the case report data that have been used to argue in favor of exercise restriction in patients with aortic stenosis. As we contemplate cost-effective means of compiling a much larger dataset that will improve the confidence intervals we can apply to both the risks and benefits of exercise participation in this population, practicing clinicians will need to continue to make this judgment on a daily basis. Our data undoubtedly do not absolutely exclude the possibility of an increased risk of exercise-associated sudden death in subjects with aortic stenosis, but they certainly provide no evidence to support it. This, coupled with the clear evidence of benefit from regular exercise participation, lead us to the opinion that current evidence does not support continuation of these restrictions.

"David W. Brown, MD
Doff B. McElhinney, MD
Steven D. Colan, MD
James E. Lock, MD

*Department of Cardiology
Children's Hospital Boston
300 Longwood Avenue
Boston, Massachusetts 02115
E-mail: david.brown@cardio.chboston.org

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Cilostazol: A Potential Therapeutic Option to Prevent In-Stent Restenosis

It was of great interest and utility to read the paper by Dangas et al. (1) pertaining to in-stent restenosis (ISR) in drug-eluting stents (DES). The authors reviewed systematically the pathophysiological, mechanical, and technical mechanisms and treatment options of ISR in DES. The proposed treatment algorithm is an important clinical tool for a challenging problem without a proven treatment regimen. We would like to present another possible treatment option available for ISR. We believe that the platelet phosphodiesterase III (PDE III) inhibitor cilostazol may potentially have a beneficial role in the treatment of ISR in DES.

Cilostazol is approved and widely used for the treatment of intermittent claudication. It has properties that inhibit several biological mechanisms, such as smooth muscle proliferation, which may lead to ISR (2). PDE III inhibitors reduce P-selectin expression on platelets and Mac-1 on the surface of neutrophils. Mac-1 has been shown to be a key protein involved in neointimal hyperplasia and in the pathophysiology of ISR, and rises during the 48 h after PCI (3).

In previous clinical trials, it has been shown that PDE III inhibitors reduce the rate of ISR. In the CREST (Cilostazol for REStenosis Trial), cilostazol was shown to significantly reduce neointimal hyperplasia and the rate of restenosis in a population of patients undergoing bare-metal stent implantation (4). Cilostazol has also been shown to reduce the rate of ISR in patients treated with DES. In a group of diabetic patients treated with DES, cilostazol was shown to reduce the rate of angiographic restenosis and target lesion revascularization without an increase in severe adverse effects (5). In 1 trial, cilostazol therapy showed a 40.2% relative risk reduction in ISR in patients with DES of >32 mm (6). Patients in the trial were also noted to have significantly lower rates of in-segment and in-stent late loss, as well as a reduced rate of target vessel revascularization. A recent meta-analysis of the effects of cilostazol in patients treated with both bare-metal stents and DES found that in 2,809 patients pooled from 10 different randomized trials, cilostazol reduced late loss by a mean difference of 0.15 mm. Binary angiographic restenosis was also significantly lower in patients treated with cilostazol, regardless of the type of stent used (7).

The use of cilostazol to prevent ISR has shown promise in the limited clinical trials available. These trials are not without limitations. Adding cilostazol use would subject patients to another antiplatelet agent that could potentially lead to an increased bleeding risk. It should also be noted that the clinical trials mentioned have a rather limited follow-up period, and the patient population in those studies is not ethnically diverse. Cilostazol was also used in the study population as an agent for primary prophylaxis and not as a secondary therapy. Though little definitive evidence is available, we believe that the data for the use of cilostazol to prevent ISR are promising, warrant further investigation, and may provide clinicians with another therapeutic option.

"Jamil B. Dihu, DO
Islam Abudayeh, MD
Hammad A. Saudye, MD
Ravi Gurujal, MD

*Division of Cardiology
Advocate Lutheran General Hospital
1775 West Dempster Street
Park Ridge, Illinois 60068
E-mail: j-dihu@md.northwestern.edu

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