CORRESPONDENCE

Juvenile Stroke—A Practice-Oriented Overview

by Dr. med. Florian Schöberl, Prof. Dr. med. Peter Arthur Ringleb, PD Dr. med. Reza Wakili, Dr. med. Sven Poli, PD Dr. med. Frank Arne Wollenweber, and PD Dr. med. Lars Kellert in issue 31–32/2017

The Interventional Effect Cannot Be Interpreted

Schöberl et al. reported the therapeutic effect of interventional patent foramen ovale (PFO) closure on the risk of ischemic cerebral insults: "However, the number needed to treat by PFO closure to prevent another stroke is 67 (e9)." (1)

Although it is desirable that a therapeutic effect should be summarized in a single number, this extremely brief reporting style is bound to result in a situation where readers cannot interpret the therapeutic effect anymore (2). The NNT is calculated by inverting the risk reduction (1/risk reduction). Without answers to the following questions, the NNT cannot be interpreted:

1. Which treatment alternative (comparator) was interventional PFO closure compared with? And:
2. What was the time frame for which the risk of ischemic cerebral insults was determined?

The risk differences determined by studies, and the NNTs crucially depend on these two factors. The meta-analysis cited by Schöberl et al. (3) included three studies with varying comparators: platelet aggregation inhibition in isolation or combined with anticoagulation. In the PFO closure group, medication treatment (platelet aggregation inhibitors) was also given; and durations of treatment differed (3).

The phrase "to prevent another stroke" is incorrect. The NNT of 67 means that if 67 patients are treated by PFO closure and 67 patients are treated with the comparator treatment, one additional ischemic cerebral insult can be expected to be prevented in the PFO group over an observation period of 2.5 years. Schöberl et al. are not referring to an additional case, but one case. I have my doubts whether the NNT was a helpful measure for doctors in terms of risk communication.

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The author declares that no conflict of interest exists.

PFO Closure and Stroke

In their article on juvenile stroke, the authors also comment on indication for interventional closure of patent foramen ovale (PFO) (1). On the basis of a US guideline from 2014, they recommend platelet aggregation inhibition in cryptogenic stroke even in the presence of PFO; in recurrent stroke, they recommend anticoagulation. PFO closure gains the status of an individual attempt to prevent cryptogenic stroke.

New data on this subject have been published in the past few years: long-term data from the RESPECT Study were presented in 2015 and published recently. This study had a mean follow-up period of 5.9 years and found a significant risk reduction in recurrent stroke for implanted PFO occluders (2). These data prompted an October 2016 licensing approval on the part of the FDA for the PFO occlude in the US. In May 2017, two large randomized studies were presented at the European Stroke Organization Conference in Prague. The REDUCE Study (664 patients) compared PFO closure with platelet aggregation only: the PFO closure group was found to have a significant absolute risk reduction of 4% for recurrence of stroke (3). The CLOSE Study (663 patients) randomized patients who had suffered from a cryptogenic stroke attributed to PFO, with associated atrial septal aneurysm or large interatrial shunt to transcatheter PFO closure plus long-term antiplatelet therapy, antiplatelet therapy alone, or oral anticoagulation. At a mean follow-up of 5.3 years, not a single stroke was observed after PFO closure, whereas 14 patients had a stroke in the antiplatelet-only group. This means that the benefit to the intervention group is highly significant (4).

According to the latest data, PFO closure should always be discussed in younger patients with cryptogenic stroke (after all other possible causes have been excluded), especially if the PFO is large, with a relevant right-left shunt or an atrial septal aneurysm).

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Dr Lange has received honoraria for training events, further professional educational events, and consultancy services from Abbott (formerly St. Jude Medical).

In Reply:

We refer to Professor Stang's critical comments in response to our article on the therapeutic effect of interventional PFO closure on the risk of recurring stroke.

As explained by Stang, in order to interpret the NNT of interventional PFO closure in a useful way, the comparators (that is, alternative treatments) and the follow-up period are crucial.

As Stang correctly reported, the follow-up period in the meta-analysis we cited in our article was 2.5 years (1, 2). Regarding the varying comparators from the three studies pooled in this meta-analysis (CLOSURE I, RESPECT, and PC), Stang's comment is not entirely correct: the alternative treatments in the control arms were not merely platelet aggregation inhibitors alone, as well as a combination of platelet aggregation inhibitors plus oral anticoagulation with a vitamin K antagonist (warfarin), but also warfarin treatment alone (1). Medication treatment using different platelet aggregation inhibitors was also given to the PFO closure groups (1).

Stang explains the term NNT by using as an example the meta-analysis by Kent et al., which we cited in our article (1): if 67 patients are treated with PFO closure and 67 patients are treated with the comparator treatment, one additional ischemic stroke can be expected to be prevented over 2.5 years of follow-up. He is therefore correct in his criticism that the formulation we used—"to prevent another stroke" is incorrect—it should have said "to prevent one additional stroke."

We agree with Lange, that in view of the latest evidence from studies, PFO closure should undergo reassessment. The studies cited by Dr Lange—REDUCE and CLOSE—were published in the *New England Journal of Medicine* on 14 September 2017; we were therefore unable to consider them in our review article on juvenile stroke (3, 4). Our article refers to the guidelines that are currently still valid. Whether and to what extent the guidelines will change as a result of these recent studies remains to be seen. Regarding content, we take the view that even in future, the indication for PFO closure will remain an individual decision. In brief, the recently published studies lead us to conclude that a selected group of patients (age <60 years, PFO with atrial septal aneurysm and/or large interatrial shunt, no rival cause of stroke except for the PFO) will benefit from PFO closure compared with platelet aggregation inhibitor treatment alone, as regards preventing recurring stroke. However, insufficient data exist regarding a comparison group receiving oral anticoagulants. A point of criticism is also the increased rate of atrial fibrillation in the intervention group. It is completely unclear what the implications of this will be, especially in view of the absence of long-term data.

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