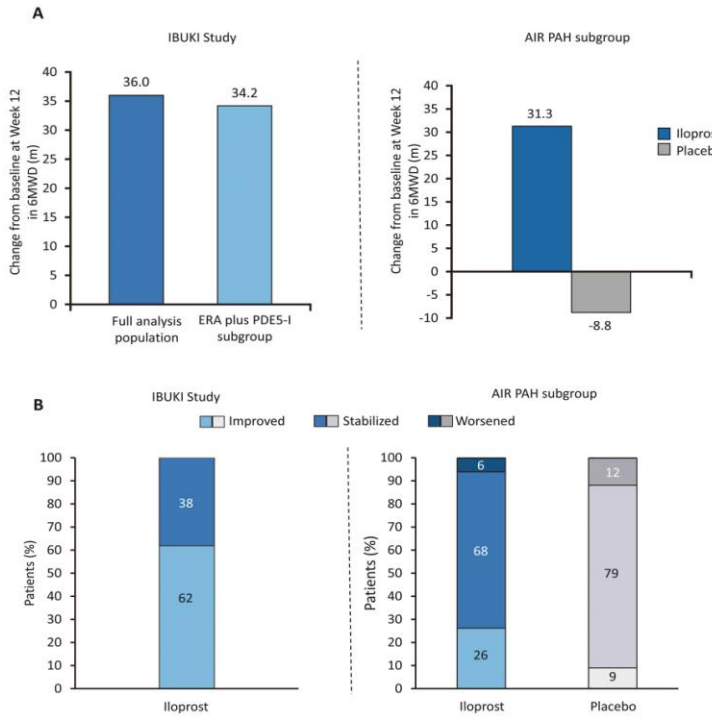
Iloprost proves itself in Japanese PAH patients

A phase III trial has shown that iloprost, an inhaled drug for treating pulmonary arterial hypertension, is safe and efficacious in Japanese patients. The results of the trial, which were reported this April in *Circulation Journal* and which led to marketing approval from the Japanese health ministry, bring Japan in line with other countries where iloprost has been approved for
over a decade. The results also suggest that iloprost could be a valuable addition to a combination therapy.

Pulmonary arterial hypertension is a type of chronic high blood pressure that leads to heightened pulmonary vascular resistance (PVR) in the lung's arteries. The increased demands on the right side of the heart can lead to heart failure. Five-year survival rates are a low 61%.



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(A) Change from baseline to week 12 post-inhalation in 6MWD and (B) percentage of patients with improved/stabilized/worsened NYHA/WHO FC in the IBUKI 12-week study and the AIR PAH subgroup*. *ITT population with PAH. 6MWD, 6-min walking distance; ERA, endothelin receptor antagonist; ITT, intent-to-treat; NYHA/WHO FC, New York Heart Association/World Health Organization functional class; PAH, pulmonary arterial hypertension; PDE5-I, phosphodiesterase type 5 inhibitor.

Prostacyclin analogs can dilate the arteries and block platelet aggregation, lowering PVR and alleviating symptoms. But previously approved synthetic prostacyclins, delivered intravenously, have sometimes resulted in systemic adverse reactions and, due to the introduction through a central venous catheter, raised the risk of sepsis.

Iloprost, an inhaled synthetic prostacyclin, avoids these undesirable effects. It was first approved in Europe following the AIR (Aerosolized Iloprost Randomized) study, and has since been approved in more than 70 countries, including the United States. But most of the clinical data has been from western patients, and its efficacy in Asians has remained a subject of conjecture.

Tsutomu Saji of Toho University led the phase III IBUKI (Iloprost Bridging study in Japanese patients with pUlmonary arterial hypertension for evaluation of PVR and pharmacoKInetics) study, a single-arm investigation of iloprost's effectiveness and safety in patients from 18 hospitals across Japan.

In the 21 patients who completed the initial twelve-week study, levels of PVR, the primary endpoint, dropped by 21%. The 6-minute walking distance among these patients, a secondary endpoint, increased by 36 meters—a 9% rise over the baseline. 62% of patients also had improved in their NYHA/WHO FC categories, which measure the degree of physical limitations caused by PAH. There were no unexpected adverse effects.

The authors note that the small number of patients in the study and its non-randomized nature limit the conclusions that can be drawn, but the solid results were enough to convince Japan's health ministry to approve iloprost (now marketed there as Ventavis) last year.

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The results are on par with results from previous studies in the west, but the IBUKI study patients, most of whom had already been taking other PAH drugs, endothelin receptor antagonists (ERAs) and phosphodiesterase type 5 inhibitors (PDE5-I), were healthier at baseline. The authors argue that the improvement offered by iloprost to the patients who had been taking other drugs suggests that it "may provide an additional and effective treatment option" in combination therapies.

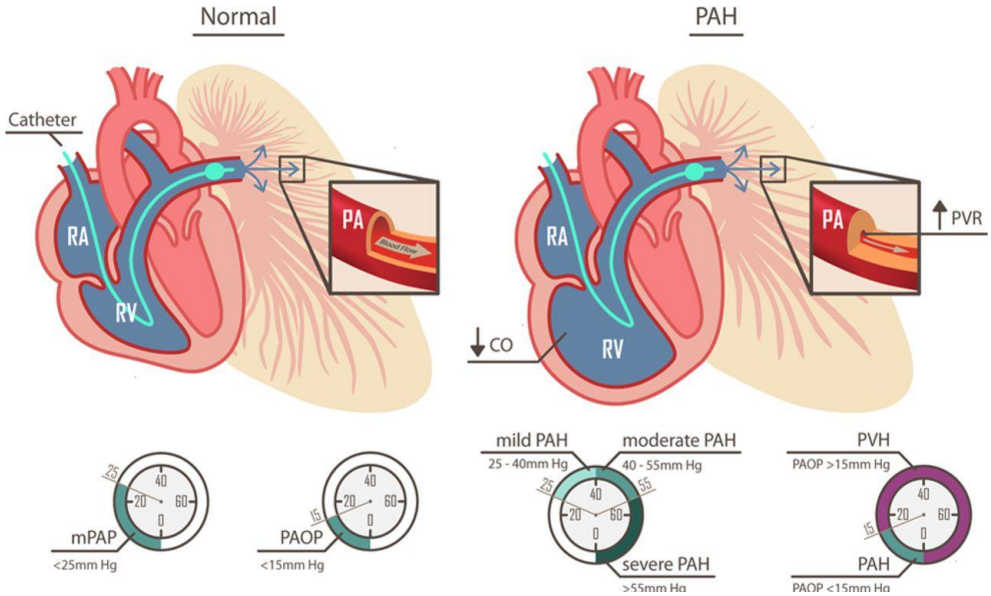

Figure (Permission from Circulation Research June 20, 2014 Vol. 115 no. 1 115-130)

Natural history of pulmonary arterial hypertension (PAH) and right heart failure. The normal pulmonary vasculature is a low-resistance, high-flow system. In the case of PAH, small pulmonary arteries (PAs) are progressively narrowed, leading to an increase in pulmonary vascular resistance (PVR) and the PA pressures. Right heart catheterization is the gold standard to diagnose PAH. When the mean PA pressure (mPAP) is elevated >25 mm Hg and the PA occlusion pressure (PAOP) is <15 mm Hg, PAH is diagnosed. The progressive increase in PVR and pulmonary pressures subsequently lead to reduced cardiac output (CO) and right heart failure. RA indicates right atrium; and RV, right ventricle.

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