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Impact on Prehospital Delay of a Stroke Preparedness Campaign: A SW-RCT (Stepped-Wedge Cluster Randomized Controlled Trial)

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IMPACT ON PREHOSPITAL DELAY OF A CAMPAIGN AIMED TO INCREASE STROKE PREPAREDNESS: A STEPPED WEDGE CLUSTER RANDOMIZED CONTROLLED TRIAL.

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Abstract.

IMPORTANCE. Public campaigns to increase stroke preparedness and reduce prehospital delay have been tested in different contexts, showing contradictory results

OBJECTIVE. To test the effectiveness of a stroke campaign, specifically designed for the local context, in reducing prehospital delay.

DESIGN, SETTING AND PARTICIPANTS. We used a stepped wedge cluster randomized controlled design. The cluster were the communities of the four provinces of Northern Emilia Romagna. The intervention was launched in the four provinces at 3-months intervals in randomized sequence and compared to usual care. The units of analysis were the patients admitted to hospital, with diagnosed or suspected stroke and Transient Ischemic Attack (TIA), over a time period of 15 months, beginning 3 months before the intervention was launched in the first province to allow for baseline data collection. (from1st August 2013 to 30th November 2014).

INTERVENTION. A public campaign, developed according to the Intervention Mapping framework, consisting in distribution of educational materials about stroke symptoms, the importance of prompt referral to the Emergency Services and the therapeutic opportunities in case of early hospital admission.

MAIN OUTCOMES AND MEASURES. The proportion of early arrivals (< 2 hours of symptom onset) was the primary outcome. Thrombolysis rate and some behavioral endpoints were the secondary outcomes. Data were analyzed using a fixed effect model (FEM), adjusting for cluster and time-trends.

RESULTS. We enrolled 1662 patients, 912 exposed and 710 non-exposed to the campaign. The proportion of early access was non-significantly lower in exposed patients (357 [38.8%] vs 315 [44.4%], adjusted OR=0.81, 95% Confidence Interval [CI]=0.60-1.08, P=.15) . As for secondary endpoints, a non-significant increase was found for stroke recognition only. Sensitivity analysis,

confirmed the lack of any effect of the campaign on prehospital delay, considered as continuous variable as well as an ordinal one, using different cut-offs.

CONCLUSIONS AND RELEVANCE. Our study confirms the inefficacy of stroke preparedness campaigns in reducing pre-hospital delay, even if some limitations of the intervention, mainly in terms of duration, should be taken into account. Overall it suggests that new communication strategies should be tested before large scale implementation

Trial registration: clinicaltrials.gov identifier: NCT01726387; June 7, 2013

Stroke preparedness, meaning the ability of patients and bystanders to recognize stroke symptoms and take immediate action to seek emergency treatment (1), is among the predictors of pre-hospital delay (2-4), which plays a critical role in acute stroke management (1-4).

Public education campaigns to increase stroke preparedness have been evaluated in several studies, with inconsistent and inconclusive results (5-7). Overall, stroke warning campaigns can increase the recognition of stroke symptoms, but their efficacy on patient behavior remains unproven (8-10). In fact, although positive intervention effects are reported in the majority of studies, some methodological weaknesses, mainly in terms of design, limit the validity of the observed effects. Besides, the theoretical basis of the intervention as well as some exploratory work for the campaign development, which are recommended for the design of complex interventions (11) are not always reported.

Two studies (12, 13), incorporating a sufficiently rigorous design (cluster randomized in one case and quasi- experimental in the other), demonstrated some benefit of different strategies, such as an educational letter mailed to the households (12) and a multilevel campaign, developed according to a strict methodology and largely employing mass media (13).

The Italian Educazione e Ritardo di Ospedalizzazione per Ictus (EROI) project had the primary objective of developing an educational campaign focused on stroke preparedness, and aimed to reducing prehospital delay. In this paper we present the results of the evaluation trial performed to assess the intervention effectiveness. At variance with previous reports, the campaign was specifically designed for the local context according to an exploratory analysis and tested according to a more rigorous design.

METHODS

We used a stepped wedge cluster randomized trial design (SW-RCT) with cross-sectional data(14-16). The choice of stepped wedge design mainly relied on the available evidence of some effectiveness of previous campaigns in increasing symptom recognition, which made unethical to withhold the intervention from a proportion of the participants. Clusters were the communities of each of the four provinces of Northern Emilia Romagna (Parma, Piacenza, Modena and Reggio Emilia), ranging between 288,000 and 702,000 inhabitants (www.istat.it/en/emilia-romagna/data). According to the cross-sectional setting, the units of analysis were patients aged ≥ 18 consecutively admitted to the 6 hospitals of the participating provinces for suspected stroke and transient ischemic attack (TIA). Informed consent to participate to the study was obtained from the patient or one of his/her relatives in case of patient severe impairment as a consequence of stroke.

Exclusion criteria were: patient living in a nursing home (which implies that stroke recognition and activation of emergency services mainly relied on health personnel), home discharge from the ED and death within the first 72 hours from admission.

The intervention was targeted at cluster level and consisted in a community campaign designed according to the Intervention Mapping framework (17).

An extensive description of the campaign development is shown in Supplemental content.

Briefly, as theoretical foundation, we used the General Model of Total Patient Delay (18,19) and. the common sense model (CSM) of self regulation (20). The message content described the most frequent symptoms, emphasized the need for calling the emergency telephone number immediately and the availability of therapies that can lead to a complete recovery, provided that they are administered early enough. The message was organized according to the narrative mode, in cartoon form (21-23) A number of educational products were produced: a brochure that was mailed to the households and distributed in public places (eFigure 1), a poster (eFigure 2), an animation video for closed circuit and an animation video clip for television broadcasting.

According to the stepped-wedge design, the campaign was launched sequentially in the four provinces with 3 month intervals, so that its duration and intensity were not the same in the four clusters, lasting for a maximum of twelve months in the first province and a minimum of three months in the last province exposed to the intervention (eFigure 3).

The order in which the participating communities received the intervention was determined as a randomized sequence generated electronically by the Study Coordinating Center in Parma.

The intervention was compared with the "usual care", meaning the spontaneous initiatives to increase stroke awareness that are usually launched by the National Health Service, Health Associations and Patients' Organizations (see Supplemental material).

The cases were identified prospectively and on a daily base by trained assessors, who had access to the administrative data of the ED and to all patient medical records during in-hospital stay. Within 72 hours from hospital admission, a semi-structured interview was administered to the patient or his/her caregiver, including questions about their behavior at symptom onset. The interview format is a modified version of a published instrument (24) (please, see eAppendix). If patients were unable to answer because of aphasia, motor impairment, or other stroke manifestations, any available relatives and any witnesses of stroke onset were interviewed.

The following data were recorded into an electronic Case Report Form: demographics, symptoms at onset, time of symptom onset defined as the time neurological deficit was first noticed by the patient or an observer; time of patient presentation to the hospital ED, as recorded in the medical chart; clinical characteristics, including scores at the National Institute of Health Stroke Scale (NIHSS) at hospital admission (the complete list of clinical characteristics is reported in the Supplemental material).

When symptom onset was reported as "morning," "midday," "afternoon," "evening," or "night," we assumed time of onset as 9 AM, 12 PM, 3 PM, 9 PM, or 3 AM, respectively.

The primary endpoint was the percentage of patients who arrived at the ED within two hours from symptom onset.

Secondary endpoints were the proportion of all cerebrovascular patients (ischemic stroke, intracranial hemorrhage, and transient ischemic attack patients) treated with intravenous rtPA and the proportion of patients with ischemic stroke treated with intravenous rtPA. Furthermore, four behavioral endpoints were analyzed: the proportion of patients/caregivers who attributed the symptoms to stroke; the proportion of patients who called the Emergency Services as first reaction; the proportion of persons to whom patients first referred who suggested calling the Emergency Service; the proportion of patients who arrived with the ambulance.

Statistical methods

Sample size was estimated taking into account that in our context 30% of stroke patients arrive at the hospital within 2 hours from symptom onset. Assuming as clinically relevant a 15% increase of the rate of early hospital presentation (from 30 to 45%), which would translate into a 6% increase in thrombolysis rate, the estimated sample size was of 326 units of analysis (alpha 0.05, power 0.80). Adjustment for the design was made according to Hemming and Taljaard (15), setting as design constraints a fixed number of clusters (4) and of steps (5). Assuming an intracluster correlation coefficient (ICC) of 0.02, the sample size increased to 240 cases per cluster (48 for each period of observation). The assumptions of the estimate, including the ICC value, were verified by a preliminary analysis of prehospital delay within the four participating hospitals for a period of 3 months. According to administrative data about the activity volume of the participating hospitals five treatment periods of three months were deemed sufficient to achieve the sample size in all clusters.

The data were stored and analyzed in the Parma coordinating center using the Statistical Package for the Social Sciences (SPSS version 18.0, SPSS inc., Chicago, Illinois, USA) and Stata 10.0 (Stata Corp, College Station, Texas).

Data cleaning was performed via SPSS syntax operations. All statistical tests were done two-tailed with 95% confidence intervals

The primary analysis was to compare stroke patients before and after the campaign implementation, according to the stepped wedge schedule, and adjusting for clustering within communities and temporal trends.

At the patient level, the primary outcome was binary (yes, no), and so logistic regression models with binary outcomes were utilized. To adjust for differences in the average level of the outcome across cluster and secular trend we applied a fixed effect model (FEM), which has been proven as more powerful than generalized estimation equations when the number of cluster is small (30).

The model incorporated intervention status as the main effect, calendar time as a continuous measure and the clustering effect, i.e. effect of communities. Where appropriate, individual level covariates and any cluster level covariates strongly correlated with the outcome were also included in the model, to adjust for any potential confounding. Covariables were selected on the basis of their clinical relevance to the outcome of interest as reported from other studies and their significance in univariable regression analysis ($P < 0.15$).

The estimated intervention effect was reported as Odds Ratio (OR) and was considered significant at the 5% level..

Analysis of the secondary outcomes took a similar form to that described for the primary outcome. For each outcome, the Intracluster Correlation Coefficient (ICC) was estimated by one-way analyses of variance.

Finally, a sensitivity analysis was performed, in order to assess the robustness of the missing data assumption made in the primary analysis and to test whether the study results were influenced by factors such as the inclusion of cases with non-exact time of onset and the assumption that the 2-hour threshold was the most appropriate to categorize the delay. For a complete description of sensitive analysis, see Supplemental material.

Because of the complex nature of the intervention, a parallel process evaluation was conducted (please see the Supplemental material) according to the indications of a published framework (26)

This study has received individual Research Ethics Board approval from all four of the participating provinces in 2012 and has been publically registered with an internet based trial archive, clinicaltrials.gov (http://clinicaltrials.gov/show/NCT01726387).

RESULTS

The trial start and finish dates were pre-specified as 1st August 2013–30th November 2014. During the 15-month study period, 1714 patients were enrolled as analysis units. In 27 cases the onset time as recorded in the CRF was not congruous with the time of hospital arrival and in 65 NIHSS scores were missing.Thus, a complete case analysis was performed on a dataset of 1622 patients, .

Figure 2 shows a diagram depicting the rollout of the campaign within the four clusters in the five periods and the number of the analysis units enrolled within each cluster in each study period. The final data set was made of 912 exposed and 710 non-exposed patients.

Demographic and clinical characteristics of all participants and according to trial mode are represented in table 1. A higher proportion of patients with more severe stroke and with a different distribution of ischemic stroke etiologies were enrolled during the intervention period.

For the comparison between clusters, which showed some differences, especially in stroke severity at admission, see Supplemental material. .

The median (inter-quartile range [IQR]) time from symptom onset/awareness to presentation at the hospital in the whole sample was 2 h and 40 min (1h and 22 min–11 h and 16 min). 669 patients (41.2%) presented less than 2h after stroke onset/symptom awareness.

According to univariate regression analysis (table 2), older age, living in urban areas, previous stroke or TIA, atrial fibrillation, diagnosis of TIA, dyslipidemia, coronary heart disease, higher severity of neurological impairment at onset and cardioembolic etiology were predictive of early hospital admission, while male gender, living alone, diabetes, smoking habits and symptom onset during night hours and at awakening were associated with later arrival. A significant association with prehospital delay was also found for cluster, with cluster 4 patients arriving earlier.

The median (IQR) time interval was 2h and 59 min (1 h and 26 min–13 h and 8 min) during the campaign exposure, and 2 h and 26 min (1 h and 59 min–8 h and 59 min) during non-exposure period.

Table 3 represents the results of the analysis of the campaign effect on early arrival and thrombolysis rate. As for early arrival, three different models were developed: the first, adjusting for cluster and time; the second, adjusting also for NIHSS score and age (the potential confounders); the third, adjusting also for the covariates variables previously identified by univariate analysis as determinants of the delay. As for thrombolysis, adjustment was made for NIHSS and age, which are two main criteria that are taken into account for patient selection.

The proportion of patients who arrived within 2 hours of stroke onset was lower during the campaign (354[38.8%] vs 315[44.4%]), but the effect estimates according to the ORs were not significant both before (OR 0.86, 95% CI 0.66-1.14, P=.29) and after adjustment for potential confounders (0.84, 95% CI 0.63-1.11, P=.23) and other delay determinants (0.81, 95% CI 0.60-1.08, P=.15).

Thrombolysis rate in the whole sample was 19.1 %, with a proportion of 24.5% of ischemic strokes. The rate was lower during the campaign, but the difference in patients with ischemic stroke was not significant both at unadjusted and adjusted analysis.

As for behavioral endpoints (table 4), exposure to the campaign was associated with an increase of the proportion of stroke recognition (from 26.3% to 34.6%) with an OR in the logistic regression of 1.48 (95% CI 1.19-1.84, P<.001). According to the FEM, adjusting for cluster and time, the positive effect estimate was confirmed, but with a loss of significance (OR 1.40, 95% CI 0.96-2.03, P=.07). No significant change was found for the other behavioral endpoints, including calling 118 and hospital arrival with an ambulance.

The results of sensitivity analyses (eTable 3) performed on multiple imputed data sets, after exclusion of cases with non-exact onset time, using different cutoffs for prehospital delay definition and according to a shared frailty model for time to event data, were qualitatively unchanged.

As for process analysis, the intervention was delivered, according to the protocol, without any significant variations, across the four clusters. However, the proportion of the 912 exposed patients

or proxies who, during the interview, spontaneously mentioned the campaign as source of knowledge of stroke was rather low (52 [5.7%]).

DISCUSSION

In our study, a public educational campaign aimed at increasing stroke awareness and preparedness was not effective in reducing prehospital time intervals, neither was it effective in increasing the rate of thrombolysis for ischemic stroke. On the contrary, it was associate with a non-significant decline in early arrival. The lack of effectiveness was accounted for by the lack of beneficial effects on behavioral endpoints, except for the slight and non-significant increase in stroke recognition.

Several factors might explain the campaign failure (27).

An inadequate implementation of the campaign is unlikely, since in our study the process evaluation ensured the homogeneous delivery of the intervention across the clusters, except for the differences in campaign duration according to the SW design.

Thus, other reasons of poor performance should be considered, such as limitations of the theoretical foundation of the intervention and of its components, notably in terms of mode, appeal and communication channels (32).

As for the appeal, that is the way of organizing the content of the message to make it more likely to persuade or convince people (28), it cannot be excluded that the emotional or fear-arousal appeals might be more effective than the positive appeal we used. However, the UK "Act FAST" campaign, which used a fear-arousing appeal, depicting stroke onset as a fire spreading in a TV advertisement (29-31), gave controversial results.

Nevertheless, our study is consistent with the evidence from previous reports, which did not find a significant reduction of prehospital delay after exposure to public education campaigns on stroke (29,30, 32-34), even when multi-level interventions, using mass media, were evaluated (13). One exception is the reduction of pre-hospital delay reported in women only by Müller- Nordhorn et al (12).

Overall, mass methods of health education are scarcely effective in increasing stroke preparedness, just like it has been reported for myocardial infarction (8), suggesting that other strategies, possibly multidimensional, should be tested.

It is noteworthy that education programs have been more recently developed, aimed not only at the community, but also at individuals and hospitals and including interactive educational sessions (35-37) As a matter of fact, the TLL Temple Foundation Stroke Project (13) included, in addition to the public campaign, an educational intervention aimed at professionals, which might account for the discrepancy between the benefit documented on the rate on thrombolysis use and the lack of effect on hospital arrival times.

A number of study limitations should be taken into account,. The small number of clusters (four) might represent a critical issue, since a minimum of 10 clusters is recommended to be used in each arm of a cluster randomized trial (38). Unfortunately, economic constraints prevented the involvement into the project of more Italian provinces. However, the fixed effect regression model perform quite well to modeling clustered data with very few clusters (25,39). Besides, the stepped wedge design, may mitigate some of the potential issues surrounding the small number of clusters, making the magnitudes of intra-cluster correlations less important (40). Furthermore, methodological constraints affected the selection of channels for message delivery. The risk of contamination between clusters (the four provinces) because of the potential overlapping of local media orbits, limited the use of Internet and television public service announcements, which have been shown as a powerful channel for health campaign dissemination (8). Most of all, the length of intervention might be a critical aspect (27). In our study the exposure periods ranged between 3 months in the fourth cluster and 12 months in the first one. In this view, the improvement of stroke recognition, although not significant, might be considered a promising finding which should be viewed as preliminary to further interventions, although the economic sustainability of campaigns of longest duration may represent a major issue.

Conclusions

Our study confirms the difficulty of changing people's behavior in response to stroke onset using public education campaigns that need time to penetrate and be effective, which implies problems of economic sustainability, Overall, the study demonstrates that any new communication strategies, even if rigorously designed, should be properly tested before large-scale implementation.

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Table 1. Characteristics of the sample by exposure to the campaign (trial mode)

	All (1622)	**Intervention (exposed) (912)**	**Control (unexposed) (710)**	**P value**
Age M (SD) Range	73 (13.8) 22-100	72.9 (13.5)	71.6 (13.9)	.06
Male gender % (n)	55.6 (902)	55.5 (394)	55.7 (508)	.96
Living alone % (n)	18.4 (297)	19.7 (178)	17.1 (119)	.18
Living in urban areas % (n)	42 (674)	40.9 (370)	43.4 (304)	.33
Educated to high school or above % (n)	22.9 (368)	22.8 (206)	22.9 (162)	.51
Risk factors % (n)				
Previous stroke/TIA	19.7 (320)	19.4 (177)	20.1 (143)	.75
Hypertension	69.0 (1120)	67.7 (617)	70.8 (503)	.18
Diabetes	19.4 (314)	19.2 (175)	19.6 (139)	.85
Current smoking	17.8 (288)	16.6 (151)	19.3 (137)	.17
Dyslipidemia	29.0 (470)	27.9 (254)	30.4 (216)	.27
Atrial fibrillation	18.7 (304)	17.8 (162)	20.0 (142)	.28
Coronary heart disease	15.2 (246)	15.2 (139)	15.1 (107)	.94
Peripheral Artery Disease	2.2 (35)	2.0 (18)	2.4 (17)	.61
Carotid Stenosis	9.2 (149)	8.4 (77)	10.1 (72)	.26
Diagnosis				
TIA Ischemic stroke Hemorrhagic stroke Others	12.0 (191) 72.4(1152) 7.0 (112) 8.6 (137)	12.4 (112) 71.9 (649) 6.5 (59) 9.2 (83)	11.5 (79) 73.0 (503) 7.7 (53) 7.8 (54)	.59
Stroke severity at onset				
OCPS clinical syndrome % (n)[a]: TACI PACI LACI POCI	 6.2 (71) 52.1(600) 19.2 (222) 22.6 (259)	 5.6 (36) 54.4 (354) 16.9 (110) 23 (149)	 7.1 (35) 48.7 (246) 22.2 (112) 22.0 (110)	 .08
NIHSS score at admission				
M (SD)	5.1 (5.5)	4.9 (5.4)	5.4 (5.5)	.11[b]
Median (interquartile range)	3 (0-6)	3 (0-5)	4 (0-6)	
Categories: 0-4 5-10 11-20 >20	 61.6 (999) 24.2 (393) 11.8 (192) 2.3 (38)	 62.8 (573) 25.2 (230) 9.6 (88) 2.3 (21)	 60.0 (426) 23.6 (163) 14.6 (104) 2.4	.02
Ischemic stroke etiology: Cardioembolic Large artery atherosclerosis Small vessels disease Other specific causes Undetermined	 35.7 (411) 18.0 (208) 21.8 (251) 19.5 (225) 5.0 (57)	 35.2 (228) 17.3 (112) 20.9 (136) 23.2 (151) 3.4 (22)	 36.4 (183) 18.9 (96) 23.0 (115) 14.5 (74) 7.2 (35)	.002
Admitted in Stroke Unit % (n)	89.4 (1450)	89.5 (816)	89.3 (634)	.93

Onset time: Night-awakening % (n)	32.5 (524)	31.7 (289)	33.1 (235)	.56
Onset day: Week end- festivity % (n)	30.8 (500)	29.7 (271)	32.3 (229)	.28

[a]available for 1152 patients

[b]Mann Whitney test

TIA: Transitory Ischemic Attack; OCSP: Oxfordshire Community Stroke Project; TACI: total anterior circulation infarct; PACI: partial anterior circulation infarct; LACI: lacunar infarct; POCI: posterior circulation infarct; NIHSS: National Institute of Health Stroke Scale (range 0-42)

Table 2 Characteristics of the sample by clusters

Cluster	**1 (486)**	**2 (257)**	**3 (509)**	**4 (370)**	**P value**
Age M (SD) Range	74.4 (12.5)	69.7 (14.5)	72.3 (13.8)	71.5 (14.2)	<0.001
Male gender % (n)	52.9 (257)	54.5 (140)	58.7 (299)	56.7 (206)	.30
Living alone % (n)	21.9 (106)	19.5 (50)	19.8 (100)	11.2 (41)	<0.001
Living in urban areas % (n)	44.0 (216)	39.7 (102)	40.6 (246)	41.6 (152)	.43
Educated to high school or above % (n)	22.7 (109)	35.7 (91)	17.6 (89)	21.4 (79)	
Risk factors % (n)					
Previous stroke/TIA	21.4 (104)	20.2 (52)	19.1 (97	18.1 (67)	.65
Hypertension	70.8 (344)	62.6 (161)	75.2 (383)	62.7 (232)	<0.001
Diabetes	20.0 (97)	19.8 (51)	21.0 (107)	15.9 (59)	.28
Current smoking	15.4 (75)	21.4 (55)	20.0 (102)	115.1 (56)	.05
Dyslipidemia	29.4 (143)	20.2 (52)	33.0 (168)	28.9 (107)	.003
Atrial fibrillation	22.2 (108)	12.1 (31)	21.4 (109)	15.1 (56)	.001
Coronary heart disease	15.8 (77)	11.7 (30)	12.2 (62)	20.8 (77)	.002
Peripheral Artery Disease	1.6 (8)	0.8 (2)	2.3(12)	3.5 (13)	.10
Carotid Stenosis	8.4 (41)	7.4 (19)	11.0 (56)	8.9 (33)	.34
Diagnosis					
TIA Ischemic stroke Hemorrhagic stroke Others	15.4 (75) 71.4 (347) 4.5 (22) 8.6 (42)	14.0 (36) 64.2(165) 7.0 (18) 14.8 (38)	7.9 (40) 81.9(417) 8.1 (41) 2.2 (11)	10.5 (39) 68.4 (253) 8.4 (31) 12.7 (47)	<0.001
Stroke severity at onset					
OCPS clinical syndrome % (n)[a]: TACI PACI LACI POCI	3.8 (18) 59.1 (287) 10.7 (52) 26.4 (129)	3.2 (8) 62.4 (160) 9.6 825) 24.8 (64)	5.2 (26) 51.2 (36) 26.5 (135) 17.1 (87)	14.1 (52) 35.6 (132) 25.0 (92) 25.5 (94)	<0.001
NIHSS score at admission					
M (SD)	4.2 (4.4)	3.2 (3.9)	6.6 (6.5)	5.5 (5.6)	<0.001[b]
Median (interquartile range)	3 (1-5)	2 (0-4)	4 (1-7)	4 (1-7)	
Categories: 0-4 5-10 11-20 >20	 67.1(326) 24.1 (117) 7.8 (38) 1.0 (5)	 77.0 (198) 16.7 (43) 6.2 (16) 0 (0)	 52.1 (265) 26.9 (137) 15.9 (81) 5.1 (26)	 56.8 (210) 25.9 (96) 15.4 (57) 1.9 (7)	<0.001
Ischemic stroke etiology: Cardioembolic	 32.5 (107)	 44.7 (73)	 30.5 (127)	 48.8 (118)	<0.001

Large artery atherosclerosis	19.9 (66)	19.7 (32)	16.5 (69)	17.6 (42)	
Small vessels disease	11.9 (39)	23.7 (39)	28.2 (117)	22.4 (54)	
Other specific causes					
Undetermined	33.2 (110)	5.6 (9)	20.3 (84)	1.8 (4)	
	2.5 (9)	6.3 (10)	4.6 (19)	9.4 (23)	
Admitted in Stroke Unit % (n)	91.6 (445)	94.2 (242)	89.2 454)	83.5 (309)	<0.001
Onset time: Night-awakening % (n)	32.1 (156)	32.3 883)	35 (178)	28.9 (107)	.31
Onset day: Week end-festivity % (n)	29.0 (141)	30.0 (77)	31.6 (161)	32.7 (121)	.66

[a]available for 1152 patients

[b]Median test for k independent samples

TIA: Transitory Ischemic Attack; OCSP: Oxfordshire Community Stroke Project; TACI: total anterior circulation infarct; PACI: partial anterior circulation infarct; LACI: lacunar infarct; POCI: posterior circulation infarct; NIHSS: National Institute of Health Stroke Scale (range 0-42)

Table 3

Univariate analysis of factors correlated with early arrival (pre-hospital time interval < 2 hours)

	OR (95% CI)	**P value**
Age (for 1 year increase)	1.01 (1.00-1.02)	.04
Male gender	0.84 (0.69-1.02)	.08
Living alone	0.73(0.56-0.95)	.02
Living in urban areas	1.24 (1.02-1.52)	.03
Educated to high school or above	1.10 (0.87-1.40)	.40
Risk factors		
Previous stroke/TIA	1.21(0.95-1.55)	.13
Hypertension	1.06 (0.85-1.32)	.58
Diabetes	0.72 (0.56-0.93)	.01
Current smoking	0.74 (0.57-0.97)	.03
Dyslipidemia	1.22 (0.98-1.51)	.07
Atrial fibrillation	1.38 (1.07-1.77)	.01
Coronary heart disease	1.30 (0.99-1.71)	.06
Peripheral Artery Disease	1.07 (0.54-2.10)	.84
Carotid Stenosis	1.22 (0.87-1.71)	.24
Diagnosis		
TIA Ischemic stroke Hemorrhagic stroke Others	1.39 (1.02-1.88) 0.91 (0.61-1.35) 0.94 (0.75-1.17) 0.58 (0.40-0.85)	.03 .98 .91 .03
Stroke severity at onset		
OCPS clinical syndrome: TACI PACI LACI POCI	 1 0.31 (0.18-0.54) 0.16 (0.09-0.30) 0.17 (0.09-0.31)	 <0.001 <0.001 <0.001
NIHSS score at admission (for 1-point increase)	1.09 (1.07-1.11)	<0.001
NIHSS categories: 0-4 5-10 11-20 >20	 1 1.67 (1.32-2.13) 3.35 (2.43-4.61) 7.37 (3.34-16.24)	 <0.001 <0.001 <0.001
Cardioembolic etiology Non-cardiomebolic etiology	1 1.77 (1.38-2.26)	 <0.001
Onset time: Overnight-on awakening Others	 1 1.30 (1.05-1.60)	 .02
Onset day: Week end Week day	 1 0.96 (0.78-1.19)	 .72
Cluster 1	 1	

2	0.84 (0.61-1-14)	.28
3	1.14 (0.88-1.47)	.31
4	1.38 (1.05-1.82)	.02

Table 4

Effects of the campaign on early arrival (arrival within 2 hours) and thrombolysis rate, according to a fixed effect model including intervention , cluster and calendar time

	Intervention (exposed) (912)	**Control (unexposed) (710)**	**ICC**	**Effect estimates OR (95% CI) P value**		
Primary endpoint						
Early arrival	Percentage (N) of patients			Unadjusted	Adjusted for confounders	Adjusted for confounders and other delay determinants[b]
	38.8 (354)	44.4 (315)	0.016	0.86 (0.66-1.14) .29	0.84 (0.63-1.11)[a] .23	0.81 (0.60-1.08) .15
Secondary endpoints						
All cerebrovascular patients (ischemic stroke, transient ischemic attack, intracranial hemorrhage)						
rTPA iv treatment % (N)	16.2 (148)	22.8(162)	0.046	0.73 (0.51-1.04) .09	0.69 (0.46-0.99)[c] .04	
Ischemic stroke patients						
rTPA iv treatment % (N)	22 (145)	29.5 (156)	0.037	0.88 (0.59-1.26) .52	0.84 (0.56-1.26)[c] .41	

[a]Age and NIHSS score

[b]Living alone, living in urban areas, diabetes, smoking, atrial fibrillation, TIA, onset overnight-on awakening

[c]Adjusted for age and NIHSS

ICC=Intra-cluster Correlation Coefficient

Table 5. Effects of the campaign on behavioral endpoints, according to a fixed effect model including intervention, cluster and calendar time

	All	**Intervention (exposed)**	**Control (unexposed)**	**ICC**	**Effect estimates OR (95% CI) P value**
	Percentage (N) of patients				
Knowledge					
Symptoms attributed to stroke or TIA	31 (503)	34.6 (316)	26.3 (187)	0.04	1.40 (0.96-2.03) .07
First reaction					
Calling 118	8.2 (133)	8.3 (75)	8.0 (57)	0.06	0.75 (0.39-1.43) .38
Calling a relative or friend	74.0 (1201)	72.2 (686)	75.5 (515)	0.02	0.95 (0.64-1.41) .81
Calling the GP	8.1 (132)	7.6 (69)	8.9 (63)	0.03	0.78 (0.41-1.48) .45
Reaction of the relative or friend or GP (1489)					
Calling 118	50.3 (749)	50.1 (419)	50.5 (330)	0.04	1.47 (1.10-1.96) .009
Mode of arrival					
With an ambulance	63.8 (1035)	65.5 (597)	61.7 (438)	0.02	0.87 (0.60-1.24) .44

Figure 1

Diagrammathic illustration of the study design. Each cell represents a period of data gathering. Shaded cells represent intervention periods, blank cells represent control periods.

							Total
Participant clusters	Cluster 4 (Reggio Emilia)	48	59	74	69	120	370
	Cluster 3 (Modena)	72	64	115	119	139	509
	Cluster 2 (Piacenza)	59	45	58	42	53	257
	Cluster 1 (Parma)	105	70	95	108	108	486
	Total	284	238	342	338	420	1622
		T1	T2	T3	T4	T5	
		Time periods (each of 3 months)					