# Treatment of Unruptured Cerebral Aneurysms with the Mineralocorticoid Receptor Blocker Eplerenone—Pilot Study

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*Background:* Currently there are no pharmacological therapies for patients with unruptured cerebral aneurysms. Elsewhere we showed that the mineralocorticoid receptor antagonist eplerenone prevented the formation of cerebral aneurysms in our ovariectomized hypertensive aneurysm rat model. The current pilot study evaluated whether it can be used to prevent the growth and rupture of cerebral aneurysms in hypertensive patients. *Methods:* Between August 2011 and May 2014, we enrolled 82 patients with 90 aneurysms in an open-label uncontrolled clinical trial. All provided prior informed consent for inclusion in this study, and all were treated with eplerenone (25-100 mg/d). The primary end points of our study were the rupture and enlargement of the cerebral aneurysms. *Results:* Of the 82 patients, 80 (88 unruptured aneurysms) were followed for a mean of 21.3 months (153.4 aneurysm-years); 12 patients (15.0%) permanently discontinued taking the drug. One month after the start of eplerenone administration and throughout the follow-up period, eplerenone kept the blood pressure within the normal range. Most notably, no aneurysms smaller than 9 mm ruptured or enlarged. However, of 2 large thrombosed aneurysms, 1 enlarged and the other ruptured. The overall annual rupture rate was .65%; it was 13.16% for aneurysms larger than 10 mm; the overall annual rate for reaching the primary end points was 1.30%. *Conclusion:* Our observations suggest that eplerenone may help to prevent the growth and rupture of unruptured cerebral aneurysms smaller than 9 mm. To assess its

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potential long-term clinical benefits, large clinical trials are needed. **Key Words:** Mineralocorticoid receptor blocker—eplerenone—hypertension—unruptured cerebral aneurysms.



## Introduction

Subarachnoid hemorrhage (SAH) due to the rupture of cerebral aneurysms carries a high mortality risk.[1] Advances in imaging techniques have led to the incidental discovery of unruptured cerebral aneurysms. Indications for surgical treatment depend on the patient's life expectancy and the size and site of the aneurysms. The mortality and morbidity rates after the clipping and coiling of unruptured aneurysms are not negligible. Therefore, pharmacological means to prevent aneurysmal growth and rupture are an attractive option, especially in patients with a high surgical risk.

Based on epidemiological data that show a high incidence of cerebral aneurysms and SAH in postmenopausal women, we established a cerebral aneurysm model in female rats subjected to estrogen deficiency, hypertension, and hemodynamic stress.[2] In this model, pharmacological treatment with 17β-estradiol, antihypertensive drugs, or a phosphodiesterase 4 inhibitor reduced the incidence of cerebral aneurysms via their antioxidative and anti-inflammatory effects.[3-6] The mineralocorticoid receptor eplerenone effectively, and blood pressure (BP) independently, prevented the formation of cerebral aneurysm in our model rats.[4] We also found that in eplerenone-untreated model rats, the expression of CD68, monocyte chemoattractant protein-1, and matrix metalloproteinase-9 increased. Eplerenone abrogated these adverse changes.

To obtain knowledge on the potential effectiveness of eplerenone for the prevention of human aneurysmal growth and rupture, we performed a pilot study and recorded the clinical course of hypertensive, eplerenone-treated patients with unruptured cerebral aneurysms.

## Methods

### *Patient Recruitment*

Investigators at the 11 participating hospitals obtained the approval of their local institutional review boards before joining the study. Table 1 is a list of the institutions, investigators, and cases. All patients gave their written informed consent before enrollment. Our inclusion criteria were as follows: (1) They had at least 1 previously or newly diagnosed unruptured aneurysm whose diameter was 2 mm or larger in the maximum external diameter in any direction without referable clinical symptoms or signs. Aneurysm discovery was by angiography, magnetic resonance imaging, magnetic resonance angiography, or computed tomography angiography studies performed for reasons other than a suspicion of an index aneurysm. (2) They have no included unruptured aneurysms that had been treated by surgical clipping or endovascular coiling. (3) They have hypertension, defined as a systolic BP of 140 mm Hg or higher or a diastolic BP of 90 mm Hg or higher, or use antihypertensive medication. (4) They are aged between 40 and 84 years. (5) They have a modified Rankin Scale of ≤2.

### *Exclusion Criteria and Study End Points*

We imposed 6 exclusion criteria: (1) a history of mycotic, traumatic, vasculitic, or previously treated aneurysms; (2) severe coexisting or terminal systemic disease such as

**Table 1.** *List of participating institutions, investigators, and cases*

| Study center | Entry case number | Valid case number | Local investigators |
|---|---|---|---|
| Anan Kyoei Hospital | 3 | 2 | D. Ebisudani, K. Bando |
| Kitajima Taoka Hospital | 3 | 3 | Y. Murayama |
| Kyoritsu Hospital | 3 | 3 | S. Yoshijima |
| Mizunomiyako Kinen Hospital | 1 | 1 | I. Sasaki |
| Yoshinogawa Medical Center | 1 | 1 | N. Asano, K. Hara |
| Taoka Hospital | 7 | 7 | S. Manabe |
| Tezuka Hospital | 3 | 3 | T. Soga |
| Tokusima Prefectural Central Hospital | 1 | 1 | H. Hondo |
| Tokushima Prefecture Naruto Hospital | 2 | 2 | M. Agawa |
| Tokushima Red Cross Hospital | 6 | 6 | K. Sato |
| Tokushima University Graduate School | 52 | 51 | S. Nagahiro |