

Table 1. ACC/AHA 2025 GL on ACHD. Recommendations for Eisenmenger Syndrome

Diagnostic	
In adults with suspected Eisenmenger syndrome, invasive hemodynamic assessment should be performed to confirm the diagnosis and to exclude concomitant disease that contributes to right-to-left shunting or PAH.	1 B-NR
Adults with Eisenmenger syndrome should be managed by specialists with expertise in both congenital cardiology and PAH to improve outcomes.	1 B-NR
Adults with Eisenmenger syndrome should be advised against pregnancy to decrease the risk associated with excess maternal morbidity and mortality.	3 Harm B-NR
Therapeutic	
In adults with Eisenmenger syndrome and an LV ejection fraction >40% who are symptomatic or have reduced exercise capacity, initial monotherapy with PAH-directed therapy is recommended to improve symptoms, hemodynamics, and overall survival.	1 B-R
In adults with Eisenmenger syndrome and an LV ejection fraction >40% who remain symptomatic or have worsening exercise capacity on a single PAH therapy, dual combination therapy with an endothelin receptor antagonist and a phosphodiesterase-5 inhibitor is recommended to improve symptoms, hemodynamics, and overall survival	1 B-NR
In adults with Eisenmenger syndrome who present with atrial arrhythmias, prompt restoration and maintenance of sinus rhythm is recommended to avoid hemodynamic deterioration.	1 C-LD
In adults with Eisenmenger syndrome, a regular exercise program in combination with directed PAH therapy can be effective in improving exercise capacity.	2a C-LD
In adults with Eisenmenger syndrome and LV ejection fraction >40% who are deemed to be at high risk for adverse outcomes† or who have rapidly progressive disease, inhaled or subcutaneous prostacyclin therapy may be considered as initial therapy or as an addition to other PAH therapy to improve symptoms, exercise capacity, and hemodynamics.	2b C-LD
In adults with Eisenmenger syndrome, anticoagulation therapy may be considered for patients with high-risk features (atrial arrhythmia, new or enlarging pulmonary arterial thrombosis, or prior thromboembolic event) and low bleeding risk to prevent thromboembolic complications.	2b C-EO
Adults with Eisenmenger syndrome should not be routinely prescribed oral anticoagulation given the high bleeding risk and lack of long-term survival benefit.	3 No benefit B-NR
In adults with Eisenmenger syndrome, closure of any intracardiac or vascular shunt should not be performed given the increased perioperative risks and risks for short- and long-term morbidity and mortality.	3 Harm B-NR

In adults with Eisenmenger syndrome and intracardiac shunts who meet indications for permanent pacing or an ICD, endocardial leads may be potentially harmful given the increased risk for systemic thromboembolism.

3 Harm B-NR

Recommendations on managing chronic cyanosis—including, but not limited to, management of iron supplementation, hyperviscosity, and risk and management of central nervous system infections—generally apply to patients with Eisenmenger syndrome and are provided in “Management of Cyanosis.”

†Patients at high risk include patients with World Health Organization functional class 3 or 4, a 6-minute walk distance <165 m, tricuspid annular plane systolic excursion <16 mm, and NT-proBNP level >1,400 pg/mL.

Table 2. ACC/AHA 2025 GL on ACHD. First-Line PAH-Directed Therapy in Patients With Eisenmenger Syndrome

Medication Class	Clinical Trial Evidence	2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension ³⁷	2025 ACC/AHA Guidelines for the Management of Adults with Congenital Heart Disease
Endothelin receptor antagonists	Two moderate-size randomized controlled trials of bosentan (BREATHE 5 trial, 54 patients) ⁹ and macitentan (MAESTRO trial, 226 patients) ¹⁰ evaluated the effects of endothelin receptor antagonists in Eisenmenger syndrome. BREATHE 5 showed improvement in hemodynamics and functional class after 16 weeks of treatment. The MAESTRO trial design was different and included a more heterogeneous patient population, including wider age range, wider spectrum of functional classes, patients on background therapy with PDE5 inhibitors, and patients with Down syndrome. The primary endpoint, which consisted of 6MWD, was neutral. Secondary endpoints of functional class and NT-proBNP levels favored macitentan therapy. In a subgroup of patients aged ≥ 18 years who had a follow-up invasive hemodynamic assessment and did not have Down syndrome, those in the macitentan group had hemodynamic improvement, which was also associated with an improvement in 6MWD.	Bosentan is a class 1 recommendation; other endothelin receptor antagonists "should be considered" in patients with Eisenmenger syndrome (class 2a recommendations).	All endothelin receptor antagonists are recommended as initial treatment in patients with Eisenmenger syndrome (class 1 recommendation).
Phosphodiesterase-5 inhibitors	A small randomized controlled trial (28 patients) ¹¹ and a retrospective observational study ¹² showed improvements in 6MWD, functional status, and hemodynamics without a significant reduction in SVR.	Phosphodiesterase-5 inhibitors "should be considered" in patients with Eisenmenger syndrome (class 2a recommendation).	All phosphodiesterase-5 inhibitors are recommended as initial treatment in patients with Eisenmenger syndrome (class 1 recommendation).
Soluble guanylate cyclase stimulator (riociguat)	Data on Eisenmenger syndrome are currently lacking. A subgroup analysis of the trials that had shown benefit in PAH (PATENT 1+2) demonstrated that in patients with persistent or recurrent PAH after congenital heart defect correction, riociguat use was associated with sustained improvement in 6MWD, PVR, NT-proBNP level, and WHO functional class at 2 years. ³⁵	Riociguat "should be considered" in patients with Eisenmenger syndrome (class 2a recommendation).	No specific recommendation due to lack of data.
Prostacyclin analogs and receptor agonists	Data on the effects of inhaled iloprost are conflicting, with 1 small randomized controlled trial (16 patients) showing no effect on 6MWD, BNP levels, or quality of life, ⁴⁵ whereas 1 small single-arm study (11 patients) showed an increase in 6MWD, subjective quality of life, and RV function. ²¹ There are no data on subcutaneous/intravenous prostacyclin or oral prostacyclin receptor agonist therapy (selexipag) as a stand-alone initial treatment.	Initial prostacyclin therapy "should be considered" in patients with Eisenmenger syndrome (class 2a recommendation).	Initial inhaled prostacyclin therapy may be considered in patients with Eisenmenger syndrome (class 2b recommendation).
Activin signaling inhibitors	No data are currently available on the activin signaling inhibitor sotatercept in patients with Eisenmenger syndrome.	No recommendation	No recommendation

6MWD indicates 6-minute walk distance; ACC, American College of Cardiology; AHA, American Heart Association; BNP, B-type natriuretic peptide; BREATHE-5, Bosentan Randomized Trial of Endothelin Antagonist Therapy-5; ERS, European Respiratory Society; ESC, European Society of Cardiology; MAESTRO, Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PATENT 1+2, Pulmonary Arterial hypertension sGC-stimulator Trial; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; and WHO, World Health Organization.

Table 3. ACC/AHA 2025 GL on ACHD.**Eisenmenger syndrome: Routine Follow-up and Testing Intervals**

Type of Follow-Up or Testing	Physiological Stage A* (mo)	Physiological Stage B* (mo)	Physiological Stage C* (mo)	Physiological Stage D* (mo)
Outpatient ACHD cardiologist	N/A	N/A	6-12	3-6
Electrocardiogram	N/A	N/A	6-12	6-12
Transthoracic echocardiogram	N/A	N/A	12	6-12

Table 4. ESC 2020 GL on ACHD. Recommendations for treatment of pulmonary arterial hypertension associated with congenital heart disease

Counsel patients with CHD and confirmed pre-capillary PH ^a against pregnancy.	I C
Risk assessment in all patients with PAH-CHD. ^b	I C
Initial oral combination therapy or sequential combination therapy in low- and intermediate-risk patients with repaired simple lesions and pre-capillary PH, and treat high-risk patients with initial combination therapy including parenteral prostanoids. ^b	I A
A treatment strategy with initial endothelin receptor antagonist monotherapy in Eisenmenger patients with reduced exercise capacity (6MWT distance <450 m), followed by combination therapy if patients fail to improve.	IIa B

^a The risk of pregnancy in patients with pre-capillary PH is very high. It may be less in pregnancies of patients with post-capillary PH, therefore, a right heart catheterization is necessary in all patients with a suspicion of pre-capillary PH to confirm the diagnosis.

^b For details see 2015 ESC/ERS Guidelines for diagnosis and treatment of PH.

6MWT = 6-minute walk test; CHD = congenital heart disease; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PH = pulmonary hypertension.