ANSWERING REVIEWERS

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: Stretta: A valuable endoscopic treatment modality for gastroesophageal reflux disease

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

The reviewer's comments are shown in *Italics*; my responses are below.

The amount of patients with refractory-GERD or partially refractory GERD is increasing. Therefore the need for some improved or complex approach to the treatment of GERD is emerging. The comprehensive analysis of STRETTA procedure is presented in the paper. The data are well and clearly presented, it is easy to read and understand, the data are interesting and informative.

I appreciate the reviewer's understanding of the issues and their favorable assessment of our work.

Nevertheless, I have some comments:

1. The majority of studies are small and not randomized? The results of studies are though positive for Stretta, but not overwhelming? It looks as these studies were influenced by industry? Industry-bias?

In the case of Stretta, and as in many other endoscopic studies, safety and efficacy have been established through the publication of smaller studies from multiple different institutions, unsupported by industry. There is only one manufacturer-funded study, the sham-controlled trial by Corley et al. (2003). I tried to present the evidence as objectively as I could.

2. There are no negative studies presented? Publication bias?

I have reviewed all the studies published. The Perry et al. meta-analysis pooled the results of all the studies and was designed to examine the weight of the evidence. There is a small study (Dundon 2008) of 32 patients that reported that the Stretta procedure did not provide long-term symptom control. This study was included in the Perry meta-analysis and did not adversely affect the strong favorable results.

3. The procedure investigated and studies performed only in some regions (mainly North America), and in experienced, well-equipped endoscopic centers?

This is incorrect. There are large institution studies, community hospital studies, free standing endoscopy center studies, and studies from the following countries: Poland, France, Italy, Mexico, Puerto Rico, USA, Japan, China. I have not listed them separately to save space but they are included in the Perry meta-analysis (Perry 2012).

4. The safety issues are not completely clarified? The mortality seems to be unacceptable performing such a procedure? The benefit-risk ratio must be discussed?

It is important to note that there are no documented perforations occurring in any of the published studies on Stretta, which includes Stretta treatment on approximately 3,000 patients, many included having had a double Stretta treatment if they were involved in RCT's with a "sham" arm. A search of the FDA MAUDE database for Stretta from 1/1/2000 to 7/12/2013 for reported clinical practice adverse events results in 26 separate reports, with just two determining that a perforation occurred (in 20,000+ procedures), one as a result of the use of the device in an "agitated patient" (11/13/2000) and one patient with pleural effusion 3 weeks post procedure. A third patient may or may not have experienced a perforation as a result of the procedure; however there is question as to if the perforation may have occurred post Stretta. One report dated 1/29/2005 indicated the following: "While perforation is noted as a potential complication in the Stretta labeling, no causal relationship has been found between the reported event and the Stretta device." The most recently dated incident was reported in April 2007 and there have been no reports to the MAUDE database since Mederi purchased Curon Medical Inc., and re-launched the product in 2011.

Regarding risk/benefit, the risks of endoscopic and surgical procedures are a procedural complication (bleeding, perforation, sedation-related complication, such as aspiration), lack of symptom resolution, return of symptoms requiring repeat procedures, dysphagia, altered GI motility, and gas bloat. Benefits of the procedure are control of symptoms that may not have completely responded to medical therapy (GERD, regurgitation, supra-esophageal symptoms) and the ability to discontinue medical therapy (including the advantages of convenience as well as freedom from potential medication-induced side effects).

5. Mechanism of action remains also not fully clarified?

I have tried to present what we know about the effect of Stretta. Indeed, Table 1 outlines the mechanisms of action as we know them today. It is the multi-factorial nature of its effect that makes Stretta attractive and useful as an adjunct to other therapies (such as surgery or PPI use).

6. Long-term results (5-years) of well-designed studies are not available

The common definition of long-term follow up, though open to interpretation, would safely include 4 years. There are 3 well-designed 4-year studies published in peer-reviewed journals. I have summarized them in the original text.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

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