

Response to "Comment on 'Clopidogrel can be an effective complementary prophylactic for drug-refractory migraine with patent foramen ovale'"

Yichen Guo 

Department of Neurology,
Xi'an Jiaotong University
Medical College First
Affiliated Hospital, Xi'an,
China

Correspondence to

Yichen Guo, Department of
Neurology, Xi'an Jiaotong
University Medical College
First Affiliated Hospital, Xi'an
710061, China;
544464092@qq.com

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Dear Editor,

We thank Haghdost and Sacco for their interest and comment¹ on our article.²

Our study is a single-center non-randomized open-label trial and each patient was enrolled with a rigorous diagnosis by the neurologist. We ensure that each patient was well represented. The sample size is very small for setting a placebo group, so our study is a self-controlled experiment. However, a meta-analysis³ to quantify the placebo effect of migraine preventive treatment reported that, in the 22 studies they included, they did not find that the percentage of responders with the placebo effect was higher than 35% and the frequency of migraine attacks was lower than 40%, and the placebo effect is significantly lower than the treatment effect. In addition, this study conducted a unified analysis of all subjects instead of a single patient. At this level, the benefit time of drug treatment is continuous and significant, which is obviously inconsistent with the effect of placebo.

Haghdost and Sacco¹ mentioned that there is no general consensus on the definition of refractory migraine. The European Headache Federation⁴ defined 'Refractory chronic migraine', and in our study, we enrolled both episodic migraine and chronic migraine. We referenced from "Migraine Intervention With STARFlex Technology (MIST) Trial".⁵ Based on the situation in China, most of the patients went to the primary-level clinics before they were enrolled in the study. Some drugs, such as divitamins, are an abbreviation of "Divitamins, Notoginseng and Cinnarizine Capsules". It is a Chinese compound medicine in which cinnarizine is a calcium channel antagonist. At the same time, although the ingredients are uncertain, herb is very common in the treatment of migraine in China, and the effect is more significant. With the standardization of migraine treatment, the prophylactics have been further standardized. It is a pity for the inevitable shortcomings in this research. We thank Haghdost *et al* who referred the newest consensus of refractory migraine by the European Headache Federation,⁶ and

in later studies, this part of the bias can be reduced.

We excluded patients with abnormalities at brain MRI because it was necessary to exclude other nervous system diseases, which may cause secondary headaches that would affect our results. The strict inclusion and exclusion criteria would not affect the diagnosis of migraine and patent foramen ovale (PFO). It excluded patients with multiple comorbidities, and such patients may make the experimental results unreliable. Therefore, at this level, the prevalence of PFO can be used as a reference in our experiments. As of the time of statistics, only 12 patients completed the 6-month period. The remaining patients will be observed in the further studies.

Clopidogrel, as a routine antithrombotic drug after PFO surgical closure, has been increasingly proven to relieve headaches.^{7,8} Although there are obvious limitations in this study, it provides clinical neurologists with an idea for medical treatment before PFO operation.

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ORCID iD

Yichen Guo <http://orcid.org/0000-0002-0417-9795>

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