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LETTERS TO THE EDITOR

Therapeutic Options for Patients With Chronic Refractory Angina Pectoris

In their state-of-the-art review, Kim et al. (1) discuss the available therapeutic options for patients with chronic therapeutically refractory angina pectoris. It is a hopeful perspective, one that offers new and challenging strategies to these severely disabled "no-option" patients. However, some criticism regarding the review is necessary.

First, one of the major problems in evaluating the outcomes of the different strategies depends on how accurate this heterogeneous group of patients is defined (2). Second, with respect to methodologic issues, we fully agree with the investigators that, owing to a lack of randomized controlled trials, the efficacy of adjunct therapies cannot always be evaluated adequately. However, for both laser and neuromodulation, a placebo effect has been investigated, making use of randomized designs. Furthermore, the long-lasting clinical effect of neuromodulation, demonstrated in a group of 517 patients by TenVaarwerk et al. (3), cannot be explained by placebo alone. Unfortunately, this study is not cited correctly, as the outcomes adhere to Creco et al. (4), who reported on only 23 patients. Moreover, we would stress that a controlled trial with angiogenic gene therapy has been performed. This study, entitled "Randomized, Single-Blind, Placebo-Controlled Pilot Study of Catheter-Based Myocardial Gene Transfer for Therapeutic Angiogenesis Using Left Ventricular Electromechanical Mapping in Patients With Chronic Myocardial Ischemia," was published recently by the Vale et al. group from Isner's group (5).

Third, regarding the mechanisms of action, clinical evidence that neuromodulation affects the sympathetic outflow is at least debatable.

Fourth, the investigators claim to give a complete overview on angiogenesis trials with gene therapy. In this respect, our major concern is that the researchers may confuse the difference between gene therapy and recombinant protein therapy. In Table 4 (entitled "Vascular Gene Therapy Trials") of the Kim et al. (1) review, two non-gene therapy trials (i.e., FGF recombinant protein) are included. This is misleading, because the term "recombinant adenoviral FGF" is used to indicate a gene therapeutic agent. In our opinion it would have been more appropriate to deal with all experimental angiogenic trials and not just the ones dealing with gene therapy. With respect to the latter, both the hallmark study by Schumacher et al. (6) and the VIVA trial (7) should have been cited, as, respectively, the first study on angiogenic therapy in patients with refractory angina pectoris and as pivotal studies.

Mike J. L. DeJongste, MD, PhD
University Hospital
Cardiology, Thoraxcenter
Hanzenplein 1
Groningen, 9751 CK
The Netherlands
E-mail: M.J.L.De.Jongste@Thorax.Azg.NL

Raymond W. M. Hautvast, MD, PhD
René A. Tio, MD, PhD

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REPLY

We thank Drs. DeJongste, Hautvast, and Tio for their comments concerning our recent article on refractory angina pectoris. We agree that defining outcomes regarding treatment modalities is difficult in this population because of the heterogeneous spectrum of patients.

Although randomized, placebo-controlled studies have now been performed using laser revascularization techniques, the data have been inconsistent in their results, leading to widespread speculation in the cardiology community regarding the efficacy of such treatment. There have been no known placebo-controlled studies investigating neurostimulation techniques. We thank the correspondents for correctly noting the error in referencing the data of TenVaarwerk et al. (1) on the long-term outcomes of spinal cord stimulation. This study, however, was retrospective in nature and did not have a control arm. A placebo effect cannot be dismissed simply on grounds of length of follow-up. We agree that the mechanism of action regarding neurostimulation is debatable.

With regards to the gene therapy section, Table 4 of our article more correctly should be entitled "Experimental Angiogenic Trials" as noted, although one can argue that the recombinant FGF proteins are a product of recombinant gene technology and, therefore, related to traditional gene therapy (2). The term "recombinant adenoviral FGF" was used correctly in the table, as the study by Grines et al. (3) was indeed a gene therapy trial. The placebo-controlled pilot study by Vale et al. (4) did demonstrate the feasibility and safety of catheter-based gene transfer but only randomized six patients, and conclusions concerning the potential of a placebo effect cannot be made from this. The VIVA trial was first presented in abstract form in the 1998 ACC meetings and has not been published. We omitted this trial in accordance with JACC guidelines, which do not recommend citing abstract data over two years old.