Changing face of pulmonary arterial hypertension in Canada

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Changing face of pulmonary arterial hypertension in Canada

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ABSTRACT
Pulmonary arterial hypertension (PAH) is a progressive, life-threatening condition with an untreated median survival of less than three years. Frequently, PAH is not initially recognized as patients are misdiagnosed with other, more common causes of exercise intolerance. This leads to potentially avoidable delays in treatment. At the same time, the prevalence of PAH is increasing as survival improves with the availability of efficacious therapies. As a consequence, patients with PAH are increasingly being encountered in many fields of medical practice. Moreover, the care of patients with PAH has become more complex as treatment decisions are being based on multi-parameter risk assessment to determine when to deploy a growing array of drugs, targeting different pathways, and often in combination.

This review provides a comprehensive look at the history, pathobiology, and modern epidemiology of PAH, the evidence behind PH-targeted medications and an update on the diagnosis and management of PAH in Canada.

KEYWORDS
Pulmonary hypertension; pulmonary arterial hypertension; survival; health-related quality of life; right heart catheterization

Introduction
Pulmonary hypertension (PH) is a clinical-physiologic syndrome characterized by elevated mean pulmonary artery pressure (PAP) and the consequent symptoms including dyspnea, fatigue, exercise intolerance, chest pain, and syncopal episodes. Patients are often disabled to the point where they are unable to pursue occupational, recreational, or social activities, with negative effects on health related quality of life (HRQoL). As well-
described in the quote by Dr. Paul Wood, in the first case series rigorously characterizing this illness, PH typically progresses to right ventricular (RV) failure. In most patients, this is heralded by increasing peripheral edema and eventually exertional chest pain and syncopal episodes. RV failure is often ultimately fatal.

PH is most commonly the result of underlying significant cardiac, pulmonary, or pulmonary thromboembolic disease. The World Health Organization (WHO) clinical classification of PH was initially devised at the 2nd World Symposium on Pulmonary Hypertension at Evian, France in 1998, and most recently revised at the 5th World Symposium in 2013 (Table 1).

WHO Group 1 PAH is a less common subset of PH typified by pre-capillary pulmonary hypertension (Table 2). A diagnosis of PAH also requires careful consideration and exclusion of other more common causes of PH. PAH can be idiopathic, hereditary due to a number of established genetic mutations (HPAH), or arise following exposure to various drugs and toxins. PAH can also be associated with specific underlying medical conditions, most commonly connective tissue disease such as scleroderma, congenital heart disease, portal hypertension in liver disease associated PAH), which define six stages of pulmonary arterial changes, including vascular smooth muscle hypertrophy and hyperplasia, intimal fibrosis, plexiform and angiomatoid lesions, and eventual arteritis.

The current understanding of the pathobiology of PAH is that it is a disease of cell proliferation in the pulmonary arteries and arterioles, especially endothelial cells (EC) and smooth muscle cells (SMC). Although the origins of PAH are not certain, the vascular pathobiology is due at least in part to EC dysfunction, associated with both increased EC apoptosis, and somewhat paradoxically, EC proliferation. Decreased EC synthesis of vasodilatory bioactive agents such as nitric oxide and prostacyclin, and increased EC synthesis and release of vasoconstrictors such as endothelin-1 and arachidonic acid-derived mediators such as thromboxane and leukotrienes have all been described, and result in disturbed regulation of the function of underlying vascular SMC. Associated pulmonary vascular pathologic features include inflammation with inflammatory cells (eg, lymphocytes and mast cells) and fibrosis of all three layers of the vascular wall: intima, media, and adventitia. Similar pathologic changes have also recently been described in pulmonary capillaries and veins, and even in the bronchial arteries.

### Table 1. WHO clinical classification of pulmonary hypertension.

1. Pulmonary arterial hypertension (PAH)
   - Idiopathic
   - Heritable (BMPR 2 mutations, other)
   - Drug and toxin induced (eg, anorexigenic, dasatinib, amphetamines, cocaine, SSRIs)
   - Associated with connective tissue disease, congenital heart disease, portal hypertension, HIV, schistosomiasis
2. Pulmonary veno–occlusive disease and pulmonary capillary hemangiomatosis
3. Pulmonary hypertension due to left heart disease
   - eg, LV systolic dysfunction, LV diastolic dysfunction, valvular disease
4. Pulmonary hypertension due to lung disease or hypoxia
   - eg, COPD, ILD, sleep–disordered breathing, obesity–hyperventilation
5. Chronic thromboembolic pulmonary hypertension / other pulmonary artery obstructions
   - CTEPH, Other (pulmonary artery angioplasty, arteritis, congenital pulmonary artery stenosis, parasitic infection)
6. Unclear or multifactorial
   - eg, Hematologic disorders (sickle cell anemia, hemolytic anemias), Systemic disorders (sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis), Metabolic disorders (eg, Gaucher’s disease), Other (eg, fibrosing mediastinitis, chronic renal failure)

### Table 2. Hemodynamic criteria for PH vs Pre-capillary PH.

<table>
<thead>
<tr>
<th>Pulmonary hypertension</th>
<th>Pre-capillary PH (PAH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP ≥ 25 mmHg</td>
<td>mPAP ≥ 25 mmHg</td>
</tr>
<tr>
<td>PAWP ≤ 15 mmHg and/or LVEDP ≤ 15 mmHg</td>
<td>PVR &gt; 3 Wood units</td>
</tr>
</tbody>
</table>

Note. A diagnosis of WHO group 1 PAH requires the presence of pre-capillary PH. However, other common causes of pre-capillary PH must be ruled out, including group 3 PH due to lung disease/hypoxia, and group 4 CTEPH. PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; LVEDP: left ventricular end diastolic pressure; PVR: pulmonary vascular resistance.

### Pathobiology of PAH

Although cases of “idiopathic” or “primary” PAH have been described for more than 100 years, the pathologic characterization of the disease was limited until recently. Given the paucity of easily observable pathologic lesions in the pulmonary arteries to explain increased PAP, simple pulmonary vasoconstriction was originally thought to be the main pathophysiologic feature. Other theories included pulmonary vascular sclerosis and atherosclerosis. The Heath–Edwards classification was the first pathologic staging system for PAH, which defined six stages of pulmonary arterial changes, including vascular smooth muscle hypertrophy and hyperplasia, intimal fibrosis, plexiform and angiomatoid lesions, and eventual arteritis.

The current understanding of the pathobiology of PAH is that it is a disease of cell proliferation in the pulmonary arteries and arterioles, especially endothelial cells (EC) and smooth muscle cells (SMC). Although the origins of PAH are not certain, the vascular pathobiology is due at least in part to EC dysfunction, associated with both increased EC apoptosis, and somewhat paradoxically, EC proliferation. Decreased EC synthesis of vasodilatory bioactive agents such as nitric oxide and prostacyclin, and increased EC synthesis and release of vasoconstrictors such as endothelin-1 and arachidonic acid-derived mediators such as thromboxane and leukotrienes have all been described, and result in disturbed regulation of the function of underlying vascular SMC. Associated pulmonary vascular pathologic features include inflammation with inflammatory cells (eg, lymphocytes and mast cells) and fibrosis of all three layers of the vascular wall: intima, media, and adventitia. Similar pathologic changes have also recently been described in pulmonary capillaries and veins, and even in the bronchial arteries.

Cumulatively, these changes constitute progressive remodeling of the pulmonary vasculature, which narrows and can occlude the small pulmonary arteries, explaining the observed increases in PAP and pulmonary vascular resistance (PVR), which increases afterload on the RV. Initially, the RV accommodates this increase in workload with hypertrophy, allowing for the preservation of cardiac output at rest. However, as the disease progresses, the RV eventually decompensates in most patients, leading to falling cardiac output and worsening fluid
retention.15 Many of the clinical features of PAH relate to RV strain and RV failure.16 Most importantly, RV function most directly determines prognosis in PAH, with RV failure portending a high risk of complications and death.17

Diagnosis of PAH

A diagnosis of PAH requires exclusion of other common causes of PH. In most patients being evaluated for PH, the cause is underlying cardiac, pulmonary, or chronic pulmonary thromboembolic disease (Table 1). As such, specific investigations are recommended to identify WHO groups 2, 3, and 4 PH prior to making a diagnosis of PAH (Table 3). Although PAH is less common than other types of PH, there is an intense global focus on appropriate diagnosis and management of PAH because it has among the worst prognosis if unrecognized or untreated. Moreover, PH–targeted medications largely only have established benefits in PAH, with limited evidence of significant benefits in WHO group 2 and 3 PH patients and, conversely, greater risk of adverse effects in some patients with PH due to LV dysfunction or pulmonary fibrosis.

Right heart catheterization (RHC) is necessary for the diagnosis of PAH, which is characterized hemodynamically by pre-capillary PH in keeping with the predominant pulmonary arterial/arteriolar distribution of pathologic changes. As such, in addition to the elevation in mean PAP (Table 2) common to all subtypes of PH, a diagnosis of PAH specifically requires the exclusion of left-sided heart disease. Practically, this is based on RHC measurement of the pulmonary artery wedge pressure (PAWP), a surrogate for left ventricular end diastolic pressure (LVEDP). Unfortunately, small errors in the measurement of PAWP have the potential to misclassify a significant number of patients. In ambiguous cases, left-heart catheterization for direct measurement of LVEDP definitively establishes or refutes a diagnosis of PAH. As mean PAP also increases in high–flow states without any coexisting pulmonary vasculopathy (eg, advanced liver disease or systemic arteriovenous shunts), an increased PVR >3 Wood units is also included as part of the definition of PAH. Finally, a diagnosis of PAH also requires exclusion of other causes of pre-capillary PH, including chronic lung disease/hypoxia (WHO group 3), chronic thromboembolic PH (WHO group 4), and the disparate group of rare conditions which comprise WHO group 5.

Some patients with normal resting pulmonary hemodynamics manifest increased PAP by echo or RHC during exercise. This entity of exercise-induced PH is currently poorly understood with no consensus definition, but is a topic of intense clinical and physiologic research.2

Modern epidemiology of PAH

PH has previously been considered a rare disease; however, this is clearly not the case. The prevalence of PH has recently been estimated at 1% of the general population and up to 10% of patients over 65 years old.18 Although the incidence and prevalence of PAH in Canada (and North America) are unknown, studies from France and Scotland suggest an incidence of 2.5 to 7.1 cases per million and an estimated prevalence of 52 cases per million adults.19,20 The incidence of PAH is believed to be relatively unchanged over the past 40 years; however, the prevalence has clearly increased, largely due to improved survival. American and French registry data suggest that about half of PAH patients have idiopathic, heritable or drug-induced PAH.19,21 The most common conditions associated with PAH are connective tissue disease (CTD, mainly scleroderma) and congenital heart disease.22

IPAH was initially described as a disease of young women. In the world’s first PAH registry reported by the NIH, 63% were female with a mean age of 36 years old (Table 4).23 Current U.S. and European registries confirm that PAH is now more frequently diagnosed in older patients, with a mean age at diagnosis between 50 and 65 years.24 This demographic shift to older patients being diagnosed with PAH is associated with a greater prevalence of underlying medical conditions, especially cardiovascular co-morbidities such as obesity, hypertension, and diabetes. This demographic shift is important, because there is frequently ambiguity between PAH and WHO group 2 PH, as many older patients with a hemodynamic profile consistent with PAH also have risk factors for left-sided heart disease. Rigorous clinical-

### Table 3. Appropriate diagnostic tests for patients with unexplained PH.

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography</td>
<td>- Echo can suggest the presence of PH (elevated RVSP &gt; 50 mmHg) and indicates the severity (eg, RV dilation and/or systolic dysfunction, reduced TAPSE &lt;18mm, dilated RA, non–collapsible IVC, pericardial effusion)</td>
</tr>
<tr>
<td></td>
<td>- Echo identifies left–heart conditions associated with WHO group 2 PH (eg, LV systolic dysfunction or diastolic dysfunction, mitral/aortic valvular disease)</td>
</tr>
<tr>
<td></td>
<td>- Echo may also identify congenital heart disease (eg, ASD, VSD) associated with PAH</td>
</tr>
<tr>
<td></td>
<td>- RHC definitively establishes the diagnosis of PH (mPAP &gt;25 mmHg)</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>- RHC definitively establishes the diagnosis of WHO group 2 PH (PAWP &gt;15 mmHg; or LVEDP &gt;15 mmHg measured during LHC)</td>
</tr>
<tr>
<td></td>
<td>- RHC permits vasoreactivity testing to identify vasodilator–responsive PH patients</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>- CXR, PFTs, Chest HRTC, and level 1 PFT identify patients with WHO group 3 PH (eg, COPD, ILD, sleep–disordered breathing, obesity–hyperventilation)</td>
</tr>
<tr>
<td>Pulmonary function testing</td>
<td>- Normal perfusion scan (eg, usually multiple segmental defects, mismatched or matched) suggests the presence of WHO group 4 CTEPH</td>
</tr>
<tr>
<td>Chest computed tomography</td>
<td>- Nuclear Ventilation/perfusion lung scanning</td>
</tr>
<tr>
<td>Polysomnography</td>
<td>- Abnormal perfusion scan (eg, usually multiple segmental defects, mismatched or matched) suggests the presence of WHO group 4 CTEPH</td>
</tr>
<tr>
<td></td>
<td>- Normal perfusion scan rules out CTEPH</td>
</tr>
<tr>
<td></td>
<td>- The extent/distribution of intraluminal thrombi, webs, and bands helps to define the severity of CTEPH and determine operability</td>
</tr>
<tr>
<td></td>
<td>- Normal CTPA is inadequate to rule out CTEPH</td>
</tr>
<tr>
<td>Pulmonary angiography (CTPA, MRA, or conventional)</td>
<td>- MRA, magnetic resonance angiography.</td>
</tr>
</tbody>
</table>

Note: Surgical lung biopsy is not recommended.

PH: pulmonary hypertension; RVSP: right ventricular systolic pressure; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; RA: right atrium; IVC: inferior vena cava; WHO: World Health Organization; LV: left ventricle; ASD: atrial septal defect; VSD: ventricular septal defect; PAH: pulmonary arterial hypertension; RHC: right heart catheterization; mPAP: mean pulmatory arterial pressure; PAWP: pulmonary artery wedge pressure; LVEDP: left ventricular end diastolic pressure; LHC: left heart catheterization; CTPA: computed tomography pulmonary angiography; MRA: magnetic resonance angiography.
hemodynamic evaluation for underlying left ventricular (LV) dysfunction, often including left heart catheterization to facilitate measurement of LVEDP, is essential to address this diagnostic challenge. Of note, older PAH patients are less likely to be aggressively treated with current PH-targeted medications and are also less likely to respond favourably to these therapies.

The prognosis of PAH has traditionally been considered very poor, with an untreated median survival of 2.8 years from the time of diagnosis. Significant delays between onset of symptoms and a formal PAH diagnosis, estimated at 2–3 years in many cases, further compound this problem. There is substantial evidence for recently improved long-term outcomes including survival, although this consists largely of open-label, uncontrolled, observational data, including that from large international registries. For example, the American REVEAL registry reports survival of 59% at 7 years for patients with IPAH and HPAH, providing compelling evidence for improved survival in the modern era.

Screening programs in high risk patients (eg, sclerosis) and greater physician awareness of PAH have resulted in an earlier diagnosis of PAH in many patients with a resulting survival improvement. However, the overall increased survival of most PAH patients is not simply the result of earlier diagnosis, as delays in diagnosis still persist. A PHA Canada Burden of Illness Survey in 2014 found that only half of patients were diagnosed within one year of the appearance of symptoms (http://www.phacanada.ca/en/about-ph/boi-report/). Improved overall PAH survival is also believed to be, in part, the result of organized multi-disciplinary care in specialized PH Expert Clinics, as is strongly recommended in international PH guidelines. Despite the limitations of the indirect evidence including numerous biases of such long-term, uncontrolled, observational data, it is widely accepted that improved long-term survival is in part the result of appropriate use of multiple PH-targeted medications, which of which have been studied, approved, and become available over the past 20 years.

**Clinical trials of PH-targeted medications**

**Background**

Extensive basic science research over the past 25 years has established several molecular pathways which contribute to the pathobiology of PAH, and three of these pathways are current targets for available medical therapies (Table 5).

<table>
<thead>
<tr>
<th>Pathobiologic target</th>
<th>Drug family</th>
<th>Drug</th>
<th>Dose/Route</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>† Endothelin−1</td>
<td>Endothelin−1 receptor antagonist (ERA)</td>
<td>Ambrisentan</td>
<td>5–10 mg po daily</td>
<td>Hepatotoxicity, anemia, peripheral edema</td>
</tr>
<tr>
<td></td>
<td>Bosentan</td>
<td>125 mg po BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>10 mg po daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sildenafil</td>
<td>20 mg po TID</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>40 mg po daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Riociguat</td>
<td>0.5–2.5 mg po TID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>† Nitric oxide</td>
<td>Phosphodiesterase type−5 inhibitor (PDE−5i)</td>
<td>Epoprostenol</td>
<td>10–40 ng/kg/min IV infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soluble guanylate cyclase stimulator (sGC−s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>† Prostacyclin</td>
<td>Prostacyclin analogue</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Intravenous: central line/central vein thrombosis, line related sepsis; subcutaneous: local skin rash, thickening, pain.
Current PH-targeted medications are Health Canada-approved specifically for PAH and mostly not for other PH sub-types given a lack of supportive evidence. Only Riociguat is currently approved for treatment of PAH and WHO group IV CTEPH patients.

**Historical RCTs**

The first randomized controlled trial (RCT) in PAH was published in 1996 and assessed the non-blinded response to continuous intravenous epoprostenol versus standard therapy in 81 patients. This landmark 12–week clinical study established a standard for PAH clinical trials, reporting improved exercise capacity as assessed by six minute walk distance (6MWD), improved pulmonary hemodynamics (reduced mean PAP and PVR), and improved survival. As a result, epoprostenol became the first medication approved by Health Canada for use in PAH in 1997.

The majority of currently available PH–targeted medications (ERAs ambrisentan and bosentan, PDE5–i’s sildenafil and tadalafil, riociguat, and SC treprostinil) have also been approved on the basis of similar, short–term (12–16 week) placebo–controlled RCTs focused on a primary outcome of improved 6MWD. Additional benefits, including improvements in NYHA FC, Borg dyspnea score, HRQoL, B–type natriuretic peptide level, and cardiopulmonary hemodynamic parameters were generally reported as secondary outcomes. Several of these RCTs also reported that treatment with PH–targeted medications prolonged the time to clinical worsening, a composite clinical endpoint typically including multiple features of progression of PAH and/or RV failure, such as worse NYHA FC and/or 6MWD, hospitalization, lung transplantation, and death (Table 6). Longer term open-label, uncontrolled studies of many PH–targeted medications have shown sustained safety/tolerability and also suggest sustained clinical and functional benefits.

**Modern RCTs**

The primary efficacy focus on 6MWD in PAH patients is not currently warranted, as it has clearly been established that improved 6MWD over the short–term is not consistently associated with improvements in clinically relevant endpoints. Although the degree of improvement in 6MWD is not predictive of better prognosis, 6MWD greater than a specific minimum threshold both at baseline and following treatment (eg, currently 440 m in IPAH) is associated with better prognosis, and conversely, 6MWD lower than the threshold is associated with very poor prognosis, including higher mortality. It should be noted that such 6MWD thresholds are only supported by weak evidence at a cohort level, and do not necessarily apply to individual patients. Moreover, regular measurement of 6MWD during follow-up is essential, but is only one component of a more complete, multi-parameter assessment of the clinical status of a PAH patient and the adequacy of their PH-targeted therapy.

Based on this concern over improved 6MWD being a poor surrogate for better prognosis, there have been dramatic changes in the design and length of more recent PAH RCTs to focus on improvements in clinically important outcomes, including composite morbidity/mortality outcomes or disease progression over longer time intervals. Indeed, the most recent Health Canada–approved PH–targeted medications, macitentan and selexipag, were both studied in such long–term event driven RCTs, showing reductions in composite endpoints which included individual outcomes such as disease progression (eg, worse NYHA functional class [FC], worse 6MWD, and/or need for more aggressive PH–targeted therapy), PAH–related hospitalization, transplant/atrial septostomy, and all-cause mortality. Such composite clinical endpoints are more relevant as they include a broad range of clinical features and potential complications of PAH, and thus better reflect the overall status of a patient, specifically improvement/stability vs disease progression. However, important limitations of such composite outcomes exist, including variable definitions between studies, lack of objective adjudication in older RCTs, statistical significance of the composite outcome often being determined by less objective elements (eg, investigator determination of need for additional PH–targeted therapy). Perhaps the most important weakness of composite outcomes in a progressive, fatal disease such as PAH is that statistical improvements in the overall composite measure of morbidity/mortality do not automatically apply to each element of the composite, ie, clinically important benefits are not necessarily associated with improved long–term survival.

The more recent larger RCTs are also clinically helpful in better defining potential treatment and response differences in smaller, specific PAH subgroups, such as CTD-associated PAH.

**Current management of PAH in Canada**

The general approach recommended for management of PAH is described in detail in the 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of PH and in a recent review. Five aspects emphasized include general medical supportive care, initial selection of PH-targeted medications, regular follow up and careful multi-parameter reassessment of each individual patient’s prognostic risk, appropriate escalation of PH-targeted medical therapy as required, and eventual consideration of eligibility for definitive surgical therapy such as lung transplantation.

**General medical care**

As in most other complex illnesses, disease and medication-specific education and psychosocial support are strongly recommended (Class I / Level C). PHA Canada is a national charitable organization that works to fulfill this mandate (www.phanca.com). Regular physical activity and supervised rehabilitation therapy are also suggested (Class Ia / Level B).

Birth control and avoidance of pregnancy are strongly recommended based on the potential for clinical worsening during pregnancy and post-partum and the potential teratogenicity of several PH–targeted medications (Class I / Level C). In women with PAH, mortality during pregnancy has been estimated at 36% in the French cohort. Care must also be exercised as PH-targeted medications (eg, bosentan) can decrease the efficacy of oral contraceptives. The safety of hormone replacement therapy in post-menopausal women with PAH is uncertain.
Hypoxemia can contribute to worsening PH through hypoxic pulmonary vasoconstriction, and thus should be avoided (Class I / Level C). Generally, resting hypoxia is only mild in most patients with PAH, unless there is concomitant congenital heart disease, lung disease (eg, COPD, pulmonary fibrosis), or a patent foramen ovale. There is no specific evidence to suggest that long term oxygen therapy is beneficial in PAH, although the usual criteria developed for COPD are generally applied.

Given the demographic shift in the PAH population to older patients with greater co-morbidities, there is more frequent need to assess and manage common medical conditions such as coronary artery disease, gallbladder disease, diverticulitis, and cancer. In general, elective surgery is associated with increased risk in patients with PAH, especially in the presence of significant RV failure. When necessary, regional anesthesia is preferable to general anesthetic (Class IIa / Level C). Optimization of volume status, RV function, and PH-targeted medications, as well as rigorous peri-operative cardio-pulmonary monitoring are all important considerations when surgery is being contemplated.

**Optimization of volume status**

Fluid overload and consequent excessive RV dilation with worsening RV dysfunction are common in patients with advanced PAH and are associated with worsening symptoms, functional status, and clinical outcomes. Deteriorating RV

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systolic function can also compromise LV function, resulting in reduced cardiac output and renal dysfunction. Volume assessment can be difficult in patients with PAH/RV failure, but is an essential aspect of the clinical monitoring of these patients. Regular treatment with diuretics is important to control fluid overload in RV failure, but must be managed carefully as excessive diuresis can also negatively affect kidney function, especially in association with dehydration, eg, poor oral intake, concomitant illnesses such as gastroenteritis.

**Anticoagulation**

Chronic treatment with oral warfarin is recommended in IPAH, HPAH, and PAH due to anorexigenic, putatively to prevent progressive in situ pulmonary vascular thrombosis, although the benefits are uncertain (Class IIb / Level C). Indeed, any potential survival benefit of long-term anticoagulation in these patients is still controversial, given the most recent conflicting data from large observational registries. Anticoagulation is typically used in patients receiving IV prostanoid infusions to reduce the risk of central venous catheter associated thrombosis. Anticoagulation is not recommended for other causes of PAH (eg, CTD, congenital heart disease, portal hypertension, HIV), given a lack of evidence of benefit and the higher risk of bleeding in some of these patients. There are no studies assessing the benefits of direct–acting oral, non–vitamin K anticoagulants, although they can be considered in patients with difficulty monitoring or using warfarin safely.

**Calcium channel blockers**

These are strongly recommended for the 10–15% of idiopathic, heritable, and anorexigen–induced PAH patients who demonstrate a favourable response to acute vasodilator testing during RHC (Class I/Level C). This acute vasodilator response to administration of inhaled nitric oxide, epoprostenol, or adenosine is rigorously defined as a fall in mean PAP by at least 10 mmHg to <40 mmHg in the absence of a decline in cardiac output. Patients with an acute vasodilator response should be treated with high doses of calcium channel blockers titrated up over several months, and require careful clinical and hemodynamic/echocardiographic follow-up, as only half of such patients have a favourable long-term response. Patients who demonstrate limited improvement, or any worsening, have a poor prognosis, and PH-targeted medications should be rapidly instituted.

**Initial PH–targeted medical therapy**

There are relatively few data to suggest superiority of any specific medication as first line therapy, and thus all approved PH–targeted medications are acceptable options, based primarily on the severity of PAH and RV failure at diagnosis. In general, the most severely ill patients in NYHA FC IV, as well as those in NYHA FC III with more severe RV failure, should be considered for IV/SC prostanoid infusion therapies. These medications are widely accepted as the most effective therapies and are therefore strongly recommended in this subset of patients who are at highest risk of clinical worsening, complications, and death (Class I/Level A). Prostanoid infusion therapies are often rapidly effective within 1–2 weeks, and mitigate the risks of progressive RV failure, need for lung transplantation, and death.

In patients who are less ill at presentation, including NYHA FC II and some patients in NYHA FC III PAH with compensated RV function, initial oral PH–targeted therapy is most often used, as per the 2015 ESC/ERS guidelines. They support use of any of the seven Health Canada–approved oral PH–targeted medications (Class I/Level A–B). Alternative therapies for such patients include oral (eg, treprostinil) and inhaled prostanoids (eg, iloprost, treprostinil), but these are not Health Canada–approved and thus not available in Canada. However, given weak evidence and often only marginal benefits despite significant side–effects, the lack of availability of these therapies does not appear to disadvantage Canadian PAH patients. PAH patients are rarely diagnosed at the earliest stage of disease (NYHA FC I), and treatment of such patients has not been formally studied and thus is not currently recommended.

**Other relevant factors in choice of therapy**

Important patient–specific considerations include their ability to safely manage the more complex PH–targeted medications (eg, prostanoid infusion therapies), contraindications for treatment with specific medications (eg, PDE5–i medications and Riociguat are contraindicated in patients receiving nitroglycerine preparations), and greater risks of known side–effects in certain patients (eg, ERA–hepatotoxicity in patients with underlying liver disease or on other hepatotoxic medications).

**Current approach to optimal PH therapy**

Although currently available PH–targeted medications clearly benefit many PAH patients, it is equally clear that none of these medications are a cure for PAH. The majority of PAH patients remain symptomatic and are typically quite limited functionally. As such, many clinical studies have assessed the effects of treatment with various combinations of PH–targeted medications. Collectively, these studies provide strong evidence in support of optimal treatment of most PAH patients with combinations of two and perhaps even three PH–targeted medications.

**Combination PH therapy**

Historically, based on provincial/territorial or private insurance funding rules, the vast majority of PAH patients could only be treated with a single PH–targeted medication. Although effective, monotherapy typically lacks dramatic benefits in most PAH patients, who often remain persistently symptomatic, limited to the point of disability, and at high risk for progression and poor clinical outcomes. Indeed, strong evidence supports that PH–targeted monotherapy is not adequate therapy for most PAH patients. Moreover, pathobiologic similarities between PAH and cancer suggest that a similar aggressive treatment approach may be appropriate, including simultaneous targeting of multiple disease pathways. In support of this concept, increasing RCT evidence and long-term clinical
experience strongly support greater short-term benefits and long-term clinical outcomes with combinations of PH-targeted therapy versus monotherapy. The best-supported benefits of combination PH-targeted therapy include stronger likelihood of improvement (eg, specifically less severe PAH hemodynamically, greater 6MWD, better NYHA FC) and decreased risk of a composite outcome of clinical worsening/disease progression (eg, worsening 6MWD, worse NYHA FC, hospitalization, need for escalation of PH-targeted therapy including parenteral prostanoid infusion therapies). Current combination PH-targeted therapy trials do not support reduced need for lung transplantation or improved survival, largely because they are limited by low event-rates and inadequate long-term data.

Fortunately, most Canadian PAH patients currently have access to many PH-targeted medications, and can typically be treated as aggressively as warranted, with combination therapy using at least two PH-targeted medications. Two approaches are commonly used and both are considered acceptable, as they have never been directly compared in a RCT: (i) initial monotherapy with subsequent sequential combination therapy in case inadequate response or progression or (ii) upfront initial dual combination therapy, typically with two oral medications from different families of medications. Regardless of choice of initial therapy, patients must be closely followed and regularly reassessed, using a panel of clinical, physiologic, and imaging parameters, as no single parameter fully captures the severity of PAH and RV failure or is fully predictive of risk of progression and/or poor clinical outcomes (Table 7).

It is increasingly appreciated that the most important prognostic factor over the long term is the status of the RV. Maintained RV function is highly predictive of survival, even in the setting of severe PAH. Conversely, deteriorating RV function is predictive of very poor outcomes irrespective of the actual level of PAP or PVR. As such, a central goal of PH–targeted medical therapy is to improve RV function and maintain it as close to normal as possible. Recognition that an individual patient is at high risk for worsening/progression and poor clinical outcomes requires consideration of intensification of therapy, including at least double oral combination drug therapy, IV/SC prostanoid infusion therapy, and potentially definitive surgical therapy, such as lung transplantation.

### Table 7. Risk assessment in PAH.

<table>
<thead>
<tr>
<th>Prognostic feature</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Rapid</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>I, II</td>
<td>Recurrent</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440m</td>
<td>&lt;165m</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>&gt;65% predicted</td>
<td>&lt;35% predicted</td>
</tr>
<tr>
<td>Peak VO₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP/NT–proBNP levels</td>
<td>BNP &lt; 50 ng/L NT–proBNP &lt; 300 ng/mL</td>
<td>BNP &gt; 300 ng/L NT–proBNP &gt; 1400 ng/mL</td>
</tr>
<tr>
<td>Imaging (echo, cardiac MR)</td>
<td>RA area &lt; 18 cm² No pericardial effusion</td>
<td>RA area &gt; 26 cm²</td>
</tr>
<tr>
<td></td>
<td>Normal RV size / function</td>
<td>Pericardial effusion RV dilation / dysfunction</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt; 8 mmHg</td>
<td>RAP &gt; 14 mmHg</td>
</tr>
<tr>
<td></td>
<td>CI ≥ 2.5 L/min/m²</td>
<td>CI &lt; 2 L/min/m²</td>
</tr>
<tr>
<td></td>
<td>SvO₂ &gt; 65%</td>
<td>SvO₂ &lt; 60%</td>
</tr>
</tbody>
</table>

**NYHA:** New York Heart Association; 6MWD: 6-minute walk distance; VO₂: oxygen consumption; BNP: brain-type natriuretic peptide; MR: magnetic resonance; RA: right atrium; RV: right ventricle; RAP: right atrial pressure; CI: cardiac index; SvO₂: mixed venous oxygen saturation.


**Triple combination PH therapy**

There is currently very limited data to support the use of triple combination PH-targeted therapy, using a medication directed at each of the three currently identified pathobiologic pathways. An uncontrolled series of 19 incident patients with severe NYHA FC IV PAH and marked RV failure treated with triple therapy (IV epoprostenol, oral sildenafil, and bosentan) reported extraordinary clinical and hemodynamic benefits over 4–12 months, and 100% 3 year survival.

In the recent placebo-controlled RCT of selexipag, a subgroup of subjects on background double oral (bosentan and sildenafil) PH-targeted therapy had better outcomes on triple oral therapy following addition of selexipag vs placebo.

Despite the best current combination therapies, PAH remains a progressive and often fatal disease in a significant proportion of patients. There is clear need for new therapies, targeted at new pathobiologic pathways.

**Lung transplantation**

Important advances with extracorporeal lung support (ECLS) as a bridge to transplant and in the perioperative period post lung transplant will likely help to improve the probability of successful outcomes with this modality. Although PAH patients in the United States have suffered increased lung transplant waitlist mortality since the introduction of the lung allocation score (LAS) in 2002, recent attempts have been made to mitigate this effect, and there is no evidence of such a trend in Canada (personal communications: Dr. John Swiston [UBC], Dr. John Granston [University of Toronto], Dr. Ali Kapasi [University of Alberta]). In fact, it seems highly likely that better risk assessment and the use of ECLS for pre- and post-operative support are improving outcomes associated with lung transplantation in PAH. In general, bilateral lung transplant is the procedure of choice for PAH patients. Heart–lung transplantation is usually reserved for patients with congenital heart disease in whom the cardiac defect is not amenable to surgical correction. Although balloon atrial septostomy is a potential option to control refractory RV failure in patients for whom lung transplant is not an option, this is not routinely performed in Canada.

**Broad implications for the management of PAH in Canada**

Changes in demographics, diagnostic testing, treatment options, and survival have resulted in a dramatic increase in the prevalence of PH patients in Canada, including those with PAH.
For PH experts and practitioners, this means providing care to greater numbers of patients often requiring not only PAH care, but other pulmonary and general medical care. With increasingly aggressive therapy, young women with well controlled PAH in the absence of RV failure are increasingly accepting the risks and having children. The complexity, range, and costs of PH-targeted therapies and the severity of the illness result in more administrative work to overcome hurdles in medication coverage, to support disability requests, and to ensure seamless care for these very high-needs patients. The increasing prevalence of PH requires greater knowledge dissemination to our specialist and primary care colleagues, as well as allied health practitioners.

For respirologists and internal medicine practitioners, the future will bring greater exposure to PAH patients in their outpatient clinics, on medical wards when these patients are hospitalized for treatment of RV failure or infectious and bleeding complications, and in the ICU when life-sustaining vasoactive medications and consideration of ECLS is necessary for management of severe RV failure. PAH patients are already being referred more frequently for assessment prior to minor and major surgery.

**Access to PH-targeted medications**

Canadian PAH patients are relatively fortunate as ten PH-targeted medications are approved for use by Health Canada. Public funding exists in most provinces and territories for at least six of these drugs, allowing for broad access. Patients have clearly benefited, in terms of fewer symptoms, greater functional capacity, better HRQoL and improved survival. However, the significant costs of these therapies, lack of direct comparison studies between approved therapies, and scarce cost-effectiveness data are increasing government attention, which may ultimately result in restrictions in funding access.

The three most recently Health Canada-approved therapies (riociguat, macitentan, and selexipag) have obtained limited provincial funding support based on negative or limited recommendations from the Canadian Agency for Drugs and Technologies in Health common drug review. As such, Canadian PAH patients may not benefit from the newest PAH therapies that ironically have the most robust data for improved long term clinical outcomes. Additionally, several provinces have limited access to funding for combination therapy, especially dual upfront combination therapy and triple combination therapy.

**Conclusion**

Over the past two decades, PAH has evolved from a rare, rapidly progressive, almost uniformly fatal disease primarily affecting young women to a chronic illness of older patients with multiple comorbidities. The survival of PAH patients has improved, often beyond ten years as a result of earlier diagnosis, integrated care at PH Expert Centres, and effective PH-targeted medical therapy, including more frequent use of combination drug therapy. The changing face of PAH has added greater complexity, emphasizing the importance of a rigorous diagnostic approach and of providing multi-disciplinary care.

In the near future, we expect earlier PAH diagnosis via screening strategies for high risk groups such as scleroderma patients, and more standard use of combination therapy, potentially including triple combination therapy. In the longer term, we anticipate new pathobiologic targets and therapies focused on EC and SMC proliferation, as well as effective therapeutic strategies for management of RV failure.

**Disclosures**

AK has served on advisory boards for Actelion and Bayer, and has been a site investigator for multicentered clinical trials sponsored by Actelion. SM has served on advisory boards and served as a consultant for Actelion and Bayer, served on a Speakers’ Bureau for Actelion, Astra–Zeneca, and Bayer, and has been a site investigator for multicentered clinical trials sponsored by Actelion, Bellerophon, Eiger, Gilead, Reata, and United Therapeutics.

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**References**


