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Relationship between Non-Specific Prescription Pill Adherence and Ischemic Stroke Outcomes

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Key Words
Adherence · Prescription · Compliance · Stroke, ischemic · Outcomes

Abstract
Background: Adherence to non-specific prescription therapy may be associated with clinical outcomes beyond a given treatment effect. We assessed the association of blinded randomized pill prescription adherence with vascular outcomes after ischemic stroke. ***Methods:*** We analyzed the Vitamin Intervention for Stroke Prevention (VISP) study database. VISP was a double-blind randomized trial, designed to determine whether high doses of vitamins (vs. low doses) would reduce recurrent stroke risk in 3,680 participants over a 2-year period. We examined the independent association of adherence with a composite endpoint (stroke, myocardial infarction, death). ***Results:*** Among 3,357 (91%) subjects with complete data, women, non-White persons, current smokers, those not on statins and those without a history of coronary artery bypass surgery were significantly less likely to be optimally adherent. Over the trial, persons who adhered well to treatment were less likely to experience the combined outcome than those who adhered poorly (13.4 vs. 20.6%, $p < 0.0001$). After multivariable analysis using various adherence measures, there were no significant differences between ≥80% vs. <80% adherence, but compared to <65% adherence, pill adherence levels of ≥90 to <99% (HR 0.56, 95% CI = 0.34–0.91; p = 0.02) and ≥99% (HR 0.46, 95% CI = 0.29–0.73; p = 0.001) were associated with lower occurrence of the combined outcome at 18 months. ***Conclusions:*** Long-term excellent adherence to non-specific pill prescription among ischemic stroke patients is independently associated with lower vascular risk, and is likely a marker of overall healthy behavior that may be helpful in targeting stroke patients with unhealthy practices.

Introduction

Although several studies have shown that medications and lifestyle modification can improve outcomes after stroke and TIA [1], adherence to these interventions is unfortunately sub-par [2, 3]. Not surprisingly, poor adherence tends to limit the effectiveness of proven therapies, resulting in lost opportunities to reduce vascular risk after stroke [4]. However, adherence itself may reflect

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compliance with other types of conduct that influence clinical outcome [5]. In other words, adherence may be more than just taking a pill [5]. Indeed, data from randomized clinical trials in cardiac patients indicate that the advantage associated with better adherence might be unrelated to the effect of a specific treatment [6–8]. For instance, it has been shown in coronary artery disease (CAD) and congestive heart failure patients that improved adherence, even to placebo, is associated with improved survival and fewer cardiovascular events [6–8].

The aforementioned findings suggest that a better understanding of the impact and nature of adherence on clinical outcomes could provide an avenue for novel interventions geared at optimizing adherence [5]. Little if anything is known about the relationship between nonspecific pill adherence and clinical outcomes among patients with established cerebrovascular disease. Since pill compliance is routinely recorded in randomized secondary stroke prevention trials, assessing its association with meaningful endpoints could provide some insight into this issue.

The objective of this study was to determine whether greater adherence to blinded randomized pill prescription within a stroke prevention trial, regardless of treatment arm, would be associated with better clinical outcomes.

Methods

Dataset

We reviewed data from the Vitamin Intervention for Stroke Prevention (VISP) trial [9]. The VISP trial was a multicenter double-blind randomized controlled clinical trial performed at centers across the USA (n = 45), Canada (n = 10) and Scotland (n = 1). It was designed to determine whether the best medical therapy and a multivitamin containing high-dose folic acid, pyridoxine, and cobalamin given to lower total homocysteine levels would reduce the incidence of recurrent cerebral infarction in patients with a non-disabling cerebral infarction [9]. The methods and results of this trial have previously been described [9]. Pertinent to the current report, the VISP population comprised persons whom neurologists had identified as having experienced an ischemic stroke from September 1996 through May 2003. Demographic, clinical, and laboratory data were collected at baseline, with subsequent clinical and laboratory information obtained in follow-up visits at 6, 12, 18, and 24 months.

Variables

Independent Variable. We took account of the date on which the pills were distributed in our measure of adherence. Adherence was calculated at each clinic visit as [(number of pills taken by the participant subtracted from number of pills distributed to the participant) divided by number of days since the last scheduled visit at which pills were dispensed] multiplied by 100. We trimmed any adherence values over 100 to 100%; negative adherence values were considered invalid and set to missing. Assessments at the 6-, 12-, and 18-month clinic visits were included here for the participants who had at least one such assessment. Not all patients had all these assessments. In all but one of our analyses of adherence, measurements of adherence made after a stroke or coronary event were excluded. Several summary measures of adherence were considered. Total pill adherence was defined as: (number of visits at which adherence was >80% divided by number of visits with adherence data) multiplied by 100. Adherence ≥80% at each measure was deemed good. Adherence was analyzed in 4 ways: (1) as a dichotomized variable (adherence ≥80% at each visit, yes vs. no [5]); (2) average overall adherence over the whole study ≥80% (yes vs. no); (3) average overall adherence of measures made prior to an event (≥80%, yes vs. no); (4) visit-specific survival analyses, using multiple categories (<65%, 65% to <80%, ≥80% to <90%, ≥90% to <99%, and ≥99%) for persons event-free until an index visit.

Dependent Variable. The endpoint for this particular analysis was a composite outcome comprising the occurrence of stroke, myocardial infarction or death from any cause.

Covariates. We included a baseline history of any symptomatic ('hard') vascular event, baseline vascular biomarkers, and factors previously associated with adherence as covariates. This included categorical variables (sex, race, history of ischemic stroke prior to randomization, smoking, and statin use) and continuous variables (age, systolic blood pressure, and fasting total cholesterol) [1, 5]. Since there were no specific measures of CAD prior to randomization and several other symptomatic cardiac conditions can impact upon mortality, we also included a history of any of the following as covariates: angina, myocardial infarction, congestive heart failure, coronary artery bypass surgery, and coronary angioplasty or stenting. We also included VISP assignment group (i.e. high-dose vs. low-dose vitamin treatment) as a covariate.

Statistical Analysis

Multiple logistic regression was used in the analysis of the association between overall adherence and outcome. Cox proportional hazard models were used in the analysis of the association between visit-specific adherence and time to outcome.

Results

A total of 3,680 ischemic stroke patients were enrolled during the study period. Figure 1 shows a breakdown of the exclusions and resulting counts of participants, leaving 3,357 subjects who had complete and verifiable data. Of these, the mean and median ages (at baseline visit) were 66.4 and 67 years, respectively; 38% were female, 81% White, and 14% African-American.

Women, non-White persons, current smokers, those with no history of coronary artery bypass surgery, and individuals not on statin treatment were less likely to be optimally adherent to prescription pill treatment (table 1).

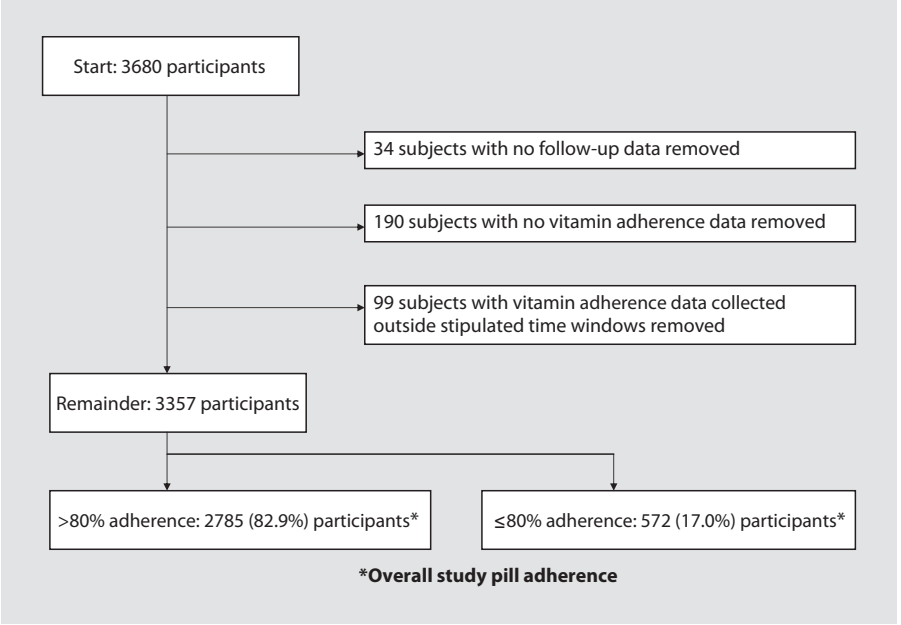

Fig. 1. Exclusions and resulting counts of study participants.

Unadjusted analyses of the combined outcome over the course of the trial, including adherence measures obtained after a stroke or coronary event, revealed that those who adhered well (≥80%) to treatment at each assessment visit over the trial period were less likely to experience the outcome than poor adherers (13.4 vs. 20.6%, $p < 0.0001$). Similar results were obtained with unadjusted analyses of the outcome by total average overall pill adherence over the duration of the trial ≥80% or not. However, when we excluded all visits that occurred after an event (i.e. only visits preceding the occurrence of an outcome were considered): 11.4% of those with an average adherence ≥80% experienced an outcome versus 12.0% of those with adherence <80% ($p = 0.73$). When this association was adjusted for potential confounders through logistic regression, the association remained non-significant. Table 2 displays the frequencies of total study prescription pill adherence (before vascular event) by study time point and primary endpoint.

When the analysis was performed as study-visit specific, including only those with no outcome prior to the index visit when adherence was assessed, unadjusted analyses showed no significant association with adherence up to the 6-month visit (table 3), but significant associations with adherence through the 12- and 18-month visits (tables 4 and 5).

After adjustment for the basic confounders of age, sex, race, and study treatment, study pill adherence ≥90% (vs. <65%) at the 12-month and 18-month study visits was significantly associated with a lower occurrence of the composite endpoint ($p < 0.05$); however, no significant association was found between study pill adherence and outcome at the 6-month visit. The results of more expansive multivariable modeling showed similar results and can be found in tables 3–5. There were no significant outcome differences by pill adherence at the 6-month visit (table 3). However, study subjects who adhered to pill prescription at the 12-month and 18-month visits either 90% to <99%, or ≥99%, of the time (compared to <65%), were significantly less likely to have experienced the composite endpoint. There were no significant interactions between study pill adherence and VISP treatment, nor any significant associations between VISP treatment and the composite endpoint.

Discussion

In this secondary analysis of a clinical trial dataset, we found that excellent adherence to study pill prescription (i.e. ≥90% of the time), regardless of treatment assignment, among individuals with a recent ischemic stroke, was independently associated with lower risk of future major vascular events at 12 and 18 months after enrollment, but not at 6 months after enrollment. Contrary to our initial hypothesis, good adherence (i.e. ≥80% of the

Table 1. Frequencies of total study prescription pill adherence (before vascular event) by baseline covariates

		Study pill adherence		p value
		<80%	≥80%	
Age (years)	35–54	97 (18.9)	414 (81.0)	0.10
	55–69	212 (15.9)	1,124 (84.1)	
	≥70	207 (14.9)	1,183 (85.1)	
Sex	female	220 (17.9)	1,010 (82.1)	0.02
	male	296 (14.8)	1,711 (85.3)	
Race	white	347 (13.3)	2,268 (86.7)	<0.0001
	black	126 (27.8)	327 (72.2)	
	other	43 (25.4)	126 (74.6)	
Current smoker	yes	119 (22.4)	412 (77.6)	<0.0001
	no	397 (14.7)	2,308 (85.3)	
BMI	<25	141(15.7)	755 (84.3)	0.68
	25–30	206 (15.5)	1,120 (84.5)	
	>30	165 (16.8)	815 (83.2)	
Alcohol use in prior year	yes	279 (14.6)	1,628 (85.4)	0.04
	no	221 (17.3)	1,057 (82.7)	
Stroke >90 days before randomization	yes	168 (16.7)	836 (83.3)	0.41
	no	348 (15.6)	1,885 (84.4)	
History of hypertension	yes	371 (15.7)	1,999 (84.4)	0.45
	no	144 (16.8)	715 (83.2)	
History of diabetes	yes	153 (16.7)	763 (83.3)	0.47
	no	363 (15.7)	1,954 (84.3)	
History of myocardial infarction	yes	78 (15.2)	434 (84.8)	0.56
	no	436 (16.1)	2,266 (83.9)	
History of congestive heart failure	yes	23 (14.7)	133 (85.3)	0.61
	no	492 (16.1)	2,573 (83.9)	
History of coronary bypass surgery	yes	40 (12.8)	272 (87.2)	0.26
	no	476 (16.3)	2,446 (83.7)	
History of coronary angioplasty	yes	34 (15.3)	189 (84.8)	0.79
	no	482 (16.0)	2,527 (83.9)	
History of carotid endarterectomy	both	1 (3.5)	28 (96.6)	0.07
	left	11 (11.1)	88 (88.9)	
	right	10 (11.2)	79 (88.8)	
	no	494 (16.4)	2,525 (83.6)	
Any antithrombotic use during trial	yes	309 (15.2)	1,728 (84.8)	0.12
	no	207 (17.3)	993 (82.8)	
Any statin use during the trial	yes	283 (14.1)	1,721 (85.9)	0.0003
	no	233 (18.9)	1,000 (81.1)	

Data presented as number of patients with percentages in parentheses; p values refer to high- vs. low-risk groups.

Total adherence was defined for each participant as: (visits >80% adherence/visits with adherence data) × 100. Visit-specific adherence was calculated using the standard VISP definition as: [(pills dispensed at last visit – pills remaining)/days between last scheduled vitamin visit and today] × 100.

Table 2. Frequencies of study prescription pill adherence (before vascular event) by study time point and primary endpoint

	Occurrence of primary endpoint		
	yes	no	total adherence
6 months			
<65%	9 (0.32)	74 (2.63)	83 (2.95)
65 to <80%	13 (0.46)	74 (2.63)	87 (3.09)
≥80 to <90%	34 (1.21)	187 (6.64)	221 (7.84)
≥90 to <99%	109 (3.87)	807 (28.64)	916 (32.51)
≥99%	159 (5.64)	1,352 (47.98)	1,511 (53.62)
Total	324 (11.50)	2,494 (88.50)	2,818 (100)
12 months			
<65%	24 (0.86)	123 (4.41)	147 (5.27)
65 to <80%	19 (0.68)	73 (2.62)	92 (3.30)
≥80 to <90%	29 (1.04)	182 (6.56)	212 (7.60)
≥90 to <99%	75 (2.69)	773 (27.72)	848 (30.41)
≥99%	138 (4.95)	1,352 (48.48)	1,490 (53.42)
Total	285 (10.22)	2,504 (89.78)	2,789 (100)
18 months			
<65%	27 (1.10)	112 (4.55)	139 (5.64)
65 to <80%	11 (0.45)	65 (2.64)	76 (3.08)
≥80 to <90%	26 (1.06)	128 (5.19)	154 (6.25)
≥90 to <99%	64 (2.60)	662 (26.87)	726 (29.46)
≥99%	106 (4.30)	1,263 (51.26)	1,369 (55.56)
Total	234 (9.50)	2,230 (90.50)	2,464 (100)

Data presented as number of patients with percentages in parentheses. Primary endpoint = Incidence of stroke, myocardial infarction, or vascular death.

time) was not associated with outcome. Since the favorable clinical effects of excellent adherence were seen across treatment groups without any interaction of adherence with VISP treatment, these benefits were likely derived beyond the biological properties of the therapies themselves. An independent link between adherence to study pill prescription (including placebo) and clinical outcomes has been shown in several studies of persons with cardiac disease [5], but we are unaware of any studies that have explored this issue among stroke patients. Furthermore, the aforementioned cardiac studies generally did not assess the impact of study pill adherence at various study time points, particularly at relatively early time points, such as within 6 months of study enrollment.

Traditionally, albeit arbitrarily, consumption of more than 80% of prescribed doses has been deemed an acceptable level of adherence to therapy in various types of chronic illness [5]. This cutoff point has been broadly

Table 3. Cox proportional hazards model: pill adherence at 6 months vs. outcome

	Hazard ratio	95% confidence limits		p value
		lower limit	upper limit	
Age at first visit	1.03	1.02	1.04	<0.0001
Black race	1.27	0.91	1.78	0.17
Other race	1.59	1.01	2.51	0.05
Current smoker	0.97	0.65	1.45	0.89
Number of strokes prior to eligibility stroke	1.04	0.99	1.10	0.15
History of angina at visit 1	1.36	0.94	1.98	0.11
History of myocardial infarction at visit 1	1.44	1.05	1.98	0.03
History of congestive heart failure at visit 1	1.75	1.16	2.64	0.01
History of coronary artery bypass at visit 1	0.88	0.60	1.30	0.52
History of coronary angioplasty at visit 1	1.62	1.11	2.36	0.01
Systolic blood pressure at visit 1	1.01	1.00	1.01	0.06
Total cholesterol at visit 1	1.00	0.99	1.00	0.38
Any statin use during the trial	0.90	0.71	1.14	0.39
VISP high-dose vitamin treatment	0.99	0.79	1.24	0.94
VISP pill adherence: 65 to <80%	1.92[1] (1.68)	0.80 (0.71)	4.60 (3.97)	0.15 (0.24)
VISP pill adherence: ≥80 to <90%	1.84[1] (1.66)	0.86 (0.78)	3.93 (3.52)	0.12 (0.19)
VISP pill adherence: ≥90 to <99%	1.33[1] (1.23)	0.66 (0.61)	2.71 (2.47)	0.43 (0.56)
VISP pill adherence: ≥99%	1.14[1] (1.05)	0.56 (0.53)	2.29 (2.09)	0.72 (0.88)

Figures in parentheses contain unadjusted results. [1] Compared to level of adherence <65%.

used in studies of patients with CAD, cancer, and hypertension, and significantly linked to clinical outcomes [5]. However, our results suggest that for stroke patients, non-specific pill adherence ≥90% of the time, and not ≥80% of the time, is the cutoff point significantly linked to favorable outcomes. Indeed, in earlier studies of adherence to therapy in HIV-infected patients, the cutoff point of good adherence was the conventional 80% cutoff [10–12], but this changed [13, 14], after a landmark study showed that HIV-infected patients with 95% or greater adherence had superior outcomes than patients with lower levels of adherence, to the extent that the percentage of patients with a favorable outcome rose by 20% when adherence increased from 90–95% to 95–100% [15].

Although the results of our study and those of others suggest a health benefit of adherence, the underlying mechanisms are not fully understood and the observational nature of these investigations limits any causal inferences. Nonetheless, several potential mechanisms have been proposed to explain this association of good adherence with favorable outcomes. For instance, it has been suggested that good adherence is a marker of a more general predisposition to beneficial lifestyle practices such as healthy eating and regular physical activity, also known as the 'healthy adherer effect' [16], while poor adherence has been associated with deleterious behaviors like smoking. Indeed, one study found that adherence to a placebo pill was associated with a greater likelihood of consuming a heart-healthy diet [17]. Our study may also in part point to a general health-oriented behavior pattern as a potential explanation for the health benefits of adherence, since like others we observed that current smokers in the VISP trial were less likely to adhere well to the VISP study pill regimen.

Some have also suggested that psychosocial factors may contribute to the association of non-specific adherence with clinical prognosis [17]. This is because depression has been associated with poor adherence to cardiac medications [18], greater social support has been linked with better adherence [19, 20], and adherent subjects seem to engage in twice the number of pleasurable social activities before their index vascular event than poor adherers [17]. The latter finding has led some to believe that the relationship between good adherence and better outcomes may simply reflect increased expectancy or belief in the prescribed regimen, in other words, a boosted placebo effect [16].

There are potential practical and research implications to our results. Pending more definitive studies, the healthy adherer effect remains the foremost explanation

Table 4. Cox proportional hazards model: pill adherence at 12 months vs. outcome

	Hazard ratio	95% confidence limits		p value
		lower limit	upper limit	
Age at first visit	1.03	1.01	1.04	<0.0001
Male sex	1.10	0.85	1.43	0.47
Black race	1.01	0.69	1.47	0.97
Other race	1.16	0.67	2.02	0.59
Current smoker	1.13	0.80	1.60	0.48
Number of strokes prior to eligibility stroke	1.04	0.98	1.11	0.15
History of angina at visit 1	1.37	0.92	2.04	0.12
History of myocardial infarction at visit 1	1.25	0.88	1.77	0.22
History of congestive heart failure at visit 1	1.91	1.24	2.95	0.003
History of coronary artery bypass at visit 1	0.80	0.52	1.23	0.31
History of coronary angioplasty at visit 1	1.56	1.01	2.40	0.04
Systolic blood pressure at visit 1	1.01	1.00	1.01	0.02
Total cholesterol at visit 1	1.00	0.99	1.00	0.60
Any statin use during the trial	0.97	0.75	1.24	0.78
VISP treatment	0.99	0.78	1.26	0.92
VISP pill adherence: 65 to <80%	1.55[1] (1.36)	0.83 (0.74)	2.92 (2.51)	0.17 (0.32)
VISP pill adherence: ≥80 to <90%	0.94[1] (0.89)	0.53 (0.51)	1.67 (1.55)	0.83 (0.68)
VISP pill adherence: ≥90 to <99%	0.61[1] (0.57)	0.37 (0.35)	0.99 (0.91)	0.05 (0.02)
VISP pill adherence: ≥99%	0.61[1] (0.59)	0.38 (0.38)	0.98 (0.92)	0.04 (0.02)

Figures in parentheses contain unadjusted results. [1] Compared to level of adherence <65%.

Table 5. Cox proportional hazards model: pill adherence at 18 months vs. outcome

	Hazard ratio	95% confidence limits		p value
		lower limit	upper limit	
Age at first visit	1.02	1.01	1.04	0.002
Male sex	1.02	0.77	1.37	0.88
Black race	1.06	0.71	1.60	0.77
Other race	0.72	0.33	1.53	0.39
Current smoker	0.97	0.65	1.45	0.89
Number of strokes prior to eligibility stroke	1.05	1.00	1.12	0.12
History of angina at visit 1	1.39	0.90	2.16	0.14
History of myocardial infarction at visit 1	1.43	0.99	2.08	0.06
History of congestive heart failure at visit 1	1.87	1.16	3.01	0.01
History of coronary artery bypass at visit 1	0.88	0.57	1.38	0.59
History of coronary angioplasty at visit 1	1.57	1.01	2.46	0.05
Systolic blood pressure at visit 1	1.01	1.00	1.02	0.04
Total cholesterol at visit 1	1.00	0.99	1.004	0.67
Any statin use during the trial	1.12	0.84	1.50	0.44
VISP treatment	0.99	0.76	1.29	0.92
VISP pill adherence: 65% to <80%	0.77[1] (0.90)	0.35 (0.44)	1.68 (1.84)	0.51 (0.77)
VISP pill adherence: ≥80% to <90%	1.09[1] (1.07)	0.60 (0.61)	1.99 (1.88)	0.77 (0.81)
VISP pill adherence: ≥90% to <99%	0.56[1] (0.53)	0.34 (0.33)	0.91 (0.85)	0.02 (0.01)
VISP pill adherence: ≥99%	0.46[1] (0.45)	0.29 (0.29)	0.73 (0.71)	0.001 (0.001)

Figures in parentheses contain unadjusted results. [1] Compared to level of adherence <65%.

for the association of good pill prescription adherence with beneficial outcomes [5]. As such, it may be useful and not necessarily laborious for clinicians to use compliance with the prescribed drug regimen by their stroke patients as an indicator of overall adherence to a healthy lifestyle. Those individuals who are noted to adhere poorly to prescribed drugs may benefit from more extensive inquiry into various aspects of their lifestyle, in order to uncover potentially unhealthy behaviors and provide additional education/counseling. Another practical consideration is that practitioners might consider using compliance with the prescribed drug regimen by their stroke patients to target those persons with underlying unhealthy psychosocial issues that may need to be resolved in order to enhance clinical outcomes. In the research arena, information on study-blinded prescription pill adherence in randomized secondary stroke prevention trials may be considered along with the usual sociodemographic and clinical prognosticator variables to further ensure that randomization was actually balanced.

The association between excellent adherence and favorable clinical outcomes at longer time points (12 and 18 months) but not at the shorter time point of 6 months has not been examined in prior studies exploring this issue, but this result seems plausible. Patients are generally much more focused on the index vascular event early after it occurs, and are thereby more likely to be compliant with the medical recommendations during relatively early periods as opposed to later on [4]. This may be further buttressed by our finding of a stronger association of excellent study pill adherence with outcomes at 18 months compared to 12 months.

Our study has limitations. As noted, it was observational and so no causal inferences can be made. Although we conducted a multivariable analysis, unmeasured confounding could still explain our results. Adherence was measured by pill count, which may overestimate adherence since subjects may not ingest all the pills they remove from a bottle [21]. It must also be pointed out that there is a limit on the extent to which we can generalize data from the VISP population, because it is conceivable that since VISP patients were encountered in a research-oriented setting, they were probably more motivated than stroke survivors seen in routine medical practice, and so pill adherence rates in the latter setting may be much worse. Finally, the post hoc nature of the study meant we could only examine the variables collected in the original study, which limited the exploration of the contribution of lifestyle practices and psychosocial factors to the associations we observed [5].

In conclusion, we found longer-term excellent adherence to pill prescription among persons who have recently experienced a recent ischemic stroke to be independently associated with lower risk of subsequent vascular events. Our results need to be confirmed independently, and the possibility of a causal relation between adherence and health outcomes investigated. However, in the meantime, clinicians may consider adherence to pill prescription as a potential marker of overall healthy behavior, which could be used in targeting stroke patients with unhealthy lifestyle practices that need to be addressed.

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References

1 Sacco RL, Adams R, Albers G, et al: Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37:577–617.

2 Holloway RG, Benesch C, Rush SR: Stroke prevention: narrowing the evidence-practice gap. Neurology 2000;54:1899–906.

3 Reeves MJ, Arora S, Broderick JP, et al: Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry. Stroke 2005;36:1232–1240.

4 Ovbiagele B, Saver JL: Ensuring management of vascular risk factors after stroke. Rev Neurol Dis 2006;3:93–100.

5 Simpson SH, Eurich DT, Majumdar SR, et al: A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006;333:15.

6 Horwitz RI, Viscoli CM, Berkman L, et al: Treatment adherence and risk of death after a myocardial infarction. Lancet 1990;336:542–545.

7 Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. N Engl J Med 1980;303:1038–1041.

8 Granger BB, Swedberg K, Ekman I, et al: Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet 2005;366:2005–2011.

9 Toole J, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, Sides EG, Wang CH, Stampfer M: Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA 2004;291:565–575.
10 Eldred LJ, Wu AW, Chaisson RE, Moore RD: Adherence to antiretroviral and pneumocystis prophylaxis in HIV disease. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 18:117–1125.
11 Lopez-Suarez A, Fernandez-Gutierrez del Alam C, Perez-Guzman E, Giron-Gonalez JA: Adherence to the antiretroviral treatment in asymptomatic HIV-infected patients. AIDS 1998;12:685–686.
12 Rodriguez-Rosado R, Jimenez-Nacher I, Soriano V, Anton P, Gonzalez-Lahoz J: Virological failure and adherence to antiretroviral therapy in HIV-infected patients. AIDS 1998;12:1112–1113.
13 García de Olalla P, Knobel H, Carmona A, Guelar A, López-Colomés JL, Caylà JA: Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. J Acquir Immune Defic Syndr 2002; 30:105–110.
14 Knobel H, Urbina O, González A, et al: Impact of different patterns of nonadherence on the outcome of highly active antiretroviral therapy in patients with long-term follow-up. HIV Med 2009;10:364–369.
15 Paterson DL, Swindells S, Mohr J, et al: Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000;133:21–30.
16 Czajkowski S, Chesney M, Smith A: Adherence and the Placebo Effect; in Shumaker S, Schron E, Ockene J (eds): The Handbook of Health Behavior Change. New York, Springer, 1990 pp 515–534.
17 Irvine J, Baker B, Smith J, et al: Poor Adherence to placebo or amiodarone therapy predicts mortality: results from the CAMIAT study. Psychosom Med 1999;61:566–575.
18 Carney R, Freedland K, Eisen S, Rich M, Jaffe A: Major depression and medication adherence in elderly patients with coronary artery disease. Health Psychol 1995;14:88–90.
19 Bastone E, Kerns R: Effects of self-efficacy and perceived social support on recovery-related behaviors after coronary artery bypass surgery. Ann Behav Med 1995;17:324–330.
20 Doherty W, Schrott H, Metcalf L, Iasiello-Vailas L: Effect of spouse support and health beliefs on medication adherence. J Fam Pract 1983;17:837–841.
21 Logan A, Irvine M: Compliance, labelling, and hypertension; in Swales J (ed): Textbook of Hypertension. Oxford, Blackwell Scientific, 1994, pp 1267–1282.