An evidence-based approach to the management of pulmonary arterial hypertension
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Purpose of review
Evidence-based therapies and guidelines for pulmonary arterial hypertension are critiqued.

Recent findings
Morbidity and mortality in pulmonary arterial hypertension reflects failure of right ventricular compensation for increased afterload caused by obstructive pulmonary arterial remodeling. This predominantly reflects excessive proliferation/impaired apoptosis of smooth muscle and endothelial cells, rather than vasoconstriction. To exclude confounding effects of cardiac output and left ventricular end-diastolic pressure, the diagnosis of pulmonary arterial hypertension should require a pulmonary vascular resistance >3 Wood-units, not simply a mean pulmonary arterial pressure >25 mmHg. A ‘positive’ response (20% fall in pulmonary arterial pressure/pulmonary vascular resistance PAP/PVR) to acute, selective, pulmonary vasodilators (e.g., inhaled nitric oxide), occurs in 20% of patients, portends a favorable prognosis and justifies a trial of calcium channel blockers. Randomized controlled trials support treatment of NYHA class III pulmonary arterial hypertension with oral endothelin antagonists or phosphodiesterase-5 inhibitors. Prostacyclin analogues (inhaled/subcutaneous) are useful adjunctive therapies. Intravenous epoprostenol remains the therapeutic mainstay for class IV PAH. Emerging antiproliferative-proapoptotic therapies that merit investigator-initiated clinical trials include: statins, Imatinib, NONO-ates, anti-survivin, potassium channel modulation, and dichloroacetate.

Summary
The diagnostic criteria for pulmonary arterial hypertension should be revised to include PVR. Sildenafil’s efficacy and price recommend it as a first-line oral therapy. New pulmonary arterial hypertension-regression therapies and therapeutic combinations offer the potential for cure of pulmonary arterial hypertension.

Keywords
apoptosis, calcium antagonists, dichloroacetate, endothelin antagonists, phosphodiesterase 5 inhibitors

Abbreviations
cGMP cyclic guanosine monophosphate
ECS European Cardiology Society
ERB endothelin receptor blocker
FDA Food and Drug Administration
NIH National Institutes of Health
NO nitric oxide
NYHA New York Heart Association
PCWP pulmonary capillary wedge pressure
PAH pulmonary arterial hypertension
PAP pulmonary artery pressure
PVR pulmonary vascular resistance
RCT randomized controlled trial

Introduction
Pulmonary arterial hypertension (PAH) is increasingly recognized as a disease of increased proliferation and impaired apoptosis of cells in the small pulmonary arteries [1,2]. The resulting increase in the right ventricular afterload results in right ventricular failure and premature death. Although the morbidity and mortality of PAH remain high, recent advances in the biology of this disease have resulted in significant changes in the definition of PAH and an explosion of clinical research that has completely transformed the field over the past 5 years. A number of approved and investigational therapies are now available for PAH patients. Here, we review the major advances in the treatment of PAH over the past 5 years. We used, as much as possible, the standard principles of evidence-based medicine.

Current definition of pulmonary arterial hypertension, its limitations and clinical implications
Idiopathic PAH (iPAH) is now grouped with PAH syndromes that are associated with connective tissue disease, cirrhosis, congenital heart shunts, HIV and anorexigen use. This is based, at least partly, on the fact that the pathology of the pulmonary arteries in these diseases can be quite similar, suggesting a common pathogenetic mechanism.
However, the results of several randomized controlled trials (RCTs) suggest that these syndromes are not homogeneous in their response to therapy or prognosis. For example, scleroderma PAH patients often respond suboptimally compared with iPAH patients. Congenital heart disease PAH patients, despite a better prognosis compared with iPAH, often have a poor response to therapy.

PAH is defined by the European Cardiology Society (ECS) guidelines simply as a resting mean pulmonary artery pressure (PAP) greater than 25 mmHg (>30 mmHg during exercise) [3]. The American College of Chest Physicians definition, based on the National Institutes of Health (NIH) PAH registry, includes the requirement for a pulmonary capillary wedge pressure (PCWP) of less than 15 mmHg [4]. Both definitions, however, do not explicitly require increased pulmonary vascular resistance (PVR) and thus might result in the over-diagnosis of PAH, with important clinical (unnecessary therapies) or research (inappropriate inclusion of non-PAH patients in RCTs) implications. For example, consider an anemic or pregnant patient, with a ‘physiological’ increase in cardiac output. This patient will have a ‘flow-induced’ increase in the mean PAP (say 35 mmHg), a normal PCWP (10 mmHg) and elevated cardiac output (10 l/m). The PVR in this patient is \((35–10)/10 = 2.5\) Wood units. Based on the current definitions, this hypothetical patient (who has histologically normal pulmonary arteries) would be inappropriately diagnosed with PAH, despite the normal PVR. Another example of potential PAH misdiagnosis is the patient with left ventricular diastolic dysfunction. Consider such a patient with a mean PAP of 35 mmHg, PCWP of 20 mmHg and cardiac output of 5 l/m. The PVR in this patient will be \((35–20)/5 = 3\) Wood units. Based on the current definition, this patient will be diagnosed with PAH (despite a PVR within normal limits), and despite the fact that the pulmonary arteries are probably normal and the increase in PAP only reflects a transmission of the elevated left ventricular-end-diastolic pressure as a result of diastolic dysfunction. Neither of these patients should be treated for PAH, or included in PAH RCTs; their mean PAP will normalize after treatment of the primary cause.

Only when PVR is increased (mean PAP > 25 mmHg and PVR > 3 Wood units) can one diagnose pulmonary arterial hypertension. Even then, the diagnosis of PAH also requires the careful exclusion of secondary causes of pulmonary hypertension, including thromboembolic disease, left ventricular disease (restriction or diastolic dysfunction), pulmonary disease or hypoxia.

**Acute vasodilator testing**

All patients who appear to have PAH after non-invasive testing should undergo a right heart catheterization to confirm the diagnosis, quantify the PAH and assess reversibility. Echocardiography is not specific enough to diagnose PAH, particularly in cases of pulmonary hypertension resulting from left ventricular diastolic dysfunction and elevated PCWP. Acute vasodilator testing, during catheterization, defines the prognosis and guides therapy. Although the majority of centers use inhaled nitric oxide (NO) as a pulmonary vasodilator (10–80 ppm), many centers, particularly in Europe, use epoprostenol, inhaled iloprost or adenosine. Despite its recent increase in price, inhaled NO is the preferred vasodilator, because of its unique selectivity for the pulmonary circulation.

The definition of a ‘positive’ response is controversial. According to the ECS, a positive acute vasodilator response requires both a fall of mean PAP of 10 mmHg or greater and final mean PAP of 40 mmHg or less, with no decrease in cardiac output [3]. We believe that this definition is insensitive, and would miss the many patients who respond with a 20% fall in PVR or mean PAP, but whose mean PAP remains above 40 mmHg. As pulmonary vasoconstriction is usually not the major determinant of PVR, a dramatic decrease in mean PAP in response to acute vasodilators is quite rare. Because the ‘responders’ have a much better prognosis when treated with calcium antagonists the ECS definition would disqualify many PAH patients from the simple and cheap calcium antagonist therapy [5]. In our practice responders who are class II–III merit a trial of calcium antagonists. This dose titration is best initiated in a monitored hospital bed, rather than in the catheterization laboratory because titration often requires prolonged observation over 1–2 days. Doses of nifedipine or diltiazem are gradually increased as tolerated by systemic blood pressure (Table 1) [5–11,12**,13*,14–19]. Alternative starting medications are sildenafil, which we favor on the basis of price, or bosentan. These medications are best initiated in a monitored setting, and although invasive hemodynamic monitoring is not usually required, we carefully monitor heart rate and systemic blood pressure. Non-responders who are class II–III are usually treated with sildenafil or bosentan, progressing to inhaled iloprost or intravenous prostacyclin therapy if their status deteriorates to class IV. In class IV patients, dose titration of flibans in a monitored setting, guided by a right heart catheterization is required. As most patients in our programme are class II–III and are non-responders we treat the majority of them with sildenafil or bosentan plus warfarin.

It remains controversial whether echocardiographic follow-up is adequate for chronic monitoring of PAH patients. We ensure that each year all patients have one or more 6-min walk tests and an echocardiographic measurement of PAP (using both tricuspid regurgitation velocity and pulmonary artery acceleration time). In
Table 1 Summary of randomized controlled trials in pulmonary arterial hypertension

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug/dose</th>
<th>WHO class</th>
<th>Caveats</th>
<th>Evidence level/recommendation</th>
<th>Δ 6-min walk</th>
<th>Adverse effects</th>
<th>Key studies</th>
</tr>
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<tr>
<td>Oral</td>
<td></td>
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<td></td>
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<tr>
<td>Calcium antagonists</td>
<td>Nifedipine(^a) 172 ± 41 mg/day</td>
<td>All</td>
<td>Only use if acute vasodilator tests show a 20% fall in PAP/PVR</td>
<td>C Class I</td>
<td>N/A</td>
<td>Hypotension</td>
<td>[5]</td>
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<tr>
<td></td>
<td>Diltiazem(^b) 720 ± 208 mg/day</td>
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<td>Anticoagulants</td>
<td>Warfarin INR 2–2.5</td>
<td>All</td>
<td>Caution when used with endothelin antagonists or in overt right heart failure</td>
<td>C Class IIa</td>
<td>N/A</td>
<td>Bleeding</td>
<td>[5,6]</td>
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<tr>
<td>Endothelin antagonists</td>
<td>Bosentan 125 mg bid</td>
<td>III</td>
<td>Caution when combined with sildenafil (decreases sildenafil levels)</td>
<td>A Class I</td>
<td>+36</td>
<td>Elevated liver enzymes – can be severe</td>
<td>[7,8]</td>
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<td></td>
<td>Sitaxsentan 100 mg qd</td>
<td></td>
<td>Not well studied in class IV patients</td>
<td>B Class IIa</td>
<td>+35</td>
<td>Flushing</td>
<td>[9]</td>
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<tr>
<td>PDE-5 inhibitors</td>
<td>Sildenafil 50–100 mg tid</td>
<td>I–III</td>
<td>The FDA-approved sildenafil dose (Revatio) may vary</td>
<td>A Class I</td>
<td>+50</td>
<td>Flushing</td>
<td>[10,11,12*,13*]</td>
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<tr>
<td></td>
<td>Tadalafil 20–60 mg qd</td>
<td></td>
<td>Not well studied in class IV patients</td>
<td>B Class IIa</td>
<td></td>
<td></td>
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<tr>
<td>SC</td>
<td>Prostacyclin analogue</td>
<td>II–IV</td>
<td>Gradual dose titration over 12 weeks</td>
<td>B Class IIa</td>
<td>+16 m</td>
<td>Injection site pain and erythema leading to 8% dropout in a 12-week RCT</td>
<td>[15]</td>
</tr>
<tr>
<td>Combination</td>
<td>PDE-5 inhibitors + prostanoid</td>
<td>II–IV</td>
<td>Larger trials testing combination vs monotherapy needed – small trial may account for large increase in 6-min walk</td>
<td>C Class IIa (for PDE-5 + prostanoid)</td>
<td>+90 m</td>
<td>See individual agents</td>
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<tr>
<td>Inhaled</td>
<td>Iloprost 2.5–5.0 μg 6–9/day</td>
<td>III–IV</td>
<td></td>
<td>B Class IIa</td>
<td>36.4 Trend to increased survival vs placebo (1 vs 4 deaths in a 12-week study)</td>
<td>[16,17]</td>
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<tr>
<td>Prostacyclin analogue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flushing, jaw pain</td>
<td></td>
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<tr>
<td>Nitric oxide</td>
<td>Nitric oxide 10–80 ppm Acute testing</td>
<td></td>
<td>Can also use epoprostenol or adenosine</td>
<td>A Class I</td>
<td>+47 m and increased survival in NYHA IV patients</td>
<td>[19]</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Prostacyclin analogue</td>
<td>IIIb and IV</td>
<td>Complex therapy requires substantial patient support. Interruption of infusion can lead to sudden death/decompensation. Catheter infections common</td>
<td></td>
<td></td>
<td>Flushing, tachycardia, jaw pain</td>
<td></td>
</tr>
</tbody>
</table>

FDA, Food and Drug Administration; INR, international normalized ratio; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; WHO, World Health Organization.

\(^a\)These are the mean ‘high dose’ doses. We advocate starting with low dose treatment.

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addition, yearly right heart catheterizations are indicated in most patients, and certainly in any patient showing apparent deterioration.

**General measures**

A number of standard therapies (including oxygen, diuretics, anticoagulant, digitalis, etc.) are commonly used in PAH patients, despite the lack of support from RCTs. These therapies and important general measures (the avoidance of pregnancy, exposure to high-altitude, aerobic exercise) have recently been reviewed [20].

**Calcium antagonists**

The calcium antagonists retain a role in PAH therapy because of their efficacy in selected patients and their low price (Table 1). In a non-randomized series of 64 iPAH patients, 26% responded to high-dose calcium antagonists with an acute decrease in the PVR of more than 20% [5]. At 5 years, there was a clear survival advantage to the initial responders versus non-responders (97 versus 55%). This prospective trial was, however, not placebo controlled and it is unclear whether calcium antagonist responsivity was primarily selecting a group of PAH patients with a better prognosis (whether because of earlier presentation or unique pathophysiology). There is little science to guide the dosing of calcium antagonists. In responders it is reasonable to start therapy with nifedipine 10 mg three times a day, and increase on a daily basis to 30 mg three times a day, prior to converting the patient to the long-acting form of the drug. If systemic blood pressure is not significantly lowered (<10%) on this regimen, additional titrations into the ‘high-dose range’ can be initiated with longer intervals of a week between dose changes (Table 1). Unfortunately, most PAH patients do not respond to vasodilators acutely, and are not candidates for calcium antagonist therapy. Furthermore, the use of high-dose calcium antagonists is limited by both symptomatic hypotension and edema, although lower doses may offer some benefit in PAH ‘responders’.

**Prostaglandin analogues**

The endothelium in PAH is characterized by the deficient production of vasodilator prostaglandins (prostacyclin) [21], providing the rationale for therapy with prostacyclin analogues (Table 1).

**Epoprostenol**

Because of its half-life of approximately 3 min, instability at room temperature and irritating effects on veins, epoprostenol must be refrigerated and administered intravenously by continuous infusion through tunneled, central venous catheters. Therapy is initiated by a dose titration beginning at 2 ng/kg per minute, increasing until symptoms occur. Most adverse effects relate to epoprostenol’s systemic vasodilator actions (e.g. jaw pain, flushing, headache, diarrhea, an erythematous rash and leg pain). Acute tachyphylaxis occurs and frequent dose titrations are required [22]. Epoprostenol is the only drug that has been shown to improve survival in PAH. The effect of epoprostenol (n = 41) versus standard therapy (n = 40) was assessed in a cohort of New York Heart Association (NYHA) class III–IV iPAH patients in a 12-week prospective, randomized, multicenter open trial [19]. Compared with standard therapy, epoprostenol improved hemodynamics (mean PAP −8% versus +3%, PVR −21% versus +9% and 6-min walk: +47 m versus −64 m). Although there was less mortality in the epoprostenol arm (0 versus eight patients) the initial 6-min walk was significantly longer than in the control group (315 versus 270 m). The small size of the study, coupled with this imbalance might have contributed to the apparent beneficial effects of epoprostenol. In another small RCT in scleroderma PAH, epoprostenol also had beneficial hemodynamic and functional effects but did not improve survival [23]. Two larger cohort studies suggest a survival benefit for epoprostenol-treated patients at 1, 2 and 3 years (88, 76 and 63%) versus historical controls (59, 46 and 35%) [24]. These non-randomized studies may, however, say more about evolving excellence in PAH care than they do about epoprostenol [24,25]. The beneficial effects of epoprostenol can be sustained for years, and as a result many patients have been removed from heart–lung transplantation lists [24,26–28]. Occasionally, the disease improves sufficiently that one can even replace epoprostenol with oral therapy [29]. Unfortunately, the use of epoprostenol is limited by its cost (~Can$60 000/year) and several logistical complexities.

**Treprostinil**

Treprostinil is a prostacyclin analogue with a 3-h half-life and stability at room temperature. It is delivered subcutaneously by a continuous infusion. Unfortunately, a recent 12-week, RCT of 470 PAH patients randomly assigned to treprostinil or placebo (plus conventional therapy) found only modest efficacy (6-min walk: +16 m), although several secondary endpoints improved (hemodynamics and quality of life indices). The maximum tolerable dose was often suboptimal, being limited in 85% of patients by severe pain and erythema at the injection site. This study included NYHA II patients (n = 53). Perhaps the enrollment of healthier patients was detrimental to showing benefit (class II patients improved only by 2 m compared with 54 m for class IV patients). In addition, the study included congenital heart disease PAH, and this subgroup did not improve, a reminder that the lumping of diverse PAH subgroups under a single rubric may be invalid. The recent introduction of intravenous treprostinil might prove to be more convenient (no refrigeration and longer half-life) than epoprostenol [30].
Iloprost
Although this analogue has a half-life that is marginally longer than that of epoprostenol (25 min), it can be administered by inhalation. This preparation is approved for the treatment of PAH in both Europe and the United States, but is rarely used in North America. Iloprost is administered in multiple 5-min sessions (6–9/day) using ultrasonic nebulizers [31]. Airway nebulization delivers iloprost to resistance pulmonary arteries with minimal systemic overflow. Two open-label studies of iloprost in PAH for 3 months [32] and one year [33], and a 3-month, double-blind, placebo-controlled RCT support its efficacy. Iloprost (2.5 or 5 μg) six to nine times a day (total dose < 45 μg/day) prolonged the 6-min walk in 203 patients with severe PAH or chronic thromboembolic pulmonary hypertension (NYHA functional class III–IV) without serious adverse effects [18]. Once again, the therapeutic effect was greater in the iPAH subset than the population as a whole (+59 versus +36 m). Iloprost also improved pulmonary hemodynamics, and there was a trend towards improved survival (one death in the iloprost group, four deaths in the placebo group).

Endothelin antagonists
Endothelin levels are elevated in PAH, and some of this vasoconstrictive, mitogenic peptide is synthesized in the pulmonary circulation [34], providing the rationale for the use of endothelin receptor blockers (ERBs) in PAH (Table 1).

Bosentan
Bosentan was the first oral drug approved by the Food and Drug Administration (FDA) for use in class III–IV PAH patients. The approval followed the publication of the BREATHE-1 trial. In that placebo-controlled RCT, 213 class III–IV iPAH or scleroderma PAH patients were randomly assigned to bosentan (125 mg twice a day or 250 mg twice a day) compared with placebo for approximately 16 weeks [7]. The primary endpoint, the 6-min walk, improved in the bosentan group compared with the placebo group (+36 versus −8 m). Unfortunately, although the improvement was greater at 250 versus 125 mg twice a day (+54 versus +35 m), an unacceptable incidence of abnormal liver function tests (14 versus 5%), syncope and flushing precludes the use of the higher dose. Liver toxicity is an ERB class effect, resulting from bile salt accumulation [35]. The FDA requires monthly liver function tests in all patients treated with bosentan. No survival benefits have been demonstrated for bosentan. A survival benefit was recently postulated for bosentan by comparing outcomes data from the open-label extension trials following BREATHE to that of the NIH registry [36]. The validity of this type of retrospective comparison is, however, questionable because therapy in the extension trials was not blinded. Moreover, comparison with the NIH registry is inappropriate because of the temporal changes in PAH care between the 1980s and the present, the different definitions of PAH used, and differences in patient characteristics. In a recent single-center case series of 103 consecutive NYHA III–IV iPAH patients treated with bosentan, the results were comparable to those in clinical trials, but 44% of patients required the addition of prostanoid therapy during 1–2 years of follow-up [37*], raising efficacy and economic issues. Bosentan offers some benefits to patients with moderate PAH, but suffers from a relative lack of efficacy, the need for chronic monitoring of liver function, and cost (Can$40 000/year).

Sitaxsentan
In contrast to bosentan, which is a non-selective ERB, sitaxsentan is a selective type A ERB, offering the theoretical advantage of mitigating the endothelin-A receptor-dependent vasoconstrictive and proliferative effects, while preserving the endothelin-B receptor-dependent NO-mediated vasodilation and endothelin clearance. STRIDE-1 was a randomized, 12-week, placebo-controlled RCT that compared sitaxsentan [100 mg (n = 55) or 300 mg (n = 63) a day] with placebo (n = 60). Sitaxsentan improved 6-min walk, NYHA class, cardiac index and PVR in NYHA class II–IV patients with iPAH, scleroderma PAH or congenital heart disease [9]. Sitaxsentan (100 mg) increased the 6-min walk by 35 m and the NYHA class improved in 29% of subjects. Surprisingly, there was no incremental benefit from the higher dose (just increased hepatotoxicity). When initiating sitaxsentan, warfarin doses should be reduced because inhibition of the CYP2C9 P450 enzyme will usually interfere with the metabolism of warfarin and increase the international normalized ratio [38]. In addition, ERBs decrease levels of sildenafil and may interfere with this therapy [39]. There are no prospective data to indicate that sitaxsentan reduces mortality.

Phosphodiesterase-5 inhibitors
The two main endogenous stimuli for cyclic guanosine monophosphate (cGMP) production in the pulmonary circulation and right heart are brain natriuretic peptide and NO. Phosphodiesterase-5 inhibitors (sildenafil, vardenafl, tadalafl) amplify the effects of both brain brain natriuretic peptide and NO, increasing cGMP and promoting a vasodilatory and antiproliferative effect in the pulmonary circulation (Table 1). Phosphodiesterase-5 expression is preferentially expressed in the pulmonary and genital circulations, accounting for the relative lack of systemic hypotension when sildenafil is administered (providing exogenous nitrates are avoided).

Sildenafil
Several small trials and case reports showed that sildenafil (50–100 mg three times a day) was similarly effective and selective as inhaled NO when administered acutely to
patients with PAH [10,11]. Sildenafil appears to offer advantages over inhaled NO, increasing cardiac output and reducing PCWP, whereas inhaled NO tends to increase PCWP and has little effect on cardiac output. In 2003, a small open-label series showed that 3 months of sildenafil (50 mg three times a day by mouth) produced sustained increases in 6-min walk (+110 m) and resulted in some regression of right ventricular hypertrophy [40]. In addition, it was shown that phosphodiesterase-5 is abundant in pulmonary arteries of PAH patients.

In 2005, the SUPER trial reported 278 patients from 53 centers in a 3-month, placebo-controlled, RCT that tested the addition of sildenafil (20, 40 or 80 mg) to conventional therapy [12**]. The primary endpoint was improvement in the 6-min walk. Subsequently, most patients underwent an additional 9 months of therapy (sildenafil 80 mg). Sildenafil caused a +50 m increase in 6-min walk that was sustained at one year. Although the authors suggest that there was no dose response to sildenafil (based on 6-min walk), there was a statistically significant, dose-dependent decrease in PVR, without toxicity [12**]. The main adverse effects of sildenafil were flushing, diarrhea and heartburn. Although the authors claim equivalency to bosentan and epoprostenol, it is our opinion that the efficacy, convenience and cost (particularly if 100 mg pills are split, < Can$5000/year) suggests an advantage of sildenafil as a first-line therapy for NYHA III patients. Following the 2005 approval by the FDA, sildenafil is marketed at a low-dose under a different name (Revatio; Pfizer, New York, NY, USA). One can only hope that the low dose is associated with a fair price. In our opinion/experience, patients can be safely treated with 50–100 mg doses of sildenafil. The relative value of bosentan compared with sildenafil requires examination. The SERAPH study compared the two treatments in 26 class III PAH patients with iPAH or scleroderma PAH. Subjects were randomly assigned in a double-blind fashion to receive sildenafil (50 mg twice a day for 4 weeks, then 50 mg three times a day) or bosentan (62.5 mg twice a day for 4 weeks, then 125 mg twice a day) over 16 weeks [13*]. There was a trend towards a greater increase in 6-min walk with sildenafil (+114 m) versus bosentan (+59 m). In addition, only sildenafil reduced right ventricular mass. One sildenafil patient did die suddenly, although it is uncertain if this was related to therapy.

In an acute trial in 60 class II–IV PAH patients, all three phosphodiesterase-5 inhibitors caused similar PVR reductions; however, only sildenafil and tadalafil avoided changing the pulmonary/systemic vascular resistance ratio [14]. Only sildenafil, the least selective for phosphodiesterase-5, improved systemic oxygenation. That study suggested that all phosphodiesterase-5 inhibitors are not equally selective for the pulmonary circulation nor equally beneficial in PAH [14]. Sildenafil is also useful in preventing rebound in PAH during withdrawal of chronic inhaled NO therapy [10], and is beneficial in cor pulmonale [41] and pediatric PAH [42].

Combination therapies
Following the model that has been successfully used to treat tuberculosis, HIV infections or cancer, practitioners have begun the search for combinations of drugs for PAH. Adding bosentan to epoprostenol has, in our view, yielded disappointing results [43]. In contrast, the addition of sildenafil to inhaled iloprost has, in our view, improved the 6-min walk and decreased right ventricular pressure in some subjects without adverse events [46*]. A large RCT is required to assess efficacy.

Emerging therapies
It has recently been recognized that a decrease of proliferation and induction of apoptosis in the wall of pulmonary arteries causes regression of established PAH.

Simvastatin
Monocrotaline-induced PAH in rodents was reduced by simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor. Simvastatin caused benefit by inducing the apoptosis of neointimal smooth muscle cells [45]. Subsequently, an open-label observational study was performed on 16 PAH patients, World Health Organization class I–IV. Simvastatin (20–80 mg/day) improved 6-min walk and decreased right ventricular pressure in some subjects without adverse events [46*]. A large RCT is required to assess efficacy.

Fluoxetine
In monocrotaline-induced PAH, disease progression is associated with increased lung expression of the serotonin transporter, which promotes the proliferation of pulmonary artery smooth muscle cells. The selective serotonin transporter inhibitor fluoxetine prevented or reversed PAH in this model [47]. Considering the good safety profile and wide use of fluoxetine in humans as an antidepressant, a PAH RCT is justified. However, a recent trial suggested that maternal fluoxetine (taken in the third trimester) increases the risk of primary pulmonary hypertension of the newborn [48].

Imatinib
Platelet-derived growth factor can drive smooth muscle cell proliferation, and dietary fish oil, which antagonizes this pathway, reduces experimental PAH [49]. It has been suggested that endothelial damage and exposure of the media to circulating platelet-derived growth factor might contribute to obstructive vascular remodeling. A recent
case report and a rodent study [50] suggested that imatinib, a platelet-derived growth factor-antagonist may reduce PAH [51].

Dichloroacetate
This prototypic inhibitor of mitochondrial pyruvate dehydrogenase kinase has been shown to normalize mitochondrial function, lower PVR and reduce mortality in several models of experimental PAH [52,53]. Although it has yet to be used for PAH in humans, this drug has been safely administered to patients with inherited mitochondrial diseases for the correction of lactic acidosis. An RCT is being organized.

NONO-ates
These stable adducts release NO at a stochiometrically predictable rate when adjusted to a neutral pH. Dithylenetriamine has a very slow half-life (~24 h), potentially allowing once a day therapy, and reverses experimental pulmonary vasoconstriction without causing systemic vasodilatation [54]. A pilot study confirmed our earlier animal studies, showing that nebulized dithylenetriamine (150 μmol) causes selective pulmonary vasodilatation in adult respiratory distress syndrome patients [55].

Gene therapy inhibiting endogenous survivin
Suppression of apoptosis in the pulmonary vasculature occurs partly because of the de-novo expression of survivin, an inhibitor of apoptosis that was previously thought to be solely expressed in cancer. It has recently been shown that survivin is expressed in the pulmonary arteries of PAH patients and survivin inhibition causes the regression of experimental PAH [56].

Potassium channel augmentation
A common feature in experimental [57,58] and human PAH [59] is the decreased expression of voltage-gated potassium channels, particularly Kv1.5. The loss of potassium channels causes membrane depolarization and increases cytosolic calcium, thereby promoting vasoconstriction and cell proliferation. In addition, the loss of these channels increases cytosolic potassium concentrations, which inhibits caspases and reduces apoptosis [60]. Potassium channel overexpression (whether achieved by nebulized adenosinergic Kv1.5 gene therapy [57] or oral dichloroacetate [52]) can regress experimental PAH.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
 ● of special interest
 ● of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 421).

2 Michelakis ED. Spatio-temporal diversity of apoptosis within the vascular wall in pulmonary arterial hypertension: heterogeneous BMP signaling may have therapeutic implications. Circ Res 2006; 98:172–175.
A large multicentre RCT shows sildenafil to be beneficial in class III PAH. Despite a lack of dose effect in terms of 6-min walk, there was a dose effect of sildenafil on functional class and hemodynamics with 80 mg better than 20 mg. The rationale for choosing sildenafil doses other than those used for erectile dysfunction is unclear. Our clinic has had success with managing patients with sildenafil 50–100 mg three times a day by mouth.
Sildenafil offers an advantage over bosentan in its ability to cause a regression of RVH. Interestingly, the large cost advantage of sildenafil over bosentan is not examined. There was one unexplained sudden death in the sildenafil group. This was not seen in the other small studies or the SUPER trial.


This paper has received considerable attention but as discussed it is not valid to compare outcomes between heterogeneous cohorts that were defined and treated differently more than 20 years apart. The study is interesting, but mostly for a snapshot of the current rates of survival on bosentan.


A promising small case series suggesting that statin therapy may improve PAH. An RCT is necessary to assess this relatively economical, low-risk oral therapy. The assessment of combination therapies should include an evaluation of statins.


