# Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del *CFTR*

**TO THE EDITOR:** With regard to the article by Wainwright et al. (July 16 issue),[1] randomized trials evaluating the efficacy of lumacaftor, ivacaftor, or both have included only a limited number of patients with a forced expiratory volume in 1 second ($FEV_1$) at baseline of less than 40% of the predicted value. Only 52 patients in the TRAFFIC and TRANSPORT trials and none of the patients in several other studies had this low percentage of predicted $FEV_1$ at baseline.[2,3] Since the majority of patients in resource-limited countries receive a diagnosis of cystic fibrosis later in childhood (when the disease might be advanced), the efficacy of lumacaftor–ivacaftor therapy in patients with poor pulmonary function needs to be evaluated further.

Moreover, the current cost of lumacaftor–ivacaftor therapy is almost $300,000 per year; this is much higher than the cost of conventional therapy, which is less than $300 per year. Since the magnitude of change observed with lumacaftor–ivacaftor therapy was "in the range of the magnitudes of change seen in studies of other cystic fibrosis therapeutics,"[1] the cost-effectiveness of this form of therapy should be evaluated.[4]

Finally, in some regions of the world, the Phe508del *CFTR* mutation is uncommon (e.g., one study[5] showed that only 26.9% of patients with cystic fibrosis in the United Arab Emirates are homozygous for this allele). For these patients, conventional therapy (hypertonic saline, azithromycin, or ibuprofen) remains the treatment of choice.

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No potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** We agree with Rehman et al. that more trials that include patients with lower lung function are warranted. In the clinical trials on which we reported, the response to lumacaftor–ivacaftor was independent of the percentage of predicted $FEV_1$ at baseline. A subsequent post hoc analysis involving patients with an $FEV_1$ of less than 40% of the predicted value at randomization, as compared with those with an $FEV_1$ of 40% or more of the predicted value, showed similar benefits with respect to $FEV_1$ and pulmonary exacerbations.[1] An open-label trial of lumacaftor–ivacaftor involving patients with an $FEV_1$ of less than 40% of the predicted value is ongoing (ClinicalTrials.gov number, NCT02390219).

Lumacaftor–ivacaftor and ivacaftor are very expensive; however, the estimated cost of $300 per annum for "conventional" therapies that Rehman and colleagues suggest is incorrect. Dornase alfa, inhaled antibiotic agents, pancreatic enzymes, and hospital admissions for pulmonary exacerbations — all of which are considered to be conventional therapy — cost substantially more. Once longer-term treatment benefits are understood, cost-effectiveness may be evaluated with the use of methods that are appropriate for rare diseases.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Elborn JS, Ramsay BW, Boyle MP, et al. Lumacaftor/ivacaftor combination therapy in CF patients homozygous for F508del-CFTR with severe lung dysfunction. J Cyst Fibros 2015;14:Suppl 1:S94. abstract.

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# A Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease

**TO THE EDITOR:** In reporting on the Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis (LEVANT) 2 trial, Rosenfield et al. (July 9 issue)[1] suggest that angioplasty with a paclitaxel-coated balloon, as compared with angioplasty with a standard balloon, provided superior vessel patency in patients with femoropopliteal disease at 12 months. Although these results are encouraging, it is unclear whether superior vessel patency translates into improvements in more clinically appropriate end points such as ambulatory function and quality of life.[2]

The majority of the patients in the trial (92%) had moderate intermittent claudication (Rutherford stage 2) or severe intermittent claudication (Rutherford stage 3) (the Rutherford scale ranges from 0 to 6, with higher numbers indicating worse disease), with single, short lesions of the superficial femoral artery. Yet, the primary end point of freedom from binary restenosis or target-lesion revascularization occurred in only 65% of the intervention cohort and 53% of controls. The clinical significance of this difference is unclear, and this lack of clarity highlights the need to design trials that are powered to show the effectiveness of endovascular interventions for the clinical outcomes of femoropopliteal disease, such as improvements in symptoms of claudication.[3] In the meantime, enthusiasm for techniques such as this one must be curbed.

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**TO THE EDITOR:** In the LEVANT 2 trial, Rosenfield et al. found lower rates of restenosis and a decreased need for target-lesion revascularization among patients with symptomatic femoropopliteal peripheral artery disease after angioplasty with the use of a paclitaxel-coated balloon than with a standard balloon. The clinical characteristics, history of coexisting conditions, and antiplatelet regimen were similar between the treatment groups. However, the authors did not provide information regarding other treatments to prevent cardiovascular disease, particularly statin therapy. Were statins used with equal frequency in the randomized groups? If not, we believe that stratification according to the use or nonuse of statin therapy would be appropriate because of its possible confounding effects on the efficacy of angioplasty.

Indeed, statins are associated with improved lesion patency among patients who have undergone endovascular treatment.[1,2] They are also associated with better outcomes with respect to the rate of salvage of ischemic limbs among patients with peripheral artery disease.[2-4] Moreover, statins reduce the risk of major cardiovascular events and death among such patients.[1,2,4] On the basis of these findings, the guidelines of the American College of Cardiology Foundation and the American Heart Association recom-