

ORIGINAL RESEARCH ARTICLE

Long-term benefits of policosanol plus low dose of aspirin in the functional recovery of non-cardiogenic ischemic stroke: A randomized, placebo-controlled study

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Abstract

Stroke is one of the main causes of mortality and disability worldwide. Previous studies have demonstrated the benefits of policosanol 20 mg/day (poli 20) + aspirin (AS) 125 mg/day on functional recovery after a non-cardiogenic ischemic stroke (NCIS), but the effects of poli 20 + lower doses of AS have not yet been studied. This randomized, double-blind study investigates the long-term effects of poli 20 + AS 81 mg/day (poli/AS) or placebo + AS 81 mg/day (pla/AS) on functional recovery after an NCIS. Patients who have suffered a recent (≤ 30 days from stroke onset) NCIS and with a modified Rankin Scale (mRS) score of 2–3 were randomized to receive either poli/AS or pla/AS for 12 months. The primary outcome was whether the frequency of patients in the poli/AS group achieving an mRS score ≤ 1 was higher than that in the pla/AS group. Secondary outcomes included changes in mean mRS and Barthel Index (BI) scores between the poli/AS and pla/AS groups. Effects on lipid profile were collateral outcomes. Of 100 randomized patients, 98 patients completed the study. Missing data from the two remaining patients were handled using single imputation with the last-observation-carried-forward method. Results demonstrated that significantly more poli/AS patients (46/50; 92%) achieved an mRS score ≤ 1 than pla/AS patients (23/50; 46%). Poli/AS significantly reduced the mean mRS score and increased BI score ($p < 0.01$) compared with baseline and pla/AS. Lipid profile benefits and good tolerability were confirmed. It is demonstrated for the first time that treatment with poli 20 mg/day plus a lower dose of AS (81 mg/day) significantly improved functional recovery following an NCIS compared with pla/AS.

Keywords: Non-cardiogenic ischemic stroke; Aspirin; Modified Rankin Scale; Barthel Index; Policosanol; Placebo

1. Introduction

Stroke, a leading cause of acquired permanent disability and the second most common cause of death worldwide,¹ is the acute neurological injury associated with the presence of central nervous system infarction, including brain, spinal cord, or retinal cell death.² Stroke results from either obstructed blood flow (ischemic stroke) or from a blood leakage from a ruptured brain blood vessel (hemorrhagic stroke).²⁻⁴ Ischemic stroke accounts for about 80 % of strokes and hence is the main cause of associated disability.⁴⁻⁶

Although stroke prevalence has significantly lowered due to better prevention of cardiovascular diseases and improvements in acute stroke care, the annual numbers of stroke-related deaths and disability-adjusted life years markedly increased from 1990 to 2019, a trend expected to continue until 2050.^{7,8} Indeed, most non-cardiogenic ischemic stroke (NCIS) sufferers are left with ongoing diverse disabilities affecting extremities, ambulation, swallowing, speech, vision, and others.⁷⁻⁹ Hence, improving these poor outcomes remains an unmet medical need.

In addition to reperfusion therapies for acute stroke treatment, antithrombotic drugs are used during subacute and chronic post-stroke periods to prevent NCIS recurrence. Antiplatelet therapy should be initiated as soon as possible, with aspirin (AS) remaining the most widely used single antiplatelet therapy.¹⁰⁻¹²

Aspirin inhibits platelet aggregation by irreversibly inhibiting platelet cyclooxygenase-1 (COX-1), blocking the production of thromboxane A₂ (TxA₂), a potent platelet activator, and, to a lesser extent, the COX-2 enzyme. The latter effect inhibits the production of prostaglandins, such as prostacyclin (PGI₂) (a potent vasodilator and antithrombotic agent) and prostaglandin E (a gastroprotective mediator).¹³ AS doses between 81 and 325 mg/day have been recommended for secondary stroke prevention.¹⁴ However, lower doses (75 to 100 mg/day) are considered enough for a maximal antithrombotic effect, whilst higher doses are regarded as not more effective, just increasing the bleeding risk.¹⁰⁻¹⁴ Dual antiplatelet therapy with AS + clopidogrel (or ticagrelor) may be used in certain scenarios for 21 to 90 days prior to continuing single antiplatelet therapy long term.^{14,15}

The control of cardiovascular risk factors is essential for post-stroke recovery and secondary prevention.¹⁶ Among these, blood pressure control is pivotal, as lowering systolic blood pressure below 130 mmHg may add a small benefit in secondary stroke prevention.¹⁷ Angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers,

thiazide diuretics, and calcium channel blockers are first-line antihypertensive drug options in post-stroke patients.

Additionally, elevated blood low-density lipoprotein cholesterol (LDL-C) is a pivotal risk factor for cardiovascular diseases, including NCIS. The aim for lowering LDL-C as much as possible (“the lower, the better”) is associated with a lower incidence of cardiovascular events, mainly in patients at very high risk.¹⁸⁻²⁰

Statins, whose cholesterol-lowering mechanism is inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, are by far the most effective drugs for lowering elevated LDL-C and are indicated for the recovery and secondary prevention of ischemic stroke.^{21,22} Beyond lipid regulation, statins exhibit beneficial pleiotropic effects on the vascular endothelium, including maintenance of plaque stability,²³ which could influence their effects on cardiovascular risk reduction, although the contribution of such effects has recently been challenged.²⁴

Policosanol, a mixture of eight high-molecular-weight primary alcohols isolated from sugarcane (*Saccharum officinarum* L) wax, produces antiplatelet²⁵⁻²⁹ and cholesterol-lowering³⁰⁻⁴¹ effects, characterized by moderate reductions of LDL-C and total cholesterol (TC), and modest to moderate increases of high-density lipoprotein cholesterol (HDL-C). Although some studies dismiss the cholesterol-lowering effects of policosanol,⁴²⁻⁴⁴ one early study⁴⁵ and two subsequent meta-analyses^{46,47} support its lipid-modifying effects, noting that the conflicting data may be due to many factors, including the different products used in these trials.⁴⁷

Experimental studies have shown that policosanol's antiplatelet effects are associated with a reduction in serum TxB₂ levels⁴⁸ and reversible inhibition of the COX-1 enzyme.⁴⁹ In turn, its cholesterol-lowering mechanism involves the inhibition of cholesterol synthesis through a modulatory up-regulation of HMG-CoA reductase triggered by the activation of adenosine monophosphate (AMP) kinase,⁵⁰⁻⁵⁷ and the subsequent increase in LDL receptor processing.^{50,56}

Meanwhile, the blood pressure-lowering effects of policosanol have been observed in pre-hypertensive Korean subjects,⁵⁸⁻⁶⁰ with this effect supported by a meta-analysis.⁶¹ Recently, similar results were observed in a randomized, double-blind, placebo-controlled study in 200 pre-hypertensive Cuban patients.⁶²

Considering this background, it is anticipated that policosanol may be effective in experimental and human brain ischemia. Indeed, protective effects in experimental brain ischemia studies reinforced this belief.^{63,64} Randomized, double-blind, placebo-controlled studies

showed that policosanol 20 mg/day (poli 20) + AS 125 mg/day, given for 6 or 12 months, improved the neurological recovery of patients with a recent (≤ 30 days) ischemic stroke as compared to placebo + AS,⁶⁵⁻⁶⁷ assessed primarily using the modified Rankin Scale (mRS).⁶⁸ Besides, a long-term study used the Barthel Index (BI)⁶⁹ as a neurological tool. Meanwhile, a short-term (3 months) study showed that poli 20 + AS 125 mg/day was as effective as atorvastatin 20 mg/day + AS for improving the functional outcomes in post-stroke patients.⁷⁰ Long-term open studies also found that post-stroke sufferers treated with poli 20 + AS 125 mg/day had an excellent neurological recovery.^{71,72}

However, all previous studies investigating the effects of poli 20 on the functional recovery of patients with a recent NCIS used AS at a dose of 125 mg/day. Currently, the use of a lower dose of AS (81 mg/day) has been introduced in Cuba for the secondary prevention of cardiovascular diseases, with the intention of reducing bleeding events.

Considering this background, this study investigates whether the long-term (12 months) neurological recovery of patients who had suffered a recent NCIS is better with policosanol + AS 81 mg/day than with placebo + AS 81 mg/day.

2. Methods

2.1. Study design

This randomized, double-blind study investigated long-term functional neurological recovery in patients who had suffered an NCIS. They received either poli 20 + AS 81 mg/day (poli 20/AS 81) or placebo + AS 81 mg/day (pla/AS 81) for 12 months.

The study followed the ethical principles established in the latest versions of the Declaration of Helsinki and the Tokyo Declaration. The study protocol was approved by the Institutional Review Board (IRB-002021) and was registered in the Cuban Public Registry of Clinical Trials (RPCEC00000378). All participants provided written informed consent at enrolment.

2.2. Study patients

Study patients were enrolled at external visits of the Institute of Neurology and Neurosurgery (Havana, Cuba). Enrolled patients were ambulatory men and women aged 40 years or older who had a recent first (≤ 30 days from onset) NCIS and provided their written informed consent. The diagnosis of having suffered an NCIS was confirmed through clinical assessment and computerized axial tomography performed within 24 h after stroke onset.

Patients were then eligible for randomization if they had an mRS score⁶⁸ of 2–3. The exclusion criteria

included suspected or confirmed hemorrhagic stroke, atrial fibrillation, other cardiac sources of embolism, subarachnoid hemorrhage, diastolic pressure ≥ 110 mm Hg, diagnosed cardiac valve diseases, history of myocardial infarction, unstable angina, revascularization surgery within 6 months prior to the trial, and having consumed policosanol within 6 months before enrolment.

Eligible patients were randomized to receive either poli 20/AS 81 or pla/AS 81 for 12 months and attended post-randomization control visits at 1.5, 3, 6, 8, 10, and 12 months on treatment. Patients underwent general examination and neurological assessment at each visit. Laboratory analyses were performed at baseline and at 6 and 12 months on therapy; meanwhile, treatment compliance and adverse events (AEs) were assessed at each post-randomization visit.

As part of healthy lifestyle measures, patients were advised to start or continue a low-sodium and low-fat diet and were strongly recommended to stop smoking.

2.3. Study outcomes

The primary study outcome, based on neurological recovery measured by the mRS score,^{6,8} was to determine whether the frequency of patients in the poli 20/AS 81 group achieving an mRS score ≤ 1 at study completion was significantly higher than that in the pla/AS 81 group. Additionally, the changes in mean mRS scores from the poli 20/AS 81 group were compared with those from the pla/AS 81 group, hypothesizing that the scores from the poli 20/AS 81 group were significantly lower than those from the pla/AS 81 group.

The mRS is a seven-point clinician-reported measure of global disability, ranging from 0 (no symptoms) to 6 (death), and is the most widely used outcome scale in acute stroke trials.^{68,73-77} The mRS score is interpreted as: 0: total absence of symptoms; 1: mild disability, but with symptoms such as weakness or numbness; 2: mild disability, but able to perform daily activities independently; 3: moderate disability, requiring help for daily activities; 4: moderately severe disability, requiring assistance for most daily activities; 5: severe disability, requiring bed rest and nursing care; and 6: death. The widespread use of the mRS is due to its simplicity and ease of use, and it also shows good inter-rater reliability and validity.⁷³⁻⁷⁷

The secondary outcome was to determine whether the mean BI scores of patients treated with poli 20/AS 81 were significantly higher than those receiving pla/AS 81.

The BI is a 10-item scale that assesses a patient's ability to manage activities of daily living, such as eating, grooming, bathing, dressing, bowel and bladder care,

using the toilet, ambulating, carrying objects, and climbing stairs. Higher BI scores indicate better functional ability and independence. Each item can score 0, 5 or 10 points. BI ranges from 0 to 100, corresponding to five levels of dependence: independent (100 points), low dependence (91–99), moderate dependence (61–90), severe dependence (21–60), and total dependence (0–20).^{69,78,79} It is considered that the minimal clinically important difference of the BI in stroke patients was 4–5 points,⁷⁷ and that a BI of 95–100 is a very favorable post-stroke outcome.^{78,79}

2.4. Collateral outcomes

We also assessed whether the poli 20/AS 81 group demonstrate significant reductions in LDL-C and TC, as well as increases in HDL-C levels compared to baseline and pla/AS 81.

2.5. Treatment

Treatments were randomized using computer-generated balanced block randomization in a 1:1 ratio. Treatments were assigned to patients in the order of their enrolment in the trial. To maintain blinding, none of the investigators involved in the study knew the randomization code, which was independently managed by the National Clinical Trials Coordinating Centre (CENCEC, Spanish acronym; Havana, Cuba). Sealed code-break envelopes were prepared for each participant and stored in a secure, accessible location within the Quality Assurance Unit.

Eligible patients were randomized to receive poli 20/AS 81 or pla/AS 81, administered once daily with breakfast for 12 months. Both policosanols and placebo tablets were manufactured by Laboratorios MedSol (Cuba). The placebo tablets had the same composition as the policosanols tablets, except that the active ingredient was replaced with lactose, the inert excipient in the formulation. Policosanol and placebo tablets were identical in packaging, color, shape, and flavor. If investigators judged an AE to be severe enough to require knowledge of the identity and dose of the relevant product, they were permitted to break the study code for that patient only.

Compliance with study medication was assessed by tablet counts and patients' self-reporting in daily charts. Treatment compliance was considered good if each patient consumed $\geq 85\%$ of the scheduled tablets. Overall compliance was deemed satisfactory if $>90\%$ of patients met this criterion. The use of any other drug or product with antiplatelet or lipid-lowering effects was prohibited, unless deemed medically necessary.

2.6. Laboratory analyses

Blood samples were drawn after a 12-h fast, and aliquots

were taken for laboratory analyses, scheduled according to standard practices and performed at baseline and at months 6 and 12. Plasma was separated from red blood cells by centrifugation at 4 °C and 2,000×g for 10 min (Sigma 1-16, SIGMA, Germany), and the resulting plasma was aliquoted immediately. Laboratory determinations were performed within 8 h of blood drawing. A systematic quality control of laboratory tests was conducted throughout the study.

2.7. Lipid profile and blood safety indicators

Serum levels of TC, triglycerides, HDL-C, and blood biochemistry indicators were determined using reagent kits (Roche, Switzerland) and a Hitachi 719 autoanalyzer (Japan) in the clinical laboratory of the Medical Surgical Research Centre. LDL-C values were calculated using the Friedewald equation.⁸⁰

2.8. Safety and tolerability assessment

Data from physical examinations, laboratory tests, and AE interviews were included in the safety and tolerability analysis. For this purpose, AEs were predefined as any undesired subjective experience or laboratory abnormality occurring during the study that was absent at baseline or worsened during the study, regardless of whether it was treatment-related. "Serious" AEs were defined as fatal or disabling events leading to, or prolonging, hospitalization. "Moderate" AEs were those requiring discontinuation of therapy and/or specific treatment as judged by the physician. "Mild" AEs were those that did not require withdrawal of study medication or specific treatment.

According to their potential relationship with study medication, AEs were further classified as unlikely, doubtful, possible, or probable drug-related, following the World Health Organization-Uppsala Monitoring Centre system.⁸¹

2.9. Statistical analysis

Statistical methods were pre-specified in a statistical analysis plan and performed using SPSS 21.0 (IBM, United States). Continuous variables are presented as descriptive statistics, including mean, standard deviation, and 95% confidence intervals, while categorical variables are summarized as frequency distributions. All data were analyzed according to the intention-to-treat principle, meaning that data from all randomized patients were included. Missing data were handled by single imputation using the last-observation-carried-forward method.

Continuous variables were compared using the paired *t*-test (within-group comparisons) and the independent *t*-test (between-group comparisons). Bonferroni's correction was applied to adjust significance levels for

repeated comparisons.⁸² Categorical data were analyzed using Fisher's exact test. All *p*-values were two-sided and considered significant at an α of 0.05.

2.10. Sample size calculation

The estimated minimal clinically important difference for mRS, based on opinions from academic stroke neurologists, was a change of one step at any level of the seven-level mRS scale.⁷⁴ An mRS score ≤ 1 was interpreted as a good level of post-stroke neurological function.^{75,76}

Considering this estimation, this study was designed to detect, based 80% statistical power at a two-sided α -level of 0.05, a significant reduction in the proportion of patients with mRS scores ≤ 1 in the poli 20/AS 81 group compared with the pla/AS 81 group at 12 months. Sample size calculation was performed using G*Power (version 3.1.19.2, 2014; Heinrich Heine University Düsseldorf, Germany), indicating that a total of 100 patients (approximately 50 per treatment arm) were needed for adequate power. Assuming an anticipated dropout rate of 10% over the study period, the target sample size was increased to 110 patients to ensure sufficient numbers for final analysis.

Of 110 enrolled patients, 100 (mean age: 70 years; 41

men, 59 women) were eligible for randomization, and 98 completed the study. Ten patients were excluded because they did not show up for laboratory tests (Figure 1). Two patients (one from each group) discontinued the trial prematurely. One of these withdrawals was due to a fatal AE (heart attack), which occurred in one patient treated with pla/AS 81, whilst the other was due to overseas travel in a patient treated with poli 20/AS 81, which was not AE-related. Missing data were handled by single imputation using the last-observation-carried-forward method.

3. Results

3.1. Study population

Baseline characteristics were well balanced in the two groups (Table 1). The most frequent cardiovascular risk factors at baseline were hypertension (95%), a salt-rich diet, and a sedentary lifestyle (all present in 92% of the study population), followed by overweight/obesity (49%), smoking (28%), and diabetes (17%). Concomitant therapy was also well matched between the groups, with ACEI (67%) and diuretics (33%) being the most frequent.

3.2. Effects on stroke functional outcomes

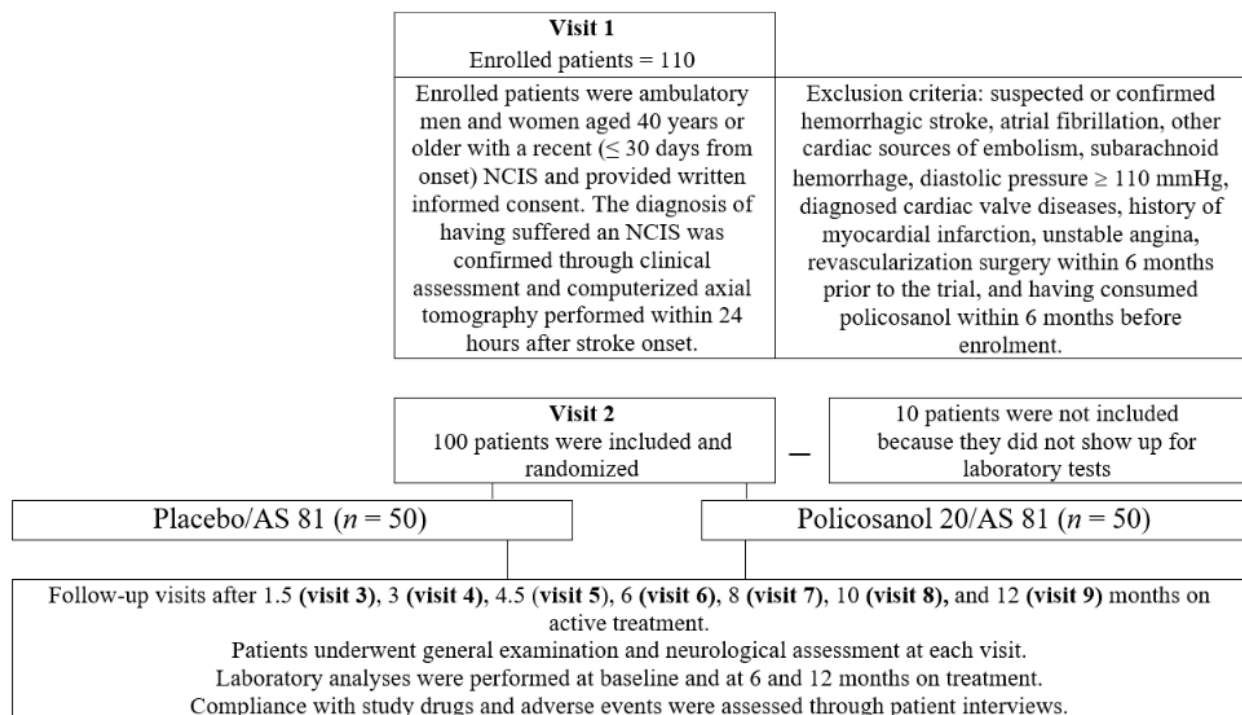


Figure 1. Flow diagram of the study. In addition to statistical analysis under the intention-to-treat principle, missing data were handled using simple imputation, including the last-observation-carried-forward

Table 1. Baseline characteristics of the study population

Characteristics	Poli 20 /AS 81 (<i>n</i> = 50)	Pla/AS 81 (<i>n</i> = 50)	Total (<i>n</i> = 100)
Age (years)	70 ± 8	69 ± 10	70 ± 9
Body mass index (kg/m ²)	24.7 ± 3.79	24.5 ± 4.30	24.6 ± 4.10
mRS score	2.32 ± 0.5	2.26 ± 0.4	2.29 ± 0.5
Women	28 (56)	31 (62)	59 (59)
Men	22 (44)	19 (38)	41 (41)
Hypertension	48 (96)	47 (94)	95 (95)
Salt-rich diet	46 (92)	46 (92)	92 (92)
Sedentary lifestyle	46 (92)	46 (92)	92 (92)
Overweight/obesity	26 (52)	23 (46)	49 (49)
Smoking	15 (30)	13 (26)	28 (28)
Diabetes	8 (16)	9 (18)	17 (17)
Coronary heart disease	6 (12)	4 (8)	10 (10)
Hypercholesterolemia	1 (2)	2 (4)	3 (3)
Concomitant therapy (≥5%)			
At least 1 concomitant therapy	50 (100)	49 (98)	99 (99)
ACEI	35 (70)	32 (64)	67 (67)
Loop-diuretics	17 (34)	16 (32)	33 (33)
Oral hypoglycemic drugs	6 (12)	7 (14)	13 (13)
β-blockers	4 (8)	3 (6.6)	7 (7)

Notes: Data are presented as mean ± standard deviation or *n* (%). The table includes those concomitant medications consumed by ≥2 study patients. Some patients were receiving > 1 concomitant therapies. All comparisons were not significant (Student's *t*-test for continuous variables, χ^2 test for categorical variables).

Abbreviations: ACEI: Angiotensin converting enzyme inhibitors; AS: Aspirin; mRS: Modified Rankin Scale; Poli: Policosanol.

Drug compliance was 95% and similar in both groups. Table 2 shows the distribution of patients across different mRS score levels, which were comparable between the two groups at baseline. At month 6 on therapy, the frequency of patients in the poli 20/AS 81 group who achieved mRS score ≤ 1 (31, 62%) was significantly higher ($p < 0.01$) than in those receiving pla/AS 81 (11, 22%). This difference was more accentuated at study completion when 46/50 (92%) and 23/50 (46%), respectively, reached the mRS score goals ($p < 0.001$).

Table 3 lists the effects of treatments on the mean scores of both stroke scales, with baseline values for each scale statistically similar in both groups. From the first interim check-up (1.5 months), poli 20/AS 81 treatment significantly decreased mRS scores versus baseline ($p < 0.001$), whilst differences versus the pla/AS 81 group were significant from month 3 onward. The decreasing effect of poli 20/AS 81 on mRS scores was enhanced over the course of the trial, resulting in a 59.2% greater decrease compared with the pla/AS 81 group at study completion ($p < 0.001$).

Compared with baseline, poli 20/AS 81 significantly

increased the mean BI scores at 1.5 months ($p < 0.001$), with this effect persisting and becoming increasingly pronounced thereafter through the end of the trial. BI scores in the poli 20/AS 81 group were significantly higher than those in the pla/AS 81 group from the third month ($p < 0.01$) to the end of the study ($p < 0.001$) (net difference 16.2%).

3.3. Effects on lipid profile

Table 4 shows the effects on lipid profile variables, which were similar in both groups at randomization. Poli 20/AS 81 lowered LDL-C significantly versus baseline at 6 and 12 months ($p < 0.05$ and $p < 0.01$, respectively), and also versus the pla/AS 81 group ($p < 0.05$ at month 6, $p < 0.01$ at month 12). At study completion, the percent reduction in LDL-C was 18.3% versus baseline and 19.7% versus the changes observed in the pla/AS 81 group. No significant change in post-treatment LDL-C values compared with baseline was observed in the pla/AS 81 group.

Similar changes, though more modest, occurred in TC values. Poli 20/AS 81 significantly lowered TC versus

Table 2. Effects on functional neurological recovery according to the distribution of patients across modified Rankin Scale (mRS) scores

mRS scores	Baseline		6 months		12 months	
	Poli 20/AS 81	Pla/AS 81	Poli 20/AS 81	Pla/AS 81	Poli 20/AS 81	Pla/AS 81
0–1	0	0	31**	11	46***	23
0	0	0	4	0	5	1
1	0	0	27	11	41	22
2–3	50	50	19**	39	4***	27
2	34	37	18**	33	4***	25
3	16	13	1	6	0	2
4	0	0	0	0	0	0

Notes: ** $p < 0.01$, *** $p < 0.001$. Comparisons versus pla/AS 81 (χ^2 test).
Abbreviations: AS: Aspirin; pla: Placebo; Poli: Policosanol.

Table 3. Effects on neurological recovery assessed using functional stroke scales scores

Treatment	Baseline	1.5 months	3 months	4.5 months	6 months	8 months	10 months	12 months
Modified Rankin Scale								
Poli 20/AS 81	2.32 ± 0.5 (2–3)	1.98 ± 0.6 (1–3)***	1.80 ± 0.7 (0–3)***#	1.56 ± 0.7 (0–3)***#	1.32 ± 0.7 (0–3)***#	1.24 ± 0.6 (0–2)***##	1.16 ± 0.5 (0–2)***##	0.98 ± 0.4 (0–2)***##
Pla/AS 81	2.26 ± 0.4 (2–3)	2.00 ± 0.6 (1–3)***	1.68 ± 0.7 (0–3)***	1.66 ± 0.6 (0–3)***	1.64 ± 0.6 (1–3)***	1.64 ± 0.6 (1–3)***	1.64 ± 0.6 (1–3)***	1.56 ± 0.6 (0–3)***
Barthel Index								
Poli 20/AS 81	80.4 ± 3.5 (75–90)	82.4 ± 4.3 (75–90)***	85.0 ± 5.3 (75–100)***	86.0 ± 5.4 (75–100)***	87.5 ± 6.1 (80–100)***	89.9 ± 4.7 (80–100)***##	91.9 ± 4.7 (80–100)***##	93.4 ± 4.7 (85–100)***##
Pla/AS 81	79.9 ± 4.3 (70–85)	82.1 ± 4.6 (70–90)***	85.0 ± 5.6 (75–100)***	85.6 ± 5.2 (75–100)***	87.0 ± 5.2 (80–100)***	86.9 ± 4.8 (80–95)***	87.2 ± 4.8 (80–95)***	87.5 ± 5.6 (75–95)***

Notes: Data are presented as mean ± standard deviation (95% confidence interval). *** $p < 0.001$, comparisons vs. baseline (Student's t -test for paired samples, Bonferroni adjustment); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, comparison vs. placebo/AS 81 (Student's t -test for independent samples). Abbreviations: AS: Aspirin; Pla: Placebo; Poli: Policosanol.

Table 4. Effects on the lipid profile (mmol/L)

Treatment	Baseline	6 months	12 months	Percentage changes (%) ^a
Low-density lipoprotein cholesterol				
Poli 20/AS 81	3.67 ± 0.9 (1.23–5.37)	3.37 ± 0.8 (1.23–5.21)**	3.00 ± 0.7 (1.55–4.79)***	–18.3**
Pla/AS 81	3.60 ± 0.9 (1.23–5.37)	3.58 ± 1.0 (1.23–5.21)	3.59 ± 0.7 (1.55–4.79)	–0.3
Total cholesterol				
Poli 20/AS 81	4.96 ± 1.0 (3.35–7.03)	4.69 ± 0.9 (3.18–6.54)**	4.39 ± 0.7 (3.17–6.32)***	–11.5**
Pla/AS 81	4.90 ± 0.9 (2.67–7.87)	4.86 ± 0.9 (2.93–7.4)	4.88 ± 0.8 (3.22–7.72)	–2.2
High-density lipoprotein cholesterol				
Poli 20/AS 81	1.05 ± 0.4 (0.83–2.6)	1.15 ± 0.5 (0.9–2.6)**	1.25 ± 0.5 (0.91–3.17)***	19.0**
Pla/AS 81	1.00 ± 0.4 (0.76–2.55)	1.03 ± 0.4 (0.91–2.61)	0.99 ± 0.3 (0.84–1.6)	–1.0
Triglycerides				
Poli 20/AS 81	1.22 ± 0.7 (0.41–4.07)	1.24 ± 0.7 (0.29–4.15)	1.16 ± 0.5 (0.42–2.32)	–4.9
Pla/AS 81	1.25 ± 0.7 (0.52–4.34)	1.20 ± 0.6 (0.44–2.06)	1.30 ± 0.5 (0.51–2.9)	4.0

Notes: ^a Percentage change between baseline and 12 months. Data are presented as mean ± standard deviation (95% confidence interval). * $p < 0.05$, ** $p < 0.01$, comparisons vs. baseline (Student's t -test for paired samples, Bonferroni adjustment); * $p < 0.05$, ** $p < 0.01$, comparison vs. placebo/AS 81 (Student's t -test for independent samples).

Abbreviations: AS: Aspirin; Pla: Placebo; Poli: Policosanol.

baseline, with a final reduction of 11.5%, while the net reduction versus the pla/AS 81 group values was 11.2%.

In contrast, poli 20/AS 81 significantly increased HDL-C versus baseline at 6 ($p < 0.05$) and 12 ($p < 0.01$) months. The percent increase in HDL-C at study completion was 19%; the net increase versus these values in the pla/AS 81 group was 20.8%.

Poli 20/AS did not change triglycerides significantly from baseline throughout the study. An insignificant upward drift, however, was observed in the pla/AS 81 group. Comparisons between groups did not show significant differences in these values at any time.

3.4. Safety and tolerability

Table 5 shows the effects on safety physical indicators. Bodyweight and pulse rate did not change significantly across comparisons. Poli 20/AS 81 significantly decreased diastolic blood pressure (DBP) versus baseline from 4.5 to

12 months ($p < 0.01$ for all comparisons), but differences versus pla/AS 81 group were significant only at 10 and 12 months ($p < 0.01$). Interestingly, in the pla/AS 81 group, DBP also decreased significantly at the end of the study ($p < 0.01$) versus baseline, but not in earlier time-point comparisons.

Furthermore, poli 20/AS 81 significantly decreased SBP versus baseline from 1.5 months ($p < 0.01$) to study completion ($p < 0.001$). The pla/AS 81 group also exhibited a similar trend, lowering SBP significantly from baseline ($p < 0.01$) throughout the study. When comparing the two groups, decreases in SBP were significantly different at 8, 10, and 12 months on therapy ($p < 0.01$).

No laboratory parameters were outside normal limits, and no significant differences between groups were found (data not included for simplicity). Treatments were well tolerated. Only two patients, both treated with pla/AS 81, referred some AE; one was the patient who suffered a

Table 5. Effects on safety physical indicators

Treatment	Baseline	1.5 months	3 months	4.5 months	6 months	8 months	10 months	12 months
Bodyweight (kg)								
Poli 20/AS 81	67.2 ± 10.6	67.3 ± 10.4	67.5 ± 10.5	67.3 ± 10.1	67.9 ± 11.9	68.1 ± 11.7	68.2 ± 11.5	67.4 ± 11.8
Pla/AS 81	65.9 ± 4.4	65.4 ± 13.8	65.5 ± 13.6	65.7 ± 13.2	64.1 ± 13.2	64.8 ± 13.0	65.1 ± 12.8	65.8 ± 13.3
Pulse (beats/min)								
Poli 20/AS 81	90.4 ± 3.5	89.4 ± 4.3	88.0 ± 5.3	88.0 ± 5.4	87.5 ± 6.1	89.9 ± 4.7	91.9 ± 4.7	90.1 ± 7.0
Pla/AS 81	89.9 ± 4.3	87.1 ± 4.6	88.0 ± 5.6	88.6 ± 5.2	87.0 ± 5.2	86.9 ± 4.8	87.2 ± 4.8	89.5 ± 5.6
Diastolic blood pressure (mmHg)								
Poli 20/AS 81	81 ± 11.4	80 ± 8.3	80 ± 8.7	79 ± 6.9**	79 ± 6.7**	78 ± 5.5**	77 ± 5.0***	76 ± 6.8***
Pla/AS 81	83 ± 11.5	81 ± 8.3	81 ± 7.1	81 ± 5.7	81 ± 7.9	81 ± 6.0	82 ± 5.9	81 ± 5.6**
Systolic blood pressure (mmHg)								
Poli 20/AS 81	139 ± 21.8	131 ± 13.6**	130 ± 4.9**	127 ± 11.2**	128 ± 14.4**	126 ± 12.6***	122 ± 7.9***	126 ± 13.4***
Pla/AS 81	141 ± 20.7	132 ± 10.5**	129 ± 11.6**	130 ± 9.8**	133 ± 16.1**	132 ± 8.2***	132 ± 9.8**	132 ± 14.0**

Notes: Data are presented as mean ± standard deviation. ** $p < 0.01$, *** $p < 0.001$, comparisons vs. baseline (Student's *t*-test for paired samples, Bonferroni adjustment); ** $p < 0.01$, comparison vs. placebo/AS 81 (Student's *t*-test for independent samples). Abbreviations: AS: Aspirin; Pla: Placebo; Poli: Policosanol.

fatal heart attack, and the other was one presenting with Parkinsonism debut.

4. Discussion

This study aims to investigate whether long-term administration of poli 20/AS 81 provides persistent and clinically relevant benefits over pla/AS on functional outcomes in patients who suffered a recent NCIS of moderate severity. Results demonstrate that treatment with poli 20/AS 81 resulted in significantly better post-stroke functional recovery than placebo/AS.

The patients were randomized within 30 days of stroke onset. Therefore, this study reflects the effects of the subacute post-ischemic stroke phase. Following the ischemic stroke management guidelines,¹⁰⁻¹² patients received AS from their admission in the stroke unit to the end of the study.

One strength of the study design is that it is randomized, double-blind, and placebo-controlled, with all patients receiving AS, the first-line antiplatelet therapy, after ischemic stroke.¹⁰⁻¹² At randomization, the study population had mRS scores of 2–3 (both limits included) to minimize the influence of varying stroke severity on outcomes. Patients had not received policosanol and were naïve to the study treatment. Both groups showed comparable baseline characteristics, including the mean mRS and BI scores, indicating that they were homogeneous at randomization. Hence, the significant and clinically relevant effects observed here for poli 20/AS 81 therapy can be attributed to the treatment rather than to any baseline disparity, a finding that provides validity to the present results. This assumption is reinforced by the exceptional (95%) treatment compliance and its comparability across groups, supporting the validity of the present results.

Our study population exhibited common stroke risk factors at baseline, including hypertension, a salt-rich diet, sedentary lifestyle (these three risk factors being present in more than 90% of participants), overweight/obesity, smoking, and diabetes. In addition to AS, consumed by all patients, antihypertensive drugs, especially ACEI, were the commonest concomitant therapies, consistent with the prevalence of hypertension in the study patients. Concomitant therapy was also well-balanced in both groups.

The effects on stroke functional recovery were assessed using two stroke scales: the mRS and the BI.^{69,70} Of these, the mRS is the most widely used stroke scale to follow stroke recovery in clinical studies.⁷⁴⁻⁷⁸

Our results demonstrate that, at study completion, the proportion of patients who achieved an mRS score

≤ 1 (primary study outcome) was significantly higher in the poli 20/AS 81 group (46/50, 92%) than in the pla/AS group (23/50, 46%). This significant difference occurred after 6 months on treatment (poli 20/AS 81: 31/50, 62%; pla/AS 81: 11/50, 22%). Since a decrease of one level on mRS is considered clinically relevant and an mRS score ≤ 1 represents good recovery,^{75,77,78} these results confirm that the combined therapy (poli 20/AS 81) provides clinical benefits in the recovery of NCIS compared with low-dose AS monotherapy.

The improvement in neurological recovery observed with poli 20/AS 81 compared with pla/AS 81 was also evident in the mean scores of both scales over the study period. At 1.5 months of treatment, the poli 20/AS 81 group showed a significant reduction in the mean mRS score versus baseline, with this effect increasing throughout the trial. Between-group differences were evident from month 3 of treatment onward. At the end of the study, the net difference compared with the pla/AS 81 group was 59.2%. Considering the 11–13% reduction in mRS scores at 12 weeks after stroke reported in the NINDS rt-PA study, in which patients were treated within the first h of acute stroke,⁸³ it is reasonable to consider the present results with poli/AS clinically meaningful.

The changes in the BI scores also support the persistent efficacy of poli 20/AS 81 over pla/AS 81. Significant increases from baseline were observed from 1.5 to 12 months after treatment initiation, with the effect increasing over the course of the trial. Between-group differences versus pla/AS 81 became evident from month 3 of treatment onward and persisted until the end of the study, when the poli 20/AS 81 group exhibited a 16.2% greater net increase compared with the pla/AS 81 group.

The BI is a stroke scale commonly used to assess the actual performance in activities of daily living in post-stroke patients in clinical studies and practice.^{78,79} Hence, the results obtained with this scale reinforce the clinical relevance of the effects of poli 20/AS 81 for managing patients with NCIS. In addition, poli 20/AS 81 produced beneficial effects on the lipid profile of patients, including a significant moderate reduction in LDL-C (18.3%), a significant modest decrease in TC (11.5%), and a significant moderate increase in HDL-C (19%), all expressed relative to baseline. These changes were also significant compared with those observed in the pla/AS 81 group.

The mechanisms by which policosanol may enhance stroke recovery lie beyond the scope of this study. Nevertheless, its antiplatelet properties²⁵⁻²⁹ likely account, at least in part, for the superior outcomes observed with poli 20/AS 81 treatment compared with pla/AS 81.

Supporting this hypothesis, a previous 6-month clinical trial in NCIS patients showed that poli 20/AS 125 not only improved functional recovery more effectively than pla/AS, but also demonstrated greater antiplatelet efficacy.⁶⁵

In addition, the lipid-modifying effects of policosanol may contribute to its benefits in stroke recovery, as LDL-C reduction is closely linked to improved outcomes and prevention.^{18–21} Policosanol reduces cholesterol synthesis by modulating HMG-CoA reductase activity through activation of AMP kinase,^{50–55} a key regulatory enzyme. In hepatoma cells, policosanol increased AMP kinase phosphorylation, suggesting that it downregulates HMG-CoA reductase activity and reduces cholesterol synthesis without directly inhibiting the enzyme.^{53,55} Further studies have shown that metabolic conversion of very long-chain alcohols into fatty acids is required to suppress cholesterol synthesis, presumably by increasing cellular AMP levels.⁵⁶

The treatments in our study were well tolerated, with only two patients treated with pla/AS 81 reporting AEs. One was due to a fatal AE (heart attack), which led to study withdrawal, and the other experienced early Parkinsonian symptoms and signs. No AEs were reported in the poli 20/AS 81 group. Interestingly, no recurrent strokes or transient ischemic attacks occurred among the patients, a particularly favorable finding given that recurrent events are frequent within the first year post-stroke.^{6–8} Additionally, poli 20/AS 81 did not affect hematological or biochemical safety parameters compared with pla/AS 81, with all values remaining within normal reference ranges. These findings indicate that poli 20/AS 81 is safe and well tolerated in post-stroke patients.

The significant decreases in SBP observed with poli 20/AS 81 versus pla/AS 81 at 8, 10, and 12 months of treatment, as well as the DBP reductions at 10 and 12 months, are not surprising, as similar results have been observed in previous studies in post-stroke patients.^{65–67} Nevertheless, as no patient had hypotensive values and most patients were hypertensive, this effect could be considered potentially beneficial rather than adverse in the context of stroke recovery. However, the significant decrease in both SBP and DBP in the pla/AS 81 group may indicate potential bias in blood pressure measurement or recording within the study.

A limitation of the present study is that the selection criteria included only patients aged 40 years or older with recent NCIS, thereby excluding patients aged 40 years or younger.

5. Conclusion

This study demonstrates, for the first time, that treatment with poli 20/AS 81 significantly improved functional recovery in NCIS patients compared with pla/AS 81. Improvements in lipid profile were also observed, and the treatment was safe and well tolerated.

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Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board (IRB) (IRB-002021) after receiving the inputs of the National Hypertension Group of the Cuban Ministry of Health and being registered in the Cuban Public Registry of Clinical Trials (RPCEC00000378). The

study followed the ethical principles established in the latest versions of the Declaration of Helsinki and the Tokyo Declaration. All participants provided written informed consent at enrolment.

Consent for publication

All participants provided written informed consent for publication at enrollment.

Availability of data

Data are available from the corresponding author upon reasonable request.

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