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ENOS NEWS

The Newsletter for the Efficacy in Nitric Oxide Stroke Trial
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Continue/Stop by Prof Tom Robinson

The current National Clinical Guideline for Stroke published by the Royal College of Physicians states that anti-hypertensive therapy in people with acute stroke is recommended in only 2 situations: hypertensive emergency (such as hypertension associated to encephalopathy, nephropathy, cardiac failure, myocardial infarction, aortic dissection, pre-eclampsia, eclampsia, and intracerebral haemorrhage with systolic blood pressure over 200mmHg) and in patients eligible for thrombolysis with blood pressure >185/110mmHg. The Stroke Guidelines produced by the National Institute for Health and Clinical Excellence go one step further, stating categorically that the safety and efficacy of early blood pressure manipulation after stroke is a key research priority.

So why should blood pressure be a key research priority in acute stroke? Firstly, hypertension is a common complication in acute stroke with about 50% of patients having systolic blood pressure >160mmHg. Such levels of hypertension are associated with poor outcome with an odds ratio of 1.048 (1.012–1.079) for every 10mm increase in systolic blood pressure above 150mmHg for two week mortality and an odds ratio of 1.009 (0.989–1.030) for six month death and dependency with putative mechanisms of haemorrhage risk, oedema risk, and early stroke recurrence. One possible conclusion of these data would be to treat hypertension in the acute stroke period whether this be the *de novo* introduction of anti-hypertensive therapy for newly diagnosed hypertensive subjects or the continuation of anti-hypertensive therapy in previously treated patients. However, there are limited data in hyperacute and acute phase to support this conclusion, particularly as there is a natural tendency for blood pressure to reduce over the early days following acute stroke, and in the presence of cerebrovascular dys-autoregulation cerebral blood flow becomes dependant on systemic blood pressure and rapid reductions in blood pressure may be associated in critical falls in cerebral blood flow. Indeed, there is an odds ratio of 1.155 (1.095–1.216) for every 10mm reduction in systolic blood pressure below 150mmHg for two week mortality and an odds ratio of 1.053 (1.012–1.095) for six month death and dependency.

So what about recent trials? The recently completed pilot phase of the Controlling Hypertension and Hypertension Immediately Post Stroke Trials (Chief Investigator: Professor John Potter) has demonstrated oral or intravenous labetalol, and oral or sublingual lisinopril used within 36 hours of acute ischaemic or haemorrhagic stroke onset and continued for two weeks produces a significantly greater systolic blood pressure reduction when compared to placebo. Though this study was not powered for efficacy, no safety concerns were raised as a consequence of acute stroke blood pressure reduction with no significant differences in neurological deterioration (defined as an increase in National Institute of Health Stroke Scale Score of 4 or more at 72 hours), in three day mortality, or in serious adverse event rates over the two week treatment period. The Continue Or Stop post-Stroke Anti-hypertensive Collaborative Study (COSSACS, Chief Investigator: Professor Tom Robinson) finished recruitment on 31st March 2009, with a total of 763 patients on pre-existing anti-hypertensive therapy randomised to Continue or Stop disc therapy within 48 hours of ischaemic or haemorrhagic stroke onset and last dose of anti-hypertensive therapy for a two week period. Baseline data following the inclusion of 500 patients reported a mean age of 74.1years, a mean time to recruitment following stroke of 24.4 hours, with Oxfordshire Community Stroke Project Classification of 42% partial anterior circulation stroke syndrome and 37% lacunar stroke syndrome, a wide range of pre-existing hypertensive therapy (45% thiazide diuretic, 40% ACE inhibitor therapy, 40% beta blockade, 40% calcium channel blockade, 15% angiotensin receptor blocker, 8% alpha blocker), with over 20% of patients taking multiple antihypertensive therapy. Though the final results of this trial are not anticipated until early 2010, no safety concerns were raised by the data and safety monitoring committee and this study is not powered to demonstrated efficacy.

It is therefore clear that the safety and efficacy of early blood pressure manipulation after stroke remains a key research priority, both for the *de novo* treatment of hypertension and for consideration of continuing or discontinuing current anti-hypertensive therapy (an issue for over 50% of the acute stroke population). The beauty of the ENOS trial is that its use of topical GTN and additionally the ability to randomise to continue or discontinuing pre-existing anti-hypertensive therapy will allow it to answer both these important questions. Hypertension and its acute treatment is an issue for the majority of our acute stroke patients, and I would urge you to recruit to this important trial. With the closure of COSSACS, I have joined and am recruiting – I would urge you to do the same!

Recruitment to 30 Jun

International	**560**
Australia	**8**
Box Hill, Melbourne	*8*
Canberra	*0*
Canada	**32**
Cape Breton	*1*
Halifax (NC)	*31*
China	**103**
Tian Tan (NC)	*16*
Wenzhou	*87*
Egypt	**4**
Ain Shams Uni (NC)	*4*
Hong Kong	**4**
India	**44**
AIIMS (NC)	*18*
Armed For Med Coll	*1*
Ludhiana, CMC	*22*
Lilavati, LKMM	*3*
Italy	**0**
Malaysia	**8**
Univer Sains Mlya (NC)	*8*
New Zealand	**39**
Dunedin	*32*
Hawkes Bay (NC)	*3*
Hutt Hospital	*3*
Auckland	*1*
Philippines	**16**
Poland	**95**
Inst Psyc & Neur (NC)	*86*
Military Med Acad	*9*
Romania	**12**
Clin Hosp, Oradea	*3*
Fogolyan Kristof Sfantu	*3*
Mures County (NC)	*6*
Singapore	**153**
Singapore General	153
Spain	**1**
Hospital La Paz (NC)	*1*
Sri Lanka	**41**
South Colombo	*6*
Univ of Kelaniya (NC)	*35*

MRC Medical Research Council
The STROKE Association
The University of Nottingham

UK	769
Aberdeen	*69*
Antrim Area Hospital, NI	*1*
Barnsley	*9*
Bishop Auckland	*60*
Blackpool Victoria	*31*
Borders Melrose	*3*
Chesterfield Royal	*6*
Countess of Chester	*7*
Cumberland Infirm, Carlisle	*1*
Derby Hospitals	*30*
Doncaster	*13*
Edinburgh Royal	*7*
Edinburgh Western	*15*
Fairfield General, Bury	*7*
Glasgow Royal Infirmary	*9*
Harrogate District	*6*
James Cook, Middlesbrgh	*4*
John Radcliffe, Oxford	*3*
Kings College London	*3*
Leeds General Infirmary	*1*
Leicester General	*4*
Lincoln County	*53*
Macclesfield DGH	*5*
Monklands Glasgow	*18*
New Cross Wolverhmptn	*4*
Newark Hospital	*2*
Newham General	*27*
Ninewells, Dundee	*1*
Northampton General	*2*
Nottingham City	*180*
Pilgrim Boston	*33*
QMC Nottingham	*23*
Royal Devon & Exeter	*14*
Royal Hallams Sheffield	*1*
Royal Lancaster	*1*
Royal Preston	*6*
Scarborough	*5*
Scunthorpe	*2*
Sherwood Forest Hospitals	*7*
Southport & Ormskirk	*1*
St Marys Isle of Wight	*2*
Staffordshire General	*1*
Stockport Stepping Hill	*20*
Stobhill Glasgow	*3*
Stoke-on-Trent	*16*
Torbay	*6*
University Hosp, Aintree	*8*
University Hosp, Coventry	*3*
Victoria Hosp Kirkcaldy Fife	*18*
Watford General	*5*
Western Infirmary, Glasgow	*2*
Yeovil District Hospital	*11*

Grand Total:

1,329

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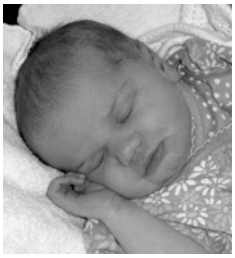
Congratulations to....



- Tanya Payne, UK Centre Coordinator, for the safe arrival of baby Florence, born 3 June 2009 and weighing 7lb13oz.
- Bishop Auckland General Hospital, UK for recruiting two patients in under 12 hours in one month and earning a chocolate hamper.
- Clinical Hospital of Neurology and Psychiatry, Oradea, Romania; Fogolyan Kristof Hospital, Sfantu-Gheorghe, Romania; Leeds General Infirmary, UK; Royal Lancaster Infirmary UK for recruiting their first ENOS patients.
- Fairfield Hospital, Bury, UK for being top of the Highest Recruiting Centres in the last 90 days.
- Watford, Aberdeen (2 patients), Stoke on Trent, Kirkcaldy Fife, Kings College London and Lancaster, UK for helping recruit 7 patients in one day on 23 June, the highest number ever in one day.
- All centres for making June 2009 the highest ever recruiting month with 50 patients.

ENOS Competition: 3 in 30

For every centre that recruits three patients in 30 days, between 15th June and 14th July we will be offering a prize of a £250 conference fund, to be used as the centre wishes.

Investigator Meetings

Many thanks to all collaborators that visited the ENOS/IST-3 stand at ESC in May 2009. We hope to see many more of you in Barcelona 25-28 May 2010. http://www.eurostroke.org/

ENOS will be represented at UK SRN Annual Meeting in Newcastle 8/9 July and at UK Stroke Forum in Glasgow, Dec 2009.

We are hosting a UK Investigator Meeting with IST-3 at UK Stroke Forum, Glasgow on Thursday 3 December at the Crowne Plaza, 12-2pm.

ENOS Teleconference Workshops

Many thanks to the 21 UK collaborators that were on the first ENOS teleconference workshop on 17 June. The FAQ will be updated with issues raised and a Powerpoint presentation on the NIHSS is now mounted on the ENOS website for reference. Dates to note for future teleconference workshops are:

Monday 6 July	13:00 GMT	International Workshop
Wed 23 September	12.30 GMT	UK Teleconference Workshop

Tips of the month

- **Recruitment** - Patients who have no history of hypertension and are not on any treatment *can* be recruited into ENOS. Inclusion is driven by BP, not previous history.
- **SAEs** - There is an expanded SAE event category list for your information. This will appear on SAE form online. If you are using the paper form, you can refer to the expanded list for more choices. The list is available on the ENOS document site (under SOP/WPDs): http://www.enos.ac.uk/EnosSopSaeEventsV10.pdf
- **Consent forms** – please ensure patients/relatives initial (not just a tick) every box on the consent form, to comply with new regulations.

******Recently Updated Forms******

- Data Monitoring Committee Approval Letter, 18 May 2009
- MHRA approval letter of substantial amendment 9, 1 May 2009 and substantial amendment form.
- Statistical Analysis Plan v1.7
- FAQ v1.9
- Site monitoring working practice document v1.1
- List of SAE Event Categories v1.0

ENOS now has 116 centres in 16 countries. More centres are welcome.