

# The tsunami of meta-analyses of patent foramen ovale closure for secondary prevention of cryptogenic stroke

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Despite the body of evidence from observational studies and meta-analyses of these to support patent foramen ovale (PFO) closure for secondary prevention of cryptogenic strokes (CS), guidelines remain conservative in their recommendations for this intervention and call for the completion of randomised controlled trials<sup>1</sup>. Data from three randomised trials, CLOSURE I, PC and RESPECT<sup>2-4</sup>, were all recently published in the New England Journal of Medicine in 2012-13. All three trials failed to find a statistically significant reduction in the primary endpoint of stroke, transient ischaemic attack  $\pm$  death and peripheral embolism using intention-to-treat analyses with PFO closure.

What is also interesting is the fact that these three trials have become the source for a multitude of meta-analyses, 13 of which have been published and included in PubMed during June-December 2013 alone, and counting, one of which recently published in EuroIntervention<sup>5</sup>. Eleven of these 13 meta-analyses were published in cardiology journals and two in neurology journals and certainly nearly all studies were affiliated to the cardiology rather than to the neurology departments of their respective institutions.

Despite pooling identical cohorts of patients (total  $n=2,303$ ) from trials with similar conclusions<sup>2-4</sup>, there was a diverse range of results, interpretations and conclusions across these 13 meta-analyses. Firstly, there were small but sometimes significant differences in the pooled ratio estimates as well as subgroup analyses, probably due to slight variations in the statistical analyses performed in terms of actual outcomes (some combination of stroke, transient ischaemic attack and death), statistical models or software used.

More importantly, there was no consensus in the interpretation of these findings. Nine studies said that there was no benefit for PFO closure, although five mentioned potential signals of benefit either in certain subgroups or with borderline non-significant  $p$ -values. The other four studies concluded that PFO closure is potentially beneficial, with one going as far as saying that their pooled evidence "strengthens the role of device closure in cryptogenic stroke". No agreement was reached regarding which subgroups benefited the most, apart perhaps from those receiving the Amplatzer device.

Whereas the randomised trials have given relatively uniform results, albeit opposite to those from observational studies, the

meta-analyses have served to lengthen the debate as to which specific, if any, indications for PFO closure exist for secondary prevention of CS. Further trials such as CLOSE, Gore-REDUCE and DEFENSE-PFO are nearing completion, but it remains to be seen whether they will help answer the question, or if the controversy will be further clouded by another flurry of meta-analyses.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

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## REPLY TO THE LETTER TO THE EDITOR

# The case for duplicate meta-analyses of patent foramen ovale closure in patients with cryptogenic stroke: more a ripple than a tsunami

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The thoughtful letter from Wang and Wang underlines the striking number of meta-analyses of patent foramen ovale (PFO) closure versus medical therapy published in 2013. I have unwittingly participated in this “bombing” by first-authoring one of the 13 simultaneous meta-analyses on the topic mentioned in the letter<sup>6</sup>. Such an unquiet proliferation of studies in spite of so few randomised trials being available betrays the hurry of the scientific community to put the final word to one of the most enduring controversies in the relatively young history of interventional cardiology.

A tsunami is “a very high, large wave in the ocean that is usually caused by an earthquake under the sea and that can cause great destruction when it reaches land”<sup>7</sup>. Perhaps the large volume of literature mentioned by Wang and Wang does not really qualify for this definition, the reason being twofold. First, the CLOSURE I, RESPECT and PC trials have not properly mimicked the disruptive effect of an earthquake with respect to our knowledge of the subject: all three studies were negative, but possibly false-negative as a reflection of the low number of events (which, indeed, supports the rationale for increasing the statistical power beyond that of the individual studies by pooling them into a meta-analysis). Second, whatever we name this wave (i.e., a tsunami or a ripple), we must recognise that its effect on current practice, in view of the controversial findings of PFO closure meta-analyses, will be anything but destructive. Probably marginal, clearly not conclusive.

In a recent issue of *EuroIntervention*, we discussed the practice of overlapping meta-analyses<sup>3</sup>. Even when exactly the same studies are pooled together, which in this case happens consistently, the results may still differ due to a number of considerations. Discordance frequently occurs at the level of study design when different primary outcomes are defined (i.e., some PFO closure meta-analyses used stroke as the primary endpoint, others used a composite of stroke or transient ischaemic attack). The use of random- versus fixed-effect models as well as other variations in the statistical methodology may also account for slight differences in the summary estimates, which becomes critical when confidence intervals are large, as in this case, and p-values borderline. Finally, it is at the interpretation level that meta-analyses of the same studies

can differ the most. Indeed, the lack of indisputable findings from the primary studies makes such meta-analyses prone to different interpretation. Importantly, interpretation should be regarded as just as important as earlier steps in the meta-analytic workflow, including study design, identification of trials, data extraction, and statistical analysis. With nine meta-analyses of PFO closure suggesting no benefit (but five conceding some signal of benefit) and four advocating potential or even strengthened benefit, the question cannot be considered closed... as a PFO treated percutaneously.

How to defend ourselves from this overwhelming attack of conflicting findings? When approaching discordant meta-analyses, readers should base their judgement on the quality of data extraction, availability of study- or patient-level outcomes, heterogeneity, quality of the primary studies, and performance of properly executed sensitivity and subgroup analyses<sup>8</sup>. Ultimately, individual interpretation of a meta-analysis stems from a complex interplay of scientific knowledge and expertise, clinical background, and personal beliefs. Waiting for upcoming trials to shed more light or more confusion, whether the glass of PFO closure is half full or half empty remains a question of instinct and attitude towards experiential or evidence-based medicine.

## Conflict of interest statement

The author has no conflicts of interest to declare.

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