Continuing versus Stopping Prestroke Antihypertensive Therapy in Acute Intracerebral Hemorrhage: A Subgroup Analysis of the Efficacy of Nitric Oxide in Stroke Trial

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Background and purpose: More than 50% of patients with acute intracerebral hemorrhage (ICH) are taking antihypertensive drugs before ictus. Although antihypertensive therapy should be given long term for secondary prevention, whether to continue or stop such treatment during the acute phase of ICH remains unclear, a question that was addressed in the Efficacy of Nitric Oxide in Stroke (ENOS) trial. *Methods:* ENOS was an international multicenter, prospective, randomized, blinded endpoint trial. Among 629 patients with ICH and systolic

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blood pressure between 140 and 220 mmHg, 246 patients who were taking antihypertensive drugs were assigned to continue (n = 119) or to stop (n = 127) taking drugs temporarily for 7 days. The primary outcome was the modified Rankin Score at 90 days. Secondary outcomes included death, length of stay in hospital, discharge destination, activities of daily living, mood, cognition, and quality of life. *Results:* Blood pressure level (baseline 171/92 mmHg) fell in both groups but was significantly lower at 7 days in those patients assigned to continue antihypertensive drugs (difference 9.4/3.5 mmHg, $P < .01$). At 90 days, the primary outcome did not differ between the groups; the adjusted common odds ratio (OR) for worse outcome with continue versus stop drugs was .92 (95% confidence interval, .45-1.89; $P = .83$). There was no difference between the treatment groups for any secondary outcome measure, or rates of death or serious adverse events. *Conclusions:* Among patients with acute ICH, immediate continuation of antihypertensive drugs during the first week did not reduce death or major disability in comparison to stopping treatment temporarily. **Key Words:** Antihypertensive therapy—blood pressure—glyceryl trinitrate—intracerebral hemorrhage—cerebrovascular disorders—randomized controlled trial.

Introduction

High blood pressure (BP) is present in 75% of patients with acute intracerebral hemorrhage (ICH) and is substantially higher than premorbid levels.[1-3] Raised BP occurs secondary to multiple factors, including neuroendocrine activation and increasing intracranial pressure, and is associated with a poor outcome.[4-7] More than 50% of patients with acute ICH are taking antihypertensive drugs before their stroke and hospital admission.

Although lowering BP long term after stroke is key for secondary prevention,[8] it remains unclear whether prestroke antihypertensive drugs should be continued or stopped temporarily during the acute phase.[9] Arguments both for and against each strategy can be postulated and guidelines lack firm recommendations related to this subject.[10,11] Continuing prior antihypertensive drugs after ICH might limit hematoma expansion, reduce the development of cerebral edema and early recurrence, and improve long-term outcome.[8,12] And yet, continuing treatment may lead to the development of hypotension, thereby compromising regional cerebral perfusion because of dysfunctional cerebral autoregulation.[13] Further, continuing treatment involves administering tablets at a time when many patients have dysphagia and limited enteral access, a risk for aspiration pneumonia. Stopping treatment may result in secondary prevention being forgotten, thereby raising the risk of recurrent events and worsening outcomes long term.

Two trials have examined the question of whether prestroke BP drugs should be continued or stopped temporarily during the acute phase of stroke. The Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) found no difference in functional outcome, death, or serious adverse events, although it had low statistical power with only 763 participants recruited from a planned analysis of 2900 patients.[14] No differential effect in patients with ICH versus ischemic stroke was reported. The Efficacy of Nitric Oxide in Stroke (ENOS) trial assessed the effects of glyceryl trinitrate (GTN) versus no GTN in 4011 participants with acute stroke; patients who were taking prestroke antihypertensive medications were also randomized to continue or stop these for 7 days in a partial factorial design.[15] Although ENOS was neutral for both interventions,[16] a subgroup of patients randomized to continue treatment within 12 hours had a worse functional outcome (unpublished data), an effect also seen in a meta-analysis of individual patient data from COSSACS and ENOS combined (Woodhouse et al, unpublished). Here, we report the results of a preplanned subgroup analysis of patients with ICH enrolled in ENOS and who were randomized to continue versus stop prestroke antihypertensive therapy,[17] including those randomized within 12 hours of stroke onset.

Methods

ENOS Trial

Details of the ENOS study protocol, statistical analysis plan, patient characteristics at baseline, and main results have been published (ISRCTN99414122).[15-18] In brief, ENOS was a prospective, international, multicenter, randomized, blinded endpoint trial recruiting patients within 48 hours of ischemic stroke or ICH. Patients aged over 18 years with systolic blood pressure (SBP) level of 140-220 mmHg and who did not have a definite need for, or contraindication to, BP-lowering treatment were eligible. Randomization was performed centrally by computer to GTN (5 mg each morning) or no GTN, and, where relevant, to continue or stop taking prior antihypertensive