A

unemonic shift with increased sympathetic activity has been repeatedly observed in acute stroke and related to worse outcome.1–3 Possible pathophysiological mechanisms include increased cardiovascular complications, arrhythmias, blood pressure (BP) derangements, nondiabetic hyperglycemia, and promotion of secondary brain injury because of local inflammation and edema.4 Thus, the modifying of impaired autonomic functions may have important therapeutic implications in acute ischemic stroke. In animal models, β-blockers (BBs) given before the induction of experimental ischemia lead to a reduction in infarct volume by 40%.5 Administration of propranolol drastically reduced mortality after middle cerebral artery occlusion in experiment.6 However, the evidence in human stroke is scarce. A study by Laowattana et al7 suggested that prestroke use of BB was independently associated with less severe stroke on presentation and that sympathetic effects may have cerebroprotective properties. Another study found that BB may reduce the risk of early death after ischemic stroke.8 Moreover, sympathetic hyperactivity is suggested to play a central role in the poststroke immunodeficiency syndrome with increased susceptibility to infections.9 Several independent studies showed that the degree of immune changes correlates with the poststroke levels of catecholamines.10 Prass et al11 showed increased occurrence of spontaneous pneumonia in a model of middle cerebral artery occlusion, which could be prevented by blocking the β-adrenergic receptors. Atenolol treatment reduced systemic inflammatory response syndrome, pneumonia, and mortality in a study including intracerebral hemorrhage patients.12 Thus, we hypothesized that (1) BB use before stroke onset and initiated in the acute phase is associated with decreased mortality and better functional outcome and (2) BB before stroke onset and during the acute phase may decrease the incidence of poststroke pneumonia.

Background and Purpose—Increased sympathetic drive after stroke is involved in the pathophysiology of several complications including poststroke immunodeficiency. β-Blocker (BB) therapy has been suggested to have neuroprotective properties and to decrease infectious complications after stroke. We aimed to examine the effects of random pre- and on-stroke BB exposure on mortality, functional outcome, and occurrence of pneumonia after ischemic stroke.

Methods—Data including standard demographic and clinical variables as well as prestroke and on-stroke antihypertensive medication, incidence of pneumonia, functional outcome defined using modified Rankin Scale and mortality at 3 months were extracted from the Virtual International Stroke Trials Archive. For statistical analysis multivariable Poisson regression was used.

Results—In total, 5212 patients were analyzed. A total of 1155 (22.2%) patients were treated with BB before stroke onset and 244 (4.7%) patients were newly started with BB in the acute phase of stroke. Mortality was 17.5%, favorable outcome (defined as modified Rankin Scale, 0–2) occurred in 58.2% and pneumonia in 8.2% of patients. Prestroke BB showed no association with mortality. On-stroke BB was associated with reduced mortality (adjusted risk ratio, 0.63; 95% confidence interval, 0.42–0.96). Neither prestroke BB nor on-stroke BB showed an association with functional outcome. Both prestroke and on-stroke BB were associated with reduced frequency of pneumonia (adjusted risk ratio, 0.77; 95% confidence interval, 0.6–0.98 and risk ratio, 0.49; 95% confidence interval, 0.25–0.95).

Conclusions—in this large nonrandomized comparison, on-stroke BB was associated with reduced mortality. Prestroke and on-stroke BB were inversely associated with incidence of nosocomial pneumonia. Randomized trials investigating the potential of β-blockade in acute stroke may be warranted. (Stroke. 2015;46:1269-1274. DOI: 10.1161/STROKEAHA.114.008260.)

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* A list of all VISTA Acute Steering Committee members is given in the Appendix.

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to pneumonia and poor outcome and, moreover, have a contraindication for BB. Records on antihypertensive medication have been checked manually exploring the text strings on medication in the final compiled database. Active substances have been identified and categorized into following groups: BBs, β-1-selective BBs, nonselective BBs, angiotensin-converting enzyme inhibitors (ACE), angiotensin-receptor antagonists (ARB), and calcium channels blockers (CA). Antihypertensive therapy was further categorized into prestroke administration and on-stroke administration. Later category has been coded if a new antihypertensive was initiated within the first 3 days after symptoms onset. Mortality at 3 months was recorded. Functional outcome at 3 months retrieved from the database was dichotomized into modified Rankin Scale 0 to 2 versus 3 to 6.

Statistical Analysis
Distribution of the data was visualized using histograms and tested using the 1-sample Kolmogorov–Smirnov test. For normally distributed data the results are presented as mean, range, and SD, for non-normally distributed data as median, range, and interquartile range. Poisson multivariate regression models were used to adjust for possible confounders. Variables showing imbalances between groups in the univariate comparison were tested for confounding effects as follows: both the treatment variable and the potential confounding variable entered a bivariable regression model and the adjusted risk ratio (RR) was calculated. When the adjusted RR deviated from the crude RR >5%, the variable was recorded as a confounder. Then a multivariable model with treatment and all variables that shifted the crude RR by >5% was built. Values of P<0.05 were considered statistically significant in all tests. All statistics were performed using statistical software SPSS 19.0 for Windows.

Results
Altogether 5212 patient data sets were analyzed. Mean age was 67 years (range, 20–98 years; SD 12.6), 54.3% of patients were men. A total of 1155 (22.2%) patients were treated with BB before stroke onset, 135 (2.6%) with nonselective BB and 1020 (19.6%) with β-1-selective BB. A total of 1215 (23.3%) patients previously had received ACE, 370 (7.1%) ARB, and 744 (14.3%) had received CA. Within the first 3 days after stroke onset, 244 (4.7%) patients were started with BB, 192 with β-1-selective BB (3.6%), and 52 (0.99%) with nonselective BB. Furthermore, 489 (9.4%) patients were started with ACE, 72 (1.4%) with ARB and 161 (3.1%) with CA. Comparison of patients with prestroke BB exposure to BB naïve patients is shown in Table 1. Comparison of patients started newly with BBs within the first 3 days after stroke onset to patients without BBs is shown in Table 2.

Mortality at 3 Months
Mortality data were available for 5212 patients. Overall mortality at 3 months was 17.5%. Mortality in patients taking BBs before stroke onset was 18.8% as compared with 17.2% of BB naïve patients (crude RR, 1.09; 95% confidence interval [CI], 0.94–1.27). In the bivariable analysis including prestroke BB and one by one the possible confounders (age, myocardial infarction, atrial fibrillation, hypertension, diabetes mellitus, ischemic heart disease, previous stroke, admission blood glucose, admission systolic BP, onset-to-treatment time, recombinant tissue-type plasminogen activator, prior statin, prior ACE, prior ARB, prior CA, on-stroke BB and on-stroke ACE), the variables age, myocardial infarction, atrial fibrillation, hypertension, and ischemic heart disease shifted the crude RR of prestroke BB by >5% (see above) and entered multivariate testing (Table 3). After...
adjustment for confounders the association between prestroke BB treatment and 3 months mortality showed an adjusted RR of 0.95 and 95% CI of 0.81 to 1.1. When β1-selective BB and nonselective BB were introduced separately (one by one) into the multivariable model instead of BB as a group, prestroke β1-selective BB showed a adjusted RR of 0.92, 95% CI of 0.78 to 1.09, whereas prestroke nonselective BB showed a adjusted RR of 1.14 and 95% CI of 0.79 to 1.64 (Table 3).

Mortality in patients started with BBs within the first 3 days of stroke onset was 9.4% as compared with 17.9% in those continuing without BBs (crude RR, 0.53; 95% CI, 0.42–0.69). When β1-selective BB and nonselective BB were introduced separately (one by one) into the model instead of BB as a group, on-stroke β1-selective BB was associated with decreased mortality (adjusted RR, 0.48; 95% CI, 0.28–0.83), whereas nonselective BB was not (adjusted RR, 1.12; 95% CI, 0.61–2.13; Table 3).

**Functional Outcome at 3 Months**

Functional outcome data were available in for 5052 patients. Favorable outcome (defined as modified Rankin Scale 0–2)
occurred in 58.2% of patients. Neither prestroke nor on-stroke BB was associated with functional outcome at 3 months (crude RR, 0.98; 95% CI, 0.9–1.07 and crude RR, 1.06; 95% CI, 0.9–1.26, respectively). After adjustments for confounders these associations changed only modestly (adjusted RR, 1.02; 95% CI, 0.9–1.12 and adjusted RR, 0.96; 95% CI, 0.8–1.15, respectively).

### Pneumonia Within 10 Days After Stroke Onset

A total of 5212 patient data sets were analyzed. Pneumonia within 10 days occurred in 427 (8.2%) subjects. For prestroke BB, the crude RR for developing pneumonia was 0.85 and 95% CI was 0.67 to 1.01. In the bivariable analysis including prestroke BB and one by one all possible confounders, only age and atrial fibrillation shifted the crude RR of prestroke BB by >5% and thus entered the multivariate testing (Table 3).

### Discussion

Our results raise the possibility that BB in the acute phase of ischemic stroke may reduce mortality independently of the usual outcome factors such as age, stroke severity, or baseline glycemia. Our observation derived from a large number of subjects seems to confirm previous reports. A retrospective study by Dziedzic including 841 consecutive ischemic stroke patients suggested lower 30-day case fatality in those treated with inhospital BB (6.8% versus 19.0%; \(P<0.001\)). Similarly, a recent study by Kalita indicated reduced mortality in patients with intracerebral hemorrhage in whom BB was acutely treated with atenolol (11.4 versus 37.3%; \(P<0.0001\)). These effects may be because of the capability of BB to reduce effects of sympathetic overactivity. Acute ischemic stroke as well as intracerebral hemorrhage are conditions associated with a robust stress response with sympathetic activation, which is in turn responsible for increased morbidity and mortality after stroke. Multiple studies have demonstrated cardioprotective effects of BBs in patients after acute myocardial infarction. BBs reduce the increased sympathetic tone after myocardial infarction leading to reduced cardiac complications and mortality. β-blockade seems to be beneficial also in other states of adrenergic hyperactivation including heart failure, sepsis, or acute respiratory distress syndrome. Interestingly, BB exposure was associated with improved survival in trauma patients, in particular, in severe traumatic brain injury. An early randomized trial on β-blockade in acute stroke yielded negative results. However, this study enrolled rather low number of subjects (n=302) and had limitations including stroke diagnosis without imaging, baseline group imbalances favoring placebo and unstandardized outcome measures. Since then, no further randomized studies have been performed.

Prestroke β-blockade was not shown to have any association with initial stroke severity (data not shown), stroke mortality, or functional outcome in our data set. This is in line with a recent large secondary analysis performed with the pooled data from 2 neuroprotection trials including 1375 patients where this hypothesis has been tested and dismissed. These data were not included in the VISTA archive. The data set of these 2 neuroprotection trials therefore does not overlap with the data set of the recent analysis. Summarized, the BB effects on stroke mortality seem to be present for inhospital BB treatment but not for the prestroke administration.

Our analysis further suggests that BB treatment may eventually reduce the incidence of nosocomial pneumonia after stroke. The central role of sympathetic activation in the poststroke immunosuppression responsible for the high
susceptibility to pneumonia has been extensively discussed. Studies by Prass et al showed that a catecholamine-mediated strong inhibition of cell-mediated immune responses is the major cause of spontaneous systemic bacterial infections in experimental stroke. In a further study, the BB propranolol, administered immediately before and twice after middle cerebral artery occlusion, followed by intranasal administration of Streptococcus pneumoniae at 4 days after stroke, drastically reduced pneumonia and completely blocked bacteremia. Interestingly, in humans having intracerebral hemorrhage, atenolol treatment significantly reduced pneumonia (8.9% versus 30.5%; \( P = 0.002 \)). Another study suggests that patients with stroke treated with BBs during hospitalization less often develop pneumonia than those not treated with BBs (4.5% versus 11.4%; \( P = 0.05 \)). In our study, both prestroke and on-stroke \( \beta \)-blockade was associated with decreased risk for developing pneumonia within 10 days after stroke onset. One could argue that history of chronic obstructive pulmonary disease could possibly bias the analysis because of the high susceptibility of chronic obstructive pulmonary disease subjects to pneumonia and low frequency of BB prescription in these patients. However, it is most unlikely that chronic obstructive pulmonary disease is a confounder in our data set as there are virtually no differences in its prevalence between the comparison groups. To limit further bias, we also preferred to analyze pneumonia only within the first 10 days, a timespan during which most nosocomial pneumonias are expected to occur. As pneumonia is thought to strongly affect outcome and mortality after stroke, it is considered to be an attractive therapeutic target. As recent anti-infective trials failed to show effectiveness, the issue of poststroke infections remains an open therapeutic challenge.

We would like to emphasize the following limitations of our study. First, BB in this study was principally uncontrolled, nonrandomized, highly heterogeneous in substances and dosages as well as in indications for administration. In particular, the main source of possible bias is the confounding by indication. We therefore performed a detailed search for possible confounders in assessing each potential confounder separately, using a bivariate regression analysis and calculating the effects on the crude RR changes of the treatment variable. As expected, relevant imbalances between the groups consisted of factors representing the indication for the prestroke BB (history of hypertension, atrial fibrillation, myocardial infarction, or ischemic heart disease). Despite having adjusted the analysis for these factors, one cannot completely rule out hidden effects. Second, one of our end points, pneumonia, was defined based on the discretion of the treating physicians who coded and reported AEs for the respective trials merged in the VISTA database, thus without having one uniform definition. Third, generalizability of our study may be hampered because the VISTA source studies used in the current analyses could not be declared according to preset VISTA regulations. Finally, the results have to be interpreted with caution because of the retrospective, nonrandomized nature of the analysis. All of these factors might have introduced unpredictable bias into the analysis. Despite the aforementioned limitations, the strength of this study is the use of a large, prospective patient cohort with rigorously collected baseline demographics, medication use both at onset and during hospitalization, precise AEs reporting, and standardized manner and timing of outcome assessments.

Conclusions
In this large nonrandomized comparison, on-stroke treatment with BBs was associated with reduced stroke mortality. Furthermore, prestroke and on-stroke \( \beta \)-blockade were associated with reduced incidence of nosocomial pneumonia after appropriate multivariable adjustment. Despite negative early trials with BBs in acute stroke, we suggest that randomized trials investigating the potential of \( \beta \)-blockade in acute stroke may be warranted. However, off-label experimental use in clinical practice should be avoided until the safety and feasibility are proven elsewhere.

Appendix

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Disclosures
None.

References


β-Blockers, Pneumonia, and Outcome After Ischemic Stroke: Evidence From Virtual International Stroke Trials Archive

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