Journal of Rare Cardiovascular Diseases 2015; 2 (4): 103–107
www.jrcd.eu

Combination therapy in the treatment of pulmonary arterial hypertension – 2015 update

Grzegorz Kopeć*, Piotr Podolec

Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, Centre for Rare Cardiovascular Diseases, John Paul II Hospital, Krakow, Poland

Abstract

Pulmonary arterial hypertension (PAH) is a disease with a poor prognosis and high mortality rates therefore in the era of advanced therapies targeting different patophysiological pathways attractive seems the idea of combining drugs from two or more classes. They can be applied sequentially or initially. Data from randomized clinical placebo controlled trials and observational studies show that both strategies can be successful in terms of improvement of functional capacity or delaying time to clinical worsening. The European Society of Cardiology guidelines on pulmonary hypertension issued in 2015 present in detail the role of combination therapy in the management of PAH. JRCD 2015; 2 (4): 103–107

Key words: combination therapy, sequential therapy, initial

Pulmonary hypertension – definition and classification

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (mPAP) measured at rest by right heart catheterisation to at least 25 mm Hg. [1] Based on hemodynamic characteristics pre-capillary PH (pulmonary artery wedge pressure, PAWP ≤15 mm Hg) and post-capillary PH (PAWP >15 mmHg) can be distinguished. Post-capillary PH can be further characterised by the diastolic pressure gradient (DPG) and pulmonary vascular resistance (PVR) and based on their values defined as isolated post-capillary PH (DPG <7 mm Hg and/or PVR ≤ 3 Wood units, WU) and combined post-capillary and pre-capillary PH (DPG>7 mm Hg and/or PVR >3 WU). According to clinical classification 5 groups of PH has been distinguished as shown in table 1. Groups 1,3, and 4 are pre-capillary forms of PH, group 2 is a post-capillary PH while conditions from group 5 can fulfil criteria for pre-, or post-capillary PH. The definition of pulmonary arterial hypertension, PAH (group 1 of the clinical classification of PH) has been changed recently to limit its use to conditions in which pulmonary vascular disease (defined as increase of PVR>3WU) has developed [2]. Recently rare forms of pulmonary hypertension has been included in the classification of rare cardiovascular diseases [3,4].

Pharmacological treatment of pulmonary arterial hypertension

Supportive therapy includes continuous long-term oxygen supplementation when arterial blood O_2 pressure is <60 mm Hg (recommendation class I, level of evidence C) and diuretics in PAH patients with signs of right ventricular failure and fluid retention (recommendation class I, level of evidence C). Anticoagulation has been commonly used in clinical practice but the level of evidence for their use is low due to a lack of randomized controlled trials. The indication for chronic anticoagulation in patients with idiopathic PAH (IPAH) has been recently questioned following the introduction of advanced PAH-specific therapy, which relieved many patients from bed rest. Additionally, recent data suggest an increased bleeding risk in patients with IPAH compared with patients chronically using vitamin K antagonists for other reasons [5,6]. Currently the use of oral anticoagulation is not mandatory and may be considered in patients with IPAH, hereditary PAH and PAH due to anorexigens (recommendation class IIb, level of evidence C).

Effectiveness and safety of pharmacological treatment of PAH has been clearly demonstrated in randomized controlled trials. [7] The choice of appropriate therapy depends mainly on the result of vasoreactivity testing and functional status of the patient as

Conflict of interest: none declared. Submitted: September 27, 2015. Accepted: October 6, 2015.

* Corresponding author: Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, Centre for Rare Cardiovascular Diseases, John Paul II Hospital, Krakow, Poland, Pradnicka str. 80, 31-202 Krakow, Poland; tel. 0048 12 614 22 87, fax 0048 12 423 43 76; e-mail: grzegorzkrakow1@gmail.com

Table 1. Clinical classification of pulmonary hypertension [1]

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1″. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease obstruction and congenital cardiomyopathies
2.5 Other
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Others

BMPR2 – bone morphogenetic protein receptor, type 2, HIV – human immunodeficiency virus

assessed by World Health Organization (WHO) classification. Patients who respond well to acute vasoreactivity testing (responders) can be treated with high doses of calcium channel blockers. The non-responders can be treated with drugs belonging to four therapeutic groups namely: prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and soluble guanylate cyclase stimulators. The mechanisms of action of PAH-specific drugs that are currently recommended are presented in table 2.

Receptors for platelet-derived growth factor have been a target in a recently published IMPRESS trial with imatinib, a drug used to treat chronic myeloid leukemia. Imatinib increased the 6-minute walking distance in patients with PAH with PVR exceeding 900 dyne × s × cm^{-5} treated with at least two PAH-specific drugs [8]. Unfortunately, 38% of the patients stopped the treatment because of side effects (compared with 18% in the placebo group); 8 patients suffered from subdural hematoma. Recently completed positive trials which tested macitentan (SERAPHIN) [9], riociguat (PATENT) [10] and selexipag (GRIPHON) [11] in PAH patients resulted in inclusion them to the therapeutic algorithm in the 2015 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of pulmonary hypertension.

Combination therapy in the treatment algorithm of PAH

The treatment goal in PAH is to achieve a low risk status of a patient defined by 1-year mortality <5%. (class of recommendation I, level of evidence C). Determinants of low risk are presented in table 3.

Current guidelines suggest that this goal can be achieved by combining two or more classes of PAH specific drugs. The combination therapy can be applied sequentially or initially.

Sequential combination therapy means an addition of PAH-specific drug in already treated patients. The therapy involves regular patient assessment and addition of another drug when the low risk status (Table 1) has not been achieved. In SERAPHIN, the pivotal trial of sequential combination therapy addition of macitentan 10 mg to sildenafil in symptomatic PAH patients resulted in reduction of the combined primary endpoint of morbidity and mortality of 38%. Importantly, in the whole group of patients treated with

Table 2. The mechanism of action of pulmonary arterial hypertension specific therapies

Group	Endothelin receptor antagonists	Phosphodiesterase 5 inhibitors	Prostanoids and nonprostanoid agonist of prostanoid receptors	Soluble guanylate cyclase stimulators
Drug	Bosentan Macitentan Ambrisentan	Sildenafil Tadalafil	Epoprostenol Treprostinil Iloprost Selexipag	Riociguat
Mechanism of action	Block endothelin-1 receptors (A or A and B)	Increase the cGMP level by inhibition of its metabolism	Increase the cAMP level	Increases the level of cGMP by direct activation of guanylate cyclase

cGMP – cyclic guanosine cyclase, cAMP – cyclic adenosine cyclase

Table 3. Determinants of low risk of 1 year mortality (<5%) in patients with pulmonary arterial hypertension

Determinant of prognosis	Characteristics
Clinical signs of right heart failure	Absent
Progression of symptoms	No
Syncope	No
WHO functional class	I, II
6 MWD	> 440 m
Cardiopulmonary exercise testing	Peak VO_2 > 15 ml/min/kg (>65% predicted), VE/VCO_2 slope <36
NT-proBNP plasma levels	BNP < 50 ng/l, NT-proBNP <300 ng/ml
Imaging (echocardiography, CMR)	RA area <18 cm^2, no pericardial effusion
Hemodynamics	RAP< 8 mmHg, CI ≥2,5 l/min/m^2, SvO_2> 65%

6MWD – 6-minute walking distance, BNP – brain natriuretic peptide, CI – cardiac index, CMR – cardiac magnetic resonance, NT-proBNP – N-terminal pro-brain natriuretic peptide, pred. – predicted, RA – right atrium, RAP – right atrial pressure, SvO_2 – mixed venous oxygen saturation, VE/VCO_2 – ventilatory equivalents for carbon dioxide, VO_2 – oxygen consumption, WHO – World Health Organization

macitentan (both treatment naive and already treated patients at enrolment) the 1-year mortality was < 5%.

The initial combination therapy means use of two or more PAH specific drugs initially after establishing the indications for PAH treatment. Its rationale comes from high mortality in PAH.

Newly diagnosed patients at low or intermediate risk (usually in functional class II or III) can be treated with initial monotherapy or initial oral combination therapy while patients at high risk (class IV and some class III patients) should be prescribed initial combination therapy including intravenous prostacyclin analogues.

In case of inadequate clinical response to initial combination therapy or initial monotherapy, sequential double or triple combination therapy is recommended.

Of note combination of riociguat and phosphodiesterase-5 inhibitors is contraindicated.

Current treatment algorithm in PAH is presented in figure 1.

Combination therapy in clinical trials – recommendations

Initial drug combination therapy

The recommendation for initial combination therapy is based mainly on two randomized trials (Breathe-2 [12], Ambition [13]) and two observational studies.

In the large scale event driven, double blind Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (Ambi-

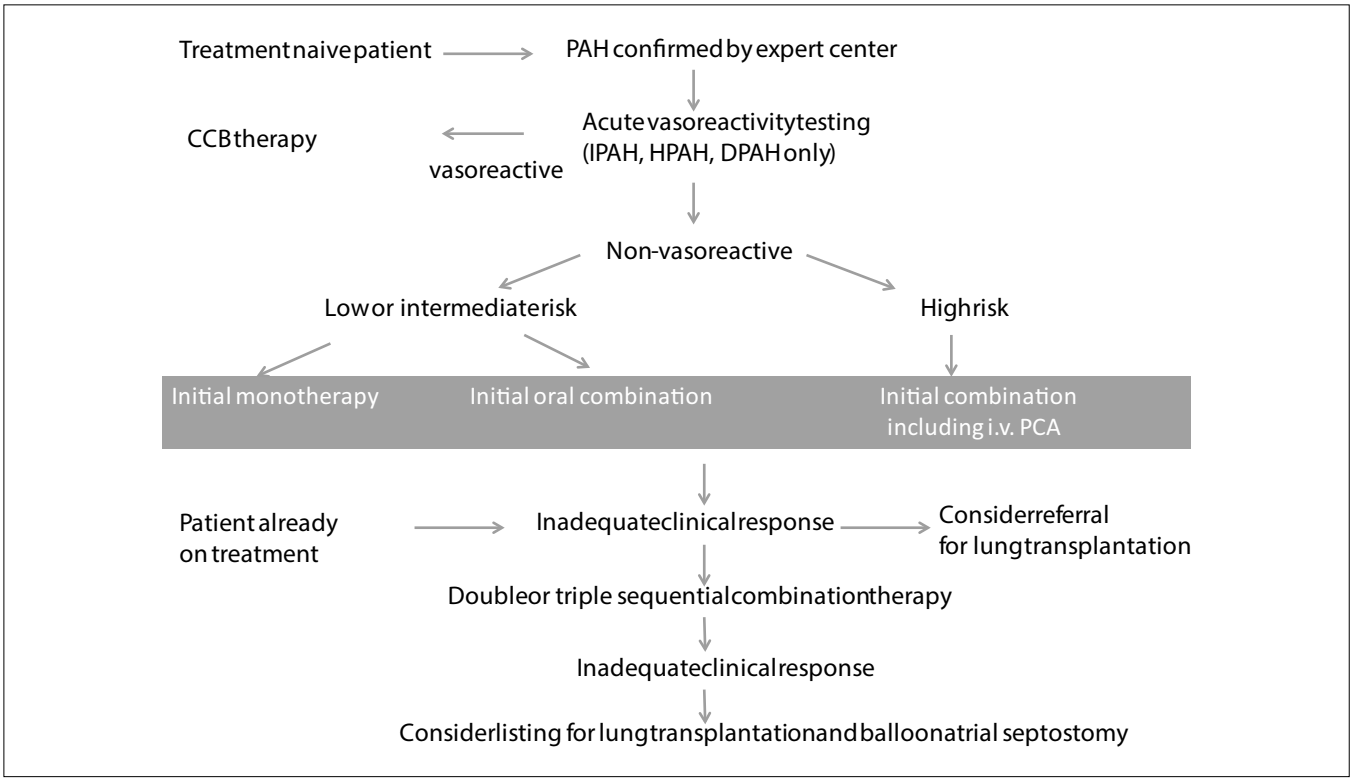

Figure 1. Pulmonary arterial hypertension treatment algorithm. CCB – calcium channel blockers, DPAH – drug-induced PAH, HPAH – heritable PAH, IPAH – idiopathic PAH, i.v. – intravenous, PAH – pulmonary arterial hypertension, PCA – prostacyclin analogues, WHO-FC – World Health Organization functional class

Table 4. Characteristics of randomized placebo controlled trials testing the effectiveness of sequential combination therapy

Drug tested	Study	Author, Data	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main results
Tadalafil [16]	PHIRST	Galie, 2009	405	16	None or bosentan	6 MWD	6MWD improved TTCW improved
Riociguat [10]	PATENT	Ghofrani, 2013	443	12	None or prostanoids, or bosentan	6MWD	6MWD improved, Hemodynamics improved
Inhaled iloprost [17]	COMBI	Hoeper, 2006	40	12	Bosentan	6MWD	Terminated for futility 6MWD not improved No clinical improvement
Inhaled iloprost [18]	STEP	McLaughlin, 2006	67	12	Bosentan	6MWD	6MWD improved (p=0.051) TTCW improved
Treprostinil [19]	Inhal TRIUMPH	McLaughlin, 2010	235	12	Bosentan or sildenafil	6MWD	6MWD improved, TTCW not improved
Macitentan [9]	SERAPHIN	Pulido, 2013	742	115	None, or sildenafil, or inh. Iloprost	TTCW	TTCW improved in monotherapy and combination
SIldenafil [20]	PACES	Simmoneau, 2008	264	16	Epoprostenol	6MWD	6MWD improved TTCW and hemodynamics improved
Treprostinil [21]	PO-Freedom C1	Tapson, 2012	354	16	ERA and/or PDE-5i	6MWD	6MWD not improved TTCW not improved
Treprostinil [21]	PO-Freedom C2	Tapson, 2013	310	16	ERA and/or PDE-5i	6MWD	6MWD not improved TTCW not improved
Bosentan [23]	COMPASS-2	McLaughlin, 2015	334	99	Sildenafil	TTCW	TTCW not improved 6MWD improved NT-proBNP imporved
Selexipag [11]	GRIPHON	McLaughlin, 2015	1156	74	ERA and/or PDE-5i	TTCW	TTCW improved

6MWD – 6-minute walking distance; TTCW – time to clinical worsening

tion) trial 500 treatment naive patients with PAH at functional class II or III were randomised to receive initial combination therapy with 10 mg of ambrisentan plus 40 mg of tadalafil (combination therapy group) or 10 mg of ambrisentan plus placebo (ambrisentan monotherapy group), or 40 mg of tadalafil plus placebo (tadalafil monotherapy group) in 2:1:1 ratio. The primary endpoint was defined as the first occurrence of a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response and it occurred in 18% of patients in the combination-therapy group, 34% in the ambrisentan-monotherapy group and 28% in the tadalafil-monotherapy group. The hazard ratio for the primary end point in the combination therapy group versus the pooled-monotherapy group was 0.5 (95% CI 0.35–0.72, p<0.001). Based on this data the initial combination therapy with ambrisentan and tadalafil has been assigned recommendation class I (level of evidence B) in patients with PAH at WHO FC II or III due to the 2015 ESC guidelines on pulmonary hypertension. Combination of other endothelin receptor antagonists with phosphodiesterase-5 inhibitors due to ESC expert opinion (with level of evidence C) should also be considered as initial PAH therapy (class IIa of recommendation).

Based on Breathe-2 trial and two observational studies the double initial combination therapy with bosentan and intravenous epoprostenol or triple initial combination therapy with bosentan and intravenous epoprostenol and sildeanfil is recommended in PAH patients at WHO FC III or IV (class of recommendation IIa, level of evidence C).

In Breath-2 patients with IPAH or PAH associated with connective tissue disease in WHO FC III or IV were randomized to epoprostenol plus placebo (n = 11) or epoprostenol plus bosentan. No significant change in the primary endpoint (total pulmonary resistance) was observed between the groups (p = 0.08). Long term benefit of initial triple combination therapy with epoprostenol, bosentan, and sildenafil has been shown recently by the group of Sitbon. In their observational pilot study this strategy resulted in 100% 3 year survival of patients in severe (WHO FC III or IV) PAH [14].

Sequential drug combination therapy

Systematic review of 9 randomized placebo controlled trials published between January 2002 and December 2013 in which additional drug or placebo was added to an existing PAH therapy showed 51% (OR 0.49; 95% CI 0.34–0.71, p<0.001) reduction in the incidence of clinical worsening in PAH patients treated with

combination therapy compared with monotherapy however no survival benefit was observed [15].

The trials reported in this systematic review are summarized in table 4. Important new studies not included into the metaanalysis, GRIPHON and COMPASS are also summarized in table 4.

Of note positive effect of sequential combination therapy on time to clinical worsening as a primary end point was shown only for selexipag and macitentan.

Based on the presenting studies the following sequential drug combination therapies should be preferred for PAH patients according to the 2015 ESC Guidelines:

- **macitentan added to sildenafil:** WHO FC class II and III (class of recommendation I, level of evidence B), and IV (class of recommendation IIa, level of evidence C)
- **riociguat added to bosentan**: WHO FC class II and III (class of recommendation I, level of evidence B), and IV (class of recommendation IIa, level of evidence C)
- **selexipag added to endothelin receptor antagonist and/or phosphodiesterase-5 inhibitor:** WHO FC class II and III (class of recommendation I, level of evidence B), and IV (class of recommendation IIa, level of evidence C)
- **sildenafil added to epoprostenol**: WHO FC class III (class of recommendation I, level of evidence B), and IV (class of recommendation IIa, level of evidence B)
- **treprostinil inhaled added to sildenafil or bosentan**: WHO FC class II and III (class of recommendation IIa, level of evidence B), and IV (class of recommendation IIa, level of evidence C)
- **tadalafil added to bosentan**: WHO FC class II, III, and IV (class of recommendation IIa, level of evidence C).

References

1. Simonneau G, Galiè N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004; 43(Suppl 1): S5–S12.
2. Podolec P. Classification of rare cardiovascular diseases. JRCD 2013; 1: 49–60.
3. Podolec P, Stępniewski J, Podolec J, Kopeć G. Rare cardiovascular diseases: from European legislations to classification and clinical practice. Kardiol Pol. 2015; 73: 135–141.
4. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society(ERS).
5. Henkens IR, Hazenoot T, Boonstra A, et al. Major bleeding with vitamin K antagonist anticoagulants in pulmonary hypertension. Eur Respir J. 2013; 41: 872–878.
6. Kopeć G, Moertl D, Steiner S, et al. Markers of thrombogenesis and fibrinolysis and their relation to inflammation and endothelial activation in patients with idiopathic pulmonary arterial hypertension. PLoS One. 2013; 8: e82 628
7. Galiè N, Palazzini M, Manes A. Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses. Eur Heart J 2010; 31: 2080–2086.
8. Hoeper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation 2013; 127: 1128–1138.
9. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. New Engl J Med 2013; 369:809–818.
10. Ghofrani HA, Galie` N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013; 369: 330–340.
11. McLaughlin VV, Channick R, Chin KM, et al. Effect of selexipag on morbidity/mortality in pulmonary arterial hypertension: results of the GRIPHON Study. J Am Coll Cardiol 2015; 65(Suppl A): A380.
12. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. Eur Respir J 2004; 24: 353–359.
13. Galie N, Barbera JA, Frost A, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. New Engl J Med 2015; 373: 834–844.
14. Sitbon O, Jaı¨s X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. Eur Respir J 2014; 43: 1691–1697.
15. Manes A, Palazzini M, Tremblay G et al. Combination therapy for pulmonary arterial hypertension reduces consistently clinical worsening as compared to monotherapy: an up-dated meta-analysis of randomized controlled trials. Eur Heart J 2014; 35 (Abstract Supplement)
16. Galie` N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009; 119: 2894–2903.
17. Hoeper M, Leuchte H, Halank M, et al. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2006; 4: 691–694.
18. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med 2006; 174: 1257–1263.
19. McLaughlin V, Rubin L, Benza RL, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol 2010; 55: 1915–1922.
20. Simonneau G, Rubin L, Galie N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension. Ann Intern Med 2008; 149: 521–530.
21. Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. Chest 2012; 142: 1383–1390.
22. Tapson VF, Jing ZC, Xu KF, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial. Chest 2013; 144: 952–958.
23. McLaughlin V, Channick RN, Ghofrani HA, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. Eur Respir J 2015; 46: 405–413.

Call for papers

Why submit to the Journal of Rare Cardiovascular Diseases?

- first journal dedicated to rare cardiovascular diseases
- a platform for communicating and exchanging, clinical information and research data
- international editorial board
- all articles peer-reviewed
- first decision in 3 weeks
- open access
- no charges for authors
- your work will reach the investigators and clinicians focused on treating rare CVD patients
- your acknowledged contribution to evolution of high-quality, common, standards in managing patients with rare cardiovascular disease

Submit to the Journal of Rare Cardiovascular Diseases via www.jrcd.eu