THE EFFICACY OF NITRIC OXIDE IN STROKE (ENOS) TRIAL – WHERE DO WE STAND IN ROMANIA?

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ABSTRACT

Introduction. Romania ranks third worldwide for stroke mortality. Although high blood pressure (BP) is a major risk factor for stroke incidence and determinant of outcome, the management of BP in acute stroke remains undefined. The present study assesses patients recruited into the 'Efficacy of Nitric Oxide in Stroke' (ENOS) trial from Romania, one of 19 participating countries.

Methods. ENOS is an international multicentre prospective randomised controlled trial that is assessing the safety and efficacy of: (i) lowering BP with transdermal glyceryl trinitrate, and (ii) whether pre-stroke antihypertensive therapy should be continued or stopped temporarily, in acute ischaemic stroke or primary intracerebral haemorrhage (PICH). Interventions are given for 7 days and the primary outcome, modified Rankin Scale (mRS), is measured at 90 days.

Results. 135 patients were recruited from 3 Romanian sites between March 2009 and August 2011; 56% of these patients were also in the continue-stop arm of the trial. In comparison with the Rest of the World (RoW), Romanian patients were recruited earlier (29 vs. 22 hr), had a higher rate of previous high BP (63 vs. 76%), had less severe stroke at baseline (Scandinavian Stroke Scale, SSS 37 vs. 43/58), were less likely to have a PICH (17 vs. 10%), and had more cases of no visible stroke lesions on baseline CT (27 vs. 49%). Impairment (SSS) at day 7 did not differ. As compared to RoW, the length of stay in hospital was shorter in Romania (14 vs. 9 days); the adjusted death rate at follow-up at 90 days was doubled (odds ratio 1.97, 95% confidence intervals 1.07-3.63) although this was not reflected by a difference in the adjusted rate of death or dependency (mRS>2) at 90 days (OR 1.04, 95% CI 0.66-1.63).

Conclusion. ENOS will continue recruiting patients until the summer of 2013. The presented data show that enrolment is feasible in Romania and the trial has been found to be easy to manage and recruit into.

Key words: stroke, blood pressure, nitric oxide, ENOS

INTRODUCTION

According to American Heart Association statistics, Romania ranks fourth worldwide for vascular death, and is third for stroke mortality. (1,2) Additionally, stroke rates have been higher in Eastern European countries over the last 30 years as compared to the West, although cerebrovascular mortality has started to decline. (3-8)

High blood pressure has been shown to have a large impact on stroke incidence and outcome. At stroke onset, 60-75% of stroke patients present with elevated blood pressure (> 160 mmHg), and 25-28% have a markedly raised BP (> 180 mmHg).

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Out of these patients, 50% to 60% have established high BP prior to the stroke. (9-11)

The management of blood pressure in acute stroke remains unclear although many small trials of vasoactive drugs have been completed. (12-15) The results of the large 'Scandinavian Candesartan Acute Stroke Trial' (SCAST) have recently been published and reported that there was no indication for careful blood-pressure lowering treatment with the angiotensin-receptor blocker candesartan in patients with acute stroke and raised blood pressure. (16) Two other large trials are ongoing: 'Efficacy of Nitric Oxide in Stroke' (ENOS) Trial (17) and 'Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial-2' (INTERACT-2). (18) Romania is one of 19 countries taking part in ENOS currently. As of 24th of August 2011, the date of pooling the data presented in this paper out of the international database, 18 countries took part in enrolment for ENOS. The present paper describes its first recruited patients and their characteristics and clinical outcomes.

METHODS

The ENOS trial

ENOS is an international multicentre prospective randomised controlled single-blind trial that is assessing the safety and efficacy of lowering blood pressure with transdermal glyceryl trinitrate (GTN) immediately after ischaemic or haemorrhagic stroke; and whether pre-stroke antihypertensive therapy should be continued or stopped temporarily for 7 days after stroke. (17) GTN, which releases nitric oxide, is a vasodilator, lowers blood pressure and may also have neuroprotective properties. (19,20)

Adult patients may be enrolled into the trial if they: (17) present with an acute stroke syndrome with residual motor weakness (Scandinavian Stroke Scale [SSS] Arm < 6 and/or leg < 6); are within 48 hours of onset; and have an elevated blood pressure (systolic blood pressure 140-220 mmHg). Additional inclusion criteria include consciousness (Glasgow Coma Scale > 8); independence prior to stroke (modified Rankin Scale [mRS] < 3); and meaningful consent from the patient, or proxy consent from a relative or carer.

The main exclusion criteria are: (17) definite need for or contraindication to nitrate therapy; definite need for pre-stroke or new antihypertensives (whether needed for blood pressure, angina or heart failure management); have already received BP lowering treatment after the onset of stroke; known need for a surgical intervention; known intracerebral pathology other than stroke (e.g. subarachnoid haemorrhage, brain tumour, cerebral abscess); another serious condition that is likely to prevent outcome assessment at 90 days (e.g. advanced cancer); previous enrolment in ENOS; current involvement in another trial of an experimental drug; not available for follow-up; females of childbearing potential where pregnancy cannot be excluded by a negative pregnancy test; or pregnancy or breastfeeding.

Patients are recruited through a process of screening new stroke patients for inclusion and exclusion criteria, and then obtaining written informed consent (or proxy consent by a relative if the patient lacks capacity, e.g. due to severe dysphasia, reduced GCS or confusion). Consent is obtained by a doctor (or nurse, depending on the country) trained in the trial and Good Clinical Practice. Baseline information (clinical history, examination) is entered online using a secure internet site (via www.enos.ac.uk); randomisation is performed in real time to GTN vs no GTN, and continue vs stop pre-stroke antihypertensive therapy (as relevant). Single blinding to the GTN patch is achieved through placing a gauze dressing over the GTN patch, or equivalent area of the skin. Interventions are given for 7 days with blood pressure and heart rate recorded daily (using the validated Omron 705CP or 705CP II automated blood pressure monitor) (21). All these trial measures are applied on top of standard evidence-based acute medical and nursing care, and secondary prevention. CT or MR brain scans are submitted over the trial's secure internet connection. ENOS was the world's first acute stroke trial to use online randomisation and data collection.

Patients are followed-up by the Local Investigator at day 7 and on discharge or death. Final follow-up is completed by telephone at day 90 after randomisation by a trained assessor (doctor or nurse) based at each National Coordinating Centre who is blind to treatment assignment and other clinical information. The primary outcome is death, dependency or independence assessed using the mRS; secondary outcome measures include recurrent stroke, neurological impairment (SSS), venous thromboembolic events, disability (Barthel Index), mood (Zung) (22), cognition (MMSE, TICS) (23,24), quality of life (EuroQoL) (25), and adverse events.

ENOS in Romania

The trial activity in Romania is led by the National Coordinator (Sz.Sz.) at the National Coordi-

nating Centre (NCC) based at the 2nd Clinic of Neurology at the Mures County Emergency Hospital. The NCC assists sites with start-up and training (with support from the International Coordinating Centre in Nottingham, UK), monitors sites for data quality and integrity, and hosts the day 90 follow-up coordinator. Romania has three active local sites based in Targu-Mures, Sfantu-Gheorghe, and Oradea.

STATISTICAL ANALYSIS

The data and analyses presented here compare patients enrolled into ENOS in Romania versus the rest of the world. Data are represented as mean (standard deviation), median [interquartile range] or number (%). Comparisons between patient characteristics and outcomes in Romania vs rest of world are performed using t-test, Mann-Whitney U test, χ^2 test, Fisher's exact test, binary logistic regression, ordinal logistic regression, ANOVA and repeated measures ANOVA. Significance is set at $p < 0.05$. Analyses were performed using SAS.

RESULTS

ENOS commenced in 2001 with the aim of recruiting 5,000 patients. A change in the statistical analysis plan in 2009 allows a more efficient statistical analysis so that the target recruitment is reduced to 3,500+ patients whilst retaining the same statistical power (1-ß = 90%). Recruitment will cease in the summer of 2013 and as of 24th August 2011, 2,453 patients (1,212 in the continue-stop pre-stroke antihypertensives arm) from 18 countries had reached the day 7 assessment (Table 1). In respect of data quality, carotid ultrasound was performed in 94.8% of Romanian patients versus 50.6% of those from the rest of world.

The Romanian NCC started to seek sites and national approvals in the autumn of 2008, and recruitment of patients started in March 2009. This report is based on recruitment of 135 patients from 3 sites as of 24th August 2011 (Table 2). Of these patients, 76 (56%) are also enrolled in the comparison of continuation vs stopping of pre-stroke antihypertensive drugs. The baseline characteristics of patients enrolled in Romania differed somewhat from those recruited elsewhere in the world; in particular, Romanian patients were less likely to have a PICH, had less severe stroke severity (higher SSS), a quicker time to recruitment, more CTs without visible lesions, and there were more cases with previously known high blood pressure (Table 2). In comparison with the rest of the world, Romanian patients had a different profile for use of antihypertensive drugs before their stroke, with more use of angiotensin converting enzyme inhibitors and diuretics, and less use of angiotensin receptor antagonists and calcium channel blockers; other antihypertensive drug classes did not differ.

***TABLE 1**. Countries participating in ENOS and their number of sites and patient recruitment as of 24th August 2011*

Country	Sites	Patients Overall	Patients Continue-stop
Australia	1	8	7 (88%)
Canada	2	33	14 (42%)
China	2	103	39 (38%)
Denmark	1	1	1 (100%)
Egypt	4	53	28 (53%)
Hong Kong	1	4	2 (50%)
India	6	110	33 (30%)
Italy	1	13	7 (54%)
Malaysia	2	12	6 (50%)
New Zealand	4	50	32 (64%)
Philippines	1	16	7 (44%)
Poland	3	112	64 (57%)
Republic of Ireland	1	6	1 (17%)
Romania	**3**	**135**	**76 (56%)**
Singapore	1	155	74 (48%)
Spain	2	7	5 (71%)
Sri Lanka	2	82	19 (23%)
United Kingdom	95	1553	797 (51%)
Total	132	2453	1212 (49%)

In unadjusted analyses, patients from Romania had less impairment by day 7 although the difference disappeared following adjustment (Table 3). In contrast, the adjusted (but not unadjusted) death rate at day 90 was higher in patients from Romania as compared with rest of world. There was no difference in the rate of death or dependency (mRS>2) in both unadjusted and adjusted analyses (Figure 1, Table 3). Length of stay was lower in Romania in both unadjusted and adjusted analyses (Table 3).

Overall, systolic blood pressure levels tended to be slightly higher in Romanian patients both at baseline and over the following 7 days of treatment (Table 4). However, systolic blood pressure was higher at baseline in patients enrolled in the continue vs stop pre-stroke antihypertensive medication part of the trial, as compared with those randomised just to GTN vs no GTN (Table 4). Analyses comparing the response of patients to GTN versus no GTN, and continuing versus stopping pre-stroke antihypertensive medication, were not possible because the trial is ongoing.

TABLE 2. *Baseline characteristics of 135 patients recruited into ENOS from Romania. Number (%), mean (standard deviation), median [IQR]. Comparisons are made using t-test, Wilcoxon Rank Sum test, χ^2 test and Fisher's exact test*

Variable	Romania	Rest of world	p
Patients	135	2318	
Age (years)	69.1 (9.1)	69.9 (12.3)	0.295
Male (%)	76 (56.3)	1346 (58.1)	0.685
Medical history			
Hypertension (%)	**102 (75.6)**	**1467 (63.3)**	**0.004**
Atrial fibrillation (%)	16 (11.9)	279 (12.0)	0.95
Prior antihypertensive treatment, n (%)	76 (56.3)	1136 (49.0)	0.100
Angiotensin converting enzyme inhibitor	**58 (43.0)**	**521 (22.5)**	**<0.001**
Angiotensin receptor antagonist	**2 (1.5)**	**194 (8.4)**	**0.004**
Beta-blocker	33 (24.4)	467 (20.1)	0.23
Calcium channel blocker	**14 (10.4)**	**416 (17.9)**	**0.024**
Diuretic	**41 (30.4)**	**376 (16.2)**	**<0.001**
Alpha-blocker	2 (1.5)	85 (3.7)	0.23
Renin inhibitor	0	2 (0.1)	1.00
Centrally acting agent	2 (1.5)	16 (0.7)	0.26
Other antihypertensive class	0	22 (0.9)	0.63
Nitrate prior to stroke (%)	11 (8.1)	100 (4.3)	0.051
Blood pressure (mmHg)			
Systolic	170.8 (19.5)	167.8 (19.4)	0.079
Diastolic	91.1 (11.9)	89.9 (13.3)	0.32
Scandinavian Stroke Scale (SSS, /58)	**43 [30, 49]**	**37 [26, 45]**	**<0.001**
Time, stroke to randomisation (hours)	**21.9 (12.1)**	**28.5 (12.6)**	**<0.001**
Type of stroke on CT/MRI (%) †			**<.0001**
Ischaemic stroke			
No lesion visible	66 (48.9)	618 (26.7)	
Infarct	56 (41.5)	1247 (53.8)	
Plus haemorrhagic transformation	0	39 (1.7)	
Primary intracerebral haemorrhage	13 (9.6)	391 (16.9)	
Non-stroke lesion	0	12 (0.5)	
Neuroimaging not performed	0	11 (0.5)	

† As reported by investigator

TABLE 3. *Comparison of outcome in patients from Romania versus rest of world. Median [IQR] or number (%), and odds ratio (95% confidence interval). Comparison by binary logistic regression or log transformed ANOVA with adjustment for age, sex, severity, systolic blood pressure, stroke type, and time to randomisation*

			Unadjusted		Adjusted	
	Romania (N=115)	Rest of world (N=2128)	Odds ratio (CI)	p-value	Odds ratio (CI)	p-value
Day 7						
Dead (%)	1 (0.9)	60 (2.8)	0.30 (0.04, 2.20)	0.24	0.29 (0.04, 2.21)	0.23
Dead or deteriorated (%)	10 (8.7)	170 (8.0)	1.10 (0.56, 2.14)	0.79	1.16 (0.58, 2.31)	0.67
Recurrent stroke (%)	0	55 (2.6)	NC	NC	NC	NC
Impairment (/58) †	**51 [33, 54]**	**44 [30, 52]**	**1.34 (1.10, 1.62)**	**0.004**	1.01 (0.88, 1.15)	0.94
Day 90						
Dead (%)	16 (13.9)	247 (11.6)	1.231 (0.714, 2.122)	0.45	**1.97 (1.07, 3.63)**	**0.030**
Dead or dependent (mRS>2, %)	62 (53.9)	1324 (62.2)	0.710 (0.487, 1.036)	0.075	1.04 (0.66, 1.63)	0.86
Length of stay in hospital (days)	**9 [8, 12]**	**14 [7, 32]**	**0.66 (0.55, 0.79)**	**<.0001**	**0.79 (0.67, 0.93)**	**0.005**

† Impairment: Scandinavian Stroke Scale, based on 114 patients from Romania and 2,093 patients from rest of the world

TABLE 4. *Blood pressure at baseline and during the 7 days of treatment for the whole trial, and whether or not randomized in the continue vs stop pre-stroke antihypertensive groups. Mean (standard deviation); comparison by repeated measures ANOVA with blinding to treatment assignment*

	Overall		Continue/stop		Not continue/stop	
Day	Romania	Rest of world	Romania	Rest of world	Romania	Rest of world
Patients	135	2,318	76	1,136	59	1,182
0 (baseline)	171/91 (19/12)	168/90 (19/13)	172/91 (20/12)	167/88 (19/13)	169/92 (19/12)	168/92 (20/14)
1	160/85 (24/13)	161/87 (23/14)	162/87 (22/12)	161/86 (23/14)	156/83 (25/14)	162/88 (23/15)
2	157/84 (23/14)	158/85 (24/15)	160/85 (21/13)	157/84 (25/15)	153/82 (25/16)	158/86 (24/15)
3	159/86 (23/13)	157/85 (25/15)	163/87 (23/14)	156/84 (25/15)	155/85 (21/12)	157/86 (25/15)
4	158/85 (23/13)	155/85 (25/15)	160/87 (23/13)	155/84 (25/15)	154/84 (23/14)	156/86 (25/15)
5	157/85 (23/15)	153/84 (26/15)	159/86 (24/14)	153/83 (26/15)	154/84 (21/15)	154/85 (26/15)
6	155/84 (22/14)	152/84 (25/15)	159/86 (23/15)	152/82 (25/14)	151/82 (20/13)	153/86 (26/15)
7	156/84 (21/12)	152/84 (24/15)	157/85 (22/12)	151/82 (25/15)	154/83 (19/13)	152/85 (24/15)

Repeated measures ANOVA SBP by country, p = 0.11
Repeated measures ANOVA SBP by country with adjustment for use of antihypertensives pre-stroke, p = 0.10
Repeated measures ANOVA DBP by country, p = 0.92
Repeated measures ANOVA DBP by country with adjustment for use of antihypertensives pre-stroke, p = 0.78

DISCUSSION

Romania is an active recruiter in the ENOS trial with three sites. Over 29 months, 135 patients have been recruited reflecting an average of 1.6 patients per site per month. The patients recruited in Romania differ in several important respects as compared with those from the rest of the world. In general, Romanian patients were more likely to have a history of high blood pressure, had less severe stroke (higher Scandinavian Stroke Scale), had less primary intracerebral haemorrhage, and less stroke lesions seen on baseline neuroimaging. Milder severity at baseline was associated with less impairment at day 7 although the difference disappeared following adjustment for baseline covariates, including baseline severity. Although the absolute rate of death at day 90 did not differ, the adjusted death rate was higher by a factor of almost two in patients from Romania. However, this was not reflected by a difference (unadjusted or adjusted) in the rate of death or dependency (mRS > 2) at 90 days. The discrepancy for findings between death, and death or dependency, is likely to reflect, in part, differences in how independence/dependence is assessed on the mRS; variability of mRS scoring has already been reported between countries. (26) Explanations for such variability do not just result from language,

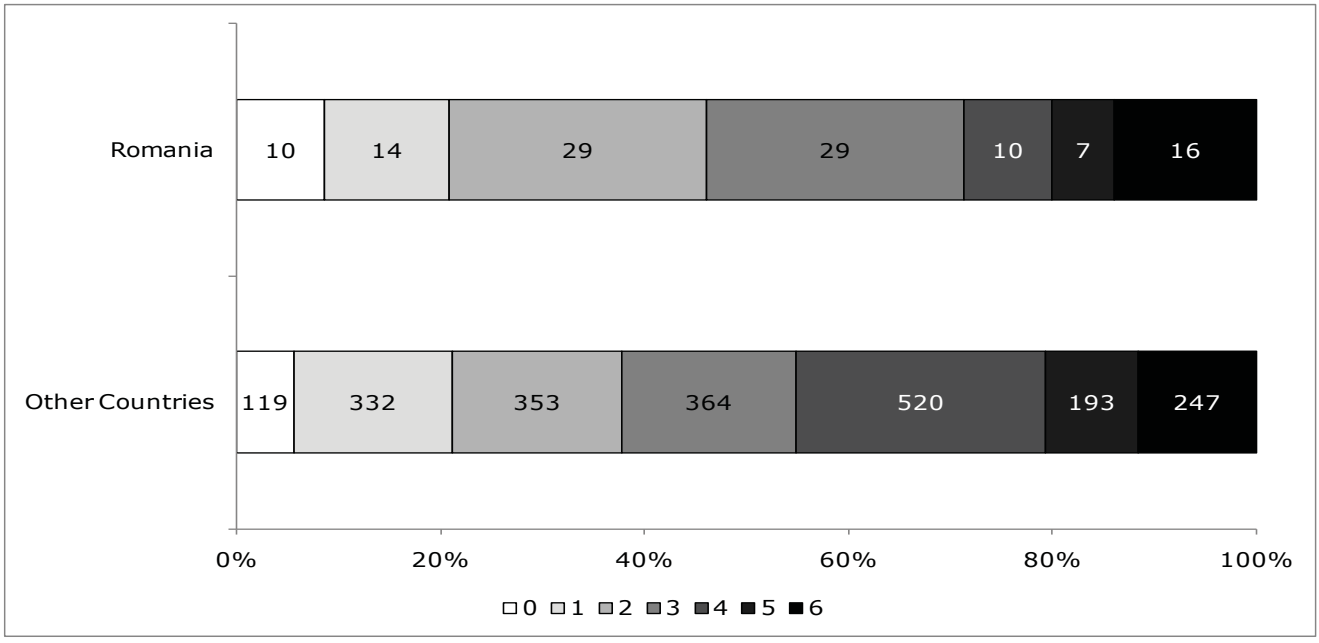

FIGURE 1. *Distribution of modified Rankin Scale in Romania and rest of the world. Numbers of patients are shown in the bar chart. Comparison by Mann-Whitney U test, p = 0.069.*

but may also occur due to socio-cultural factors related to perceptions of dependency. (26) Assuming this explanation, the difference in adjusted death rate between Romania and rest of world needs to be explained. Variation in death rates after stroke has been observed in trials previously (27-29), even when adjustments for case mix and service provision are incorporated. Whilst statistical adjustment for case mix and service provision will never truly remove differences in them between countries, it is likely that healthcare priorities and delivery is the main explanation for such variation. This latter reason is also likely to explain the variation in hospital length of stay seen here, this being ~35% shorter in patients from Romania as compared with the rest of the world.

Romanian patients were recruited an average of almost 7 hours earlier than from elsewhere in the world. Although this difference could reflect differences in service accessibility and delivery (30), it could equally reflect that ENOS is in competition with other trials in other sites worldwide, or that Romanian sites joined the trial relatively recently at a time when all sites are being asked to recruit as soon as possible after stroke onset. The shorter time to recruitment will also explain, in part, the lower rate of ischaemic lesions seen on baseline imaging.

ENOS will continue recruiting patients until the summer of 2013 and we hope to recruit more Romanian sites. The data to date show that enrolment is feasible in Romania and the trial has been found to be easy to manage and recruit into. Participating in international trials has a positive effect on patient management both in adherence to guidelines[31] and quality of care. Conversely, it is vital for international trials to have as many countries represented as possible to maximise the external validity of the trial.

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