect the likelihood of adverse events, we will use inverse probability of treatment weighting (IPW) when assessing treatment effects. IPT weighting will be accomplished in two steps: First, we will use a logistic regression model to assign a probability of treatment selection to each patient based on the distribution of a defined set of covariates (listed above). The binary outcome for the selection model will be AD treatment (Y/N). In the second step, we will weight subject by the inverse of this assigned treatment probability, resulting in a pseudo-randomization of patients to AD vs. no AD treatment. The distribution of baseline patient characteristics for each treatment group will be assessed after weighting to determine adequacy of the selection model.

Following IPW, we will compare primary and secondary endpoints between treatment groups. Unadjusted rates of all-cause mortality, all-cause readmission, CV readmission, depression-related admission and stroke/TIA readmission will be examined using a Cox proportional hazards model with AD use as the single independent variable. Adjusted event rates will then be estimated using the same model with IPW included for each subject. Within-hospital clustering will be accounted for using robust estimator approach.

Home time will be examined first as a continuous variable in a linear regression model and then as a dichotomous outcome in an IPW-weighted logistic regression model, using 100% of time spent at home over 1 year as the primary outcome of interest.

Methods will be repeated for SSRI vs. non-SSRI with corresponding modeling of clinical outcomes.

Output: Table 2 (AD vs No AD), Table 3 (SSRI vs not SSRI)

Table 2. AD use and clinical outcomes following ischemic stroke discharge.

Outcomes	AD	No AD (ref)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P-value

Table 3. SSRI vs. non-SSRI use and clinical outcomes following ischemic stroke discharge.

Outcomes	SSRI	Other AD (ref)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P-value
Home time: 100% (OR)					
All-cause mortality					
Readmission					
All-cause					
Cardiovascular					
Stroke/TIA					
Ischemic Stroke					
Hemorrhagic Stroke					
Depression-related readmission					
			Unadjusted Difference (95% CI)	**Adjusted Difference (95% CI)**	
Home time days, mean (SD)					

3. Objective 3

   Aim: To describe 1y mortality and readmission outcomes by plotting the cumulative incidence functions.

   Analysis: We will limit the population to <u>patients naïve to AD</u> on admission and construct Kaplan-Meier curves for all-cause mortality at 1 year following the index hospitalization for patients prescribed AD at hospital discharge. Log-rank tests will be used to examine mortality differences between AD treatment groups.

   For the other non-mortality endpoints, we will calculate incidence at 1 year based on estimates from the cumulative incidence function, to account for the competing risk of mortality. Gray tests will be used to test for differences between groups for these outcomes.

   We will then restrict the study population to patients receiving AD at hospital discharge and analyses will be repeated for SSRI vs. non-SSRI antidepressants.

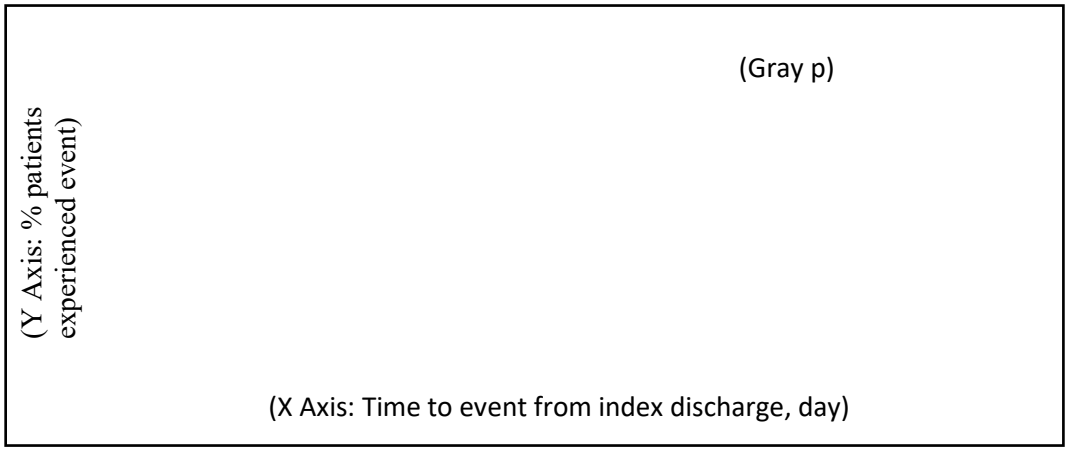


Figure X. Cumulative incidence plots for mortality and readmissions by AD types (Yes vs No, and again for SSRI vs Non-SSRI).

4. Objective 4

   Aim: Perform subgroup analyses.

   Analysis: Because AD use and outcomes may vary by patient characteristics, we will repeat modeling of these associations by the following subgroups: Age (65-80, 80-90, 90+), sex (male vs. female), race (white vs. non-white), NIH stroke scale (<16 vs. ≥16), and medical history of depression.

   Repeat Tables 2 and 3 in subgroups defined.

5. Objective 5

   Aim: To describe baseline patient and hospital characteristics in the prospectively enrolled PROSPER study population with ischemic stroke discharge by discharge antidepressant use (any vs none).

   Analysis: Patient characteristics including demographics, medical history, initial vital signs, lab results and hospital characteristics will be described for the study population by discharge AD use (any vs

none). Categorical variables will be presented as proportions, and continuous variables will be presented as mean (standard deviation). We will compare the respective distributions of baseline characteristics among patients receiving any AD vs. none. Differences between groups will be evaluated using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables.

Output: Table 5A. (patient baseline table)

Table 5A. Baseline characteristics of prospectively enrolled PROSPER patients with ischemic stroke discharge by discharge AD use.

Variables	AD at Discharge	No AD at Discharge	StdDiff, %	P-value*
Demographics				
Age, year, mean (SD)				
Gender: Female				
Race/Ethnicity				
Medical History				
Depression				
Atrial Fibrillation				
Stroke/TIA				
CAD/MI				
Carotid Stenosis				
Diabetes Mellitus				
PVD				
Hypertension				
Smoker				
Dyslipidemia				
Heart Failure				
Medications prior to admission				
Antidepressants				
Anti-hypertensives				
Cholesterol-reducers				
Diabetic medications				
Presentation				
EMS transport				
Initial NIHSS				
Onset to arrival times (Prehospital delay)				
<2 hours				
2-4 hours				
>4 hours				
Symptoms resolved at time of presentation				
Ambulatory status on admission				
Labs				
Body Mass Index, mean (SD)				
Systolic blood pressure, mean (SD)				
Hemoglobin A1C, mean (SD)				
LDL-C, mean (SD)				
Hospital characteristics				
Teaching status				
Rural location				
Region				
Primary Stroke Centers				
Comprehensive Stroke Centers				
Hospital size, mean (SD)				
Annual IS admission volume, mean (SD)				

All numbers presented are proportions of patient in the study population, unless specified otherwise.
* P-values from chi-squared tests for independence for categorical variables and Wilcoxon rank sum tests for continuous variables

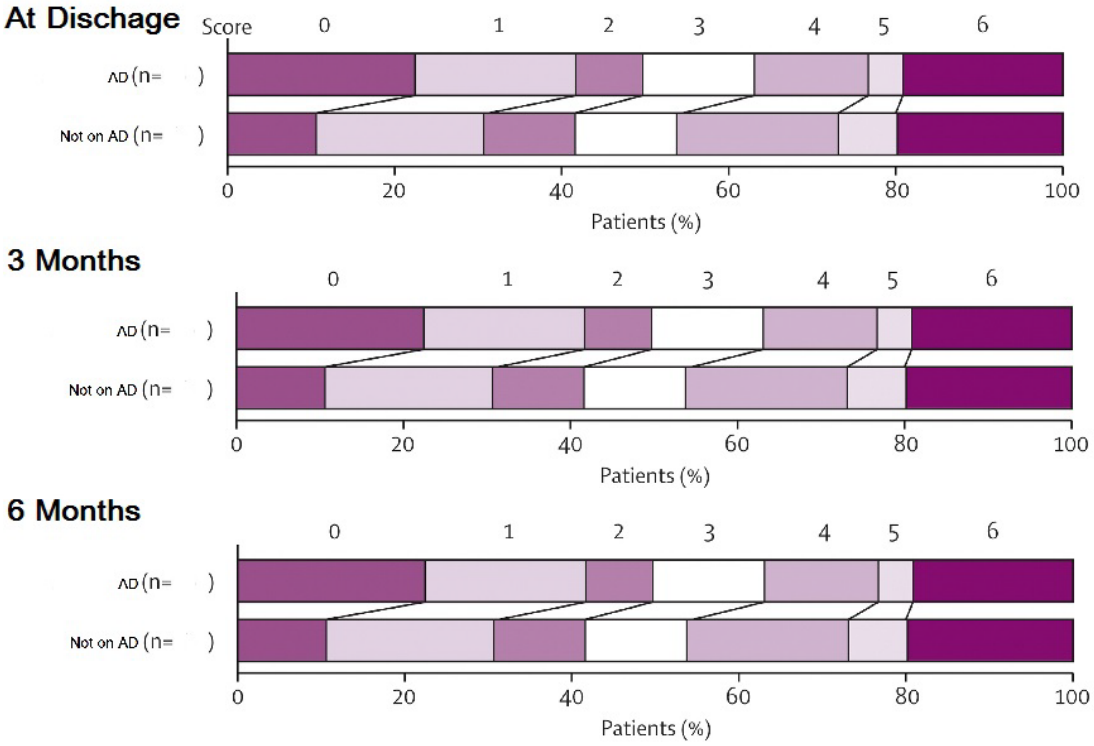
Table 5B. Baseline characteristics of prospectively enrolled PROSPER patients with ischemic stroke discharge by discharge AD type.

Variables	SSRI at Discharge	Other AD at Discharge	StdDiff, %	P-value*
Demographics				
Age, year, mean (SD)				
Gender: Female				
Race/Ethnicity				
Medical History				
Depression				
Atrial Fibrillation				
Stroke/TIA				
CAD/MI				
Carotid Stenosis				
Diabetes Mellitus				
PVD				
Hypertension				
Smoker				
Dyslipidemia				
Heart Failure				
Medications prior to admission				
Antidepressants				
Anti-hypertensives				
Cholesterol-reducers				
Diabetic medications				
Presentation				
EMS transport				
Initial NIHSS				
Onset to arrival times (Prehospital delay)				
<2 hours				
2-4 hours				
>4 hours				
Symptoms resolved at time of presentation				
Ambulatory status on admission				
Labs				
Body Mass Index, mean (SD)				
Systolic blood pressure, mean (SD)				
Hemoglobin A1C, mean (SD)				
LDL-C, mean (SD)				
Hospital characteristics				
Teaching status				
Rural location				
Region				
Primary Stroke Centers				
Comprehensive Stroke Centers				
Hospital size, mean (SD)				
Annual IS admission volume, mean (SD)				

6. Objective 6

Aim: To estimate the associations between antidepressant use (any vs. none) and patient reported outcomes (modified Rankin Scale, EQ-5D-3L Health Profile, PHQ-2 score, SIS-16 score and Fatigue Severity Scale score).

Figure 6. Grotta bar showing AD vs no AD use and mRS following ischemic stroke discharge.



EQ-5D-3L Health Profile

Table 6A. EQ-5D-3L distribution by AD use at discharge, 3 month and 6 month

EQ-5D-3L Dimension		AD (% Subjects)			Not on AD (% Subjects)		
		At discharge	3 month	6 month	At discharge	3 month	6 month
Mobility	Level 1						
	Level 2						
	Level 3						
Self-Care	Level 1						
	Level 2						
	Level 3						
Usual Activity	Level 1						
	Level 2						

	Level 3						
Pain/Discomfort	Level 1						
	Level 2						
	Level 3						
Anxiety/Depression	Level 1						
	Level 2						
	Level 3						

Table 6B. EQ-5D-3L index values

EQ-5D-3L index value	AD			Not on AD		
	At discharge	3 month	6 month	At discharge	3 month	6 month
Mean (Standard error)						
Median (25^{th} – 75^{th} percentile)						

Table 6C. EQ VAS

EQ VAS	AD			Not on AD		
	At discharge	3 month	6 month	At discharge	3 month	6 month
Mean (Standard error)						
Median (25^{th} – 75^{th} percentile)						

Table 6D. PHQ-2 Score distribution

PHQ-2 Score	AD (% Subjects)			Not on AD (% Subjects)		
	At discharge	3 month	6 month	At discharge	3 month	6 month
0						
1						
2						
3						
4						
5						
6						

Table 6E. PHQ-2 Score

PHQ-2 Score	AD			Not on AD		
	At discharge	3 month	6 month	At discharge	3 month	6 month
Mean (Standard error)						
Median (25^{th} – 75^{th} percentile)						
% Subjects >= 3						

Table 6F. Stroke Impact Scale-16

SIS-16	AD			Not on AD		
	At discharge	3 month	6 month	At discharge	3 month	6 month
Mean (Standard error)						
Median (25 – 75 percentile)						
Percent at floor (SIS16 = 0)						
Percent at Ceiling (SIS16 = 100)						

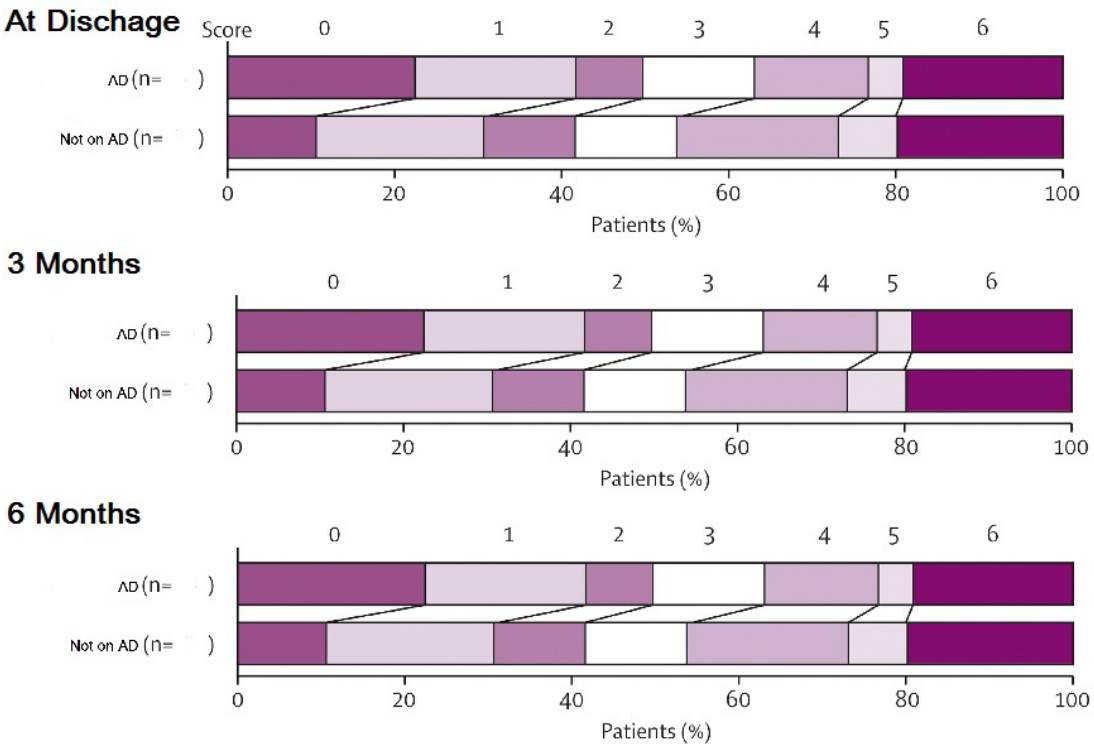
Table 6G. Fatigue Severity Scale

Fatigue Severity Scale	AD			Not on AD		
	At discharge	3 month	6 month	At discharge	3 month	6 month
Mean (Standard error)						
Median (25^{th} – 75^{th} percentile)						
% Subjects >= 36						

7. Objective 7

Aim: To estimate the associations between antidepressant use (SSRI vs. other) and patient reported outcomes (modified Rankin Scale, EQ-5D-3L Health Profile, PHQ-2 score, SIS-16 score and Fatigue Severity Scale score).

Figure 7. Grotta bar showing SSRI vs other AD use and mRS following ischemic stroke discharge.



EQ-5D-3L Health Profile

Table 7A. EQ-5D-3L distribution by AD type use at discharge, 3 month and 6 month

EQ-5D-3L Dimension		SSRI (% Subjects)			Other type AD (% Subjects)		
		At discharge	3 month	6 month	At discharge	3 month	6 month
Mobility	Level 1						
	Level 2						
	Level 3						
Self-Care	Level 1						
	Level 2						
	Level 3						
Usual Activity	Level 1						
	Level 2						
	Level 3						
Pain/Discomfort	Level 1						

	Level 2						
	Level 3						
Anxiety/Depression	Level 1						
	Level 2						
	Level 3						

Table 7B. EQ-5D-3L index values

EQ-5D-3L index value	SSRI			Other AD		
	At discharge	3 month	6 month	At discharge	3 month	6 month
Mean (Standard error)						
Median (25^{th} – 75^{th} percentile)						

Table 7C. EQ VAS

EQ VAS	SSRI			Other AD		
	At discharge	3 month	6 month	At discharge	3 month	6 month
Mean (Standard error)						
Median (25^{th} – 75^{th} percentile)						

Table 7D. PHQ-2 Score distribution

PHQ-2 Score	SSRI (% Subjects)			Other AD (% Subjects)		
	At discharge	3 month	6 month	At discharge	3 month	6 month
0						
1						
2						
3						
4						
5						
6						

Table 7E. PHQ-2 Score

PHQ-2 Score	SSRI			Other AD		
	At discharge	3 month	6 month	At discharge	3 month	6 month
Mean (Standard error)						
Median (25^{th} – 75^{th} percentile)						
% Subjects >= 3						

Table 7F. Stroke Impact Scale-16

SIS-16	SSRI			Other AD		
	At discharge	3 month	6 month	At discharge	3 month	6 month
Mean (Standard error)						
Median (25 – 75 percentile)						
Percent at floor (SIS16 = 0)						
Percent at Ceiling (SIS16 = 100)						

Table 7G. Fatigue Severity Scale

Fatigue Severity Scale	SSRI			Other AD		
	At discharge	3 month	6 month	At discharge	3 month	6 month
Mean (Standard error)						
Median (25^{th} – 75^{th} percentile)						
% Subjects >= 36						