Current management of pulmonary arterial hypertension

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The management of pulmonary arterial hypertension has been transformed by the introduction of disease-targeted therapies. This article examines the diagnosis of pulmonary arterial hypertension, the efficacy of current treatments, and the role of the GP in management.

Pulmonary hypertension refers to increased pressure in the pulmonary arterial circulation. The pulmonary circulation has to accommodate the entire cardiac output in each cardiac cycle, and evolution has adapted to this by making it a low-pressure high-flow system. However, pathology can affect both the arterial and venous components of this system. Pulmonary venous hypertension mainly refers to diseases that result in elevated venous pressure and occurs mainly from mitral valve and left-sided heart disease; these will not be discussed in this article.

As a result of greater understanding of the molecular and cellular pathways involved in the pathobiology of pulmonary arterial hypertension (PAH), novel and exciting treatments have become available to treat this condition. These new drugs represent a huge step forward in the treatment of this universally fatal disease in that they allow improvement in quality of life and survival; however, they do not as yet offer a cure.

Definition
PAH is defined by consensus as a mean pulmonary artery pressure of above 25mmHg in the setting of a normal or reduced cardiac output, with a normal pulmonary capillary wedge pressure (PCWP) and elevated pulmonary vascular resistance (PVR). The normal PCWP is required to exclude the presence of significant left heart disease and pulmonary venous hypertension. As a result, the diagnosis of pulmonary hypertension requires invasive right-heart catheterisation.

Classification
Pulmonary hypertension is an umbrella term that refers simply to elevated pressure in the pulmonary vasculature. There are a wide variety of causes of this and the 2008 WHO conference in Dana Point attempted to clarify and organise these into a more defined classification (see Figure 2). This article will focus on PAH (group 1).
The PAH group includes idiopathic (previously referred to as primary) PAH, heritable (formerly familial) PAH and associated PAH diseases. The latter includes collagen vascular (or connective tissue) diseases, HIV, anorexigens use, congenital heart disease with systemic-to-pulmonary shunts, and portal hypertension.

**Epidemiology**

For a long time, the only epidemiological data on PAH was from a prospective National Institutes of Health (NIH) registry in the USA that gathered information from 187 patients with idiopathic PAH during the mid-1980s. This demonstrated that median survival was 2.8 years untreated; patients with collagen vascular disease and HIV-related PAH had the worst prognosis, while the congenital heart disease group had the best. More recent data from a French and Scottish registry have suggested that the prevalence of the disease ranges from 15 to 52 per million population.\(^2,3\)

These studies confirmed that PAH is not recognised until late and most patients present in WHO functional class III or IV (see Table 1). Earlier detection of PAH in groups at risk is therefore felt to be important. Screening of patients with HIV, collagen vascular disease and sickle cell disease has been implemented and has shown that patients can be identified at an earlier stage in the disease with lower pulmonary pressures.

**Clinical presentation**

PAH is notoriously difficult to diagnose. Indeed, the average time from onset of symptoms until diagnosis was initially found to be two years and, despite increased awareness of PAH, more recent studies have shown this delay remains unchanged.

The initial symptoms are nonspecific and include lethargy, malaise and exercise intolerance, and are often misdiagnosed as reflecting a degree of unfitness. Dyspnoea can be mistaken as asthma, but as the disease progresses more ominous signs reflect right heart dysfunction with exertional syncope and angina. This latter symptom is often due to subendocardial hypoperfusion and increased myocardial oxygen demand.

Physical examination in the early stages of disease can be normal. The first sign is an increased intensity of the second heart sound, which is subtle and easily missed. A left parasternal heave may be felt as the right chambers hypertrophy, and as the ventricle fails, peripheral oedema, ascites and elevated jugular venous pressure can result. Tricuspid regurgitation can be heard as a pansystolic murmur accentuated on inspiration and this leads to pulsatile hepatomegaly.

The evidence-based treatment algorithm for PAH patients from the European Society of Cardiology (ESC) and the 2015 European Respiratory Society (ERS) Guidelines is shown in Figure 3,\(^4\) and an example of a CT scan of the chest showing a dilated pulmonary artery in idiopathic PAH is shown in Figure 1.

**Treatment**

Treatment can be divided into the therapies that most patients with PAH find themselves on and those that are specifically aimed at the PAH pathological process itself – so-called disease-targeted therapy. However, disease-targeted therapy is
Treatment naïve patient → PAH confirmed by expert centre → General measures

CCB therapy → Acute vasoreactivity test (IPAH/HPAH/DPAH only)

Vasoreactive

Low or intermediate risk (WHO FC II–III) → Initial monotherapy

Non-vasoreactive

High risk (WHO FC IV) → Initial combination including iv PCA

Patient already on treatment → Inadequate clinical response

Double or triple sequential combination → Inadequate clinical response → Consider listing for lung transplantation

General measures

Supportive therapy

PAH = pulmonary arterial hypertension; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; CCB = calcium channel blockers; PCA = prostacyclin analogues; iv = intravenous

WHO-FC = World Health Organization functional class

a Some WHO-FC III patients may be considered high risk

b Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure

c Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high-risk PAH patients also as monotherapy.

d Consider also balloon atrial septostomy

Patients with pulmonary hypertension with inability to result, side-effects are often encountered, including peripheral oedema and systemic hypotension. Close follow-up of these patients is warranted, and if they do not improve functional class by three to six months then they should be started on additional therapy.

Prostanoids
These are prostacyclin (PGI$_2$) analogues that have both pulmonary vasodilatory and antiproliferative effects. The ones in clinical use are epoprostenol and iloprost. A third prostacyclin analogue, treprostinil, is not discussed here as it is not currently licensed for use in the UK. Epoprostenol This is a short-acting sodium salt of PGI$_2$ that has been shown in studies to improve haemodynamics, six-minute walks and also survival. In what was the first prospective randomised trial of treatment in PAH, an improvement was shown in patients’ six-minute walk distance (by an average of 50m) and importantly this was the only trial to have demonstrated improved survival in PAH.$^6$ Treatment with epoprostenol is generally reserved for the sickest patients with the poorest functional class.

There are significant problems with the use of any intravenous prostanoid, in particular epoprostenol. Due to the short half-life, epoprostenol needs to be administered continuously via an indwelling vascular catheter, and if the drug flow is interrupted, serious life-threatening rebound increases in pulmonary vascular resistance can occur leading to acute right-heart failure and death. Other complications arise through the route of administration: the intravascular catheter can cause many problems including infection, thrombosis and embolism, leakage and pneumothorax at the time of insertion. In addition, epoprostenol is thermolabile, requiring it to be made up daily and the cassette to be administered with ice packs. This can be cumbersome for the patient. However, there are newer preparations that are now available that improve this. More thermolabile preparations (Flolan with pH12 solvent, and Veletri) have now been produced, which means the ice packs are no longer required and the drug can be made up in advance and stored at 4°C until needed.

Iloprost This synthetic analogue of PGI$_2$ has a longer half-life than epoprostenol. The main form of administration is via nebuliser; intravenous iloprost is available and has been used in salvage therapy for patients not managing inhaled therapy. The advantage of using inhaled therapy is that it allows a degree of pulmonary selectivity, avoiding the potentially harmful systemic hypotension seen with intravenous prostanoids. Iloprost has been shown to be a more potent pulmonary vasodilator than nitric oxide. However, with iloprost the effect only lasts 120 minutes and so has to be taken between 6 and 12 times per day.

It is generally felt that inhaled prostanoids should be seen as an adjunctive therapy rather than monotherapy and should not be regarded as equivalent to continuous intravenous prostanoids. Endothelin-receptor antagonists Bosentan This is an orally active dual-receptor blocker (ET$_A$ and ET$_B$) of the endothelin system and is licensed for treat-

<table>
<thead>
<tr>
<th>Functional class</th>
<th>Symptomatic profile</th>
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<tbody>
<tr>
<td>I</td>
<td>Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnoea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>III</td>
<td>Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope</td>
</tr>
<tr>
<td>IV</td>
<td>Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity</td>
</tr>
</tbody>
</table>

Table 1. WHO functional classification of pulmonary arterial hypertension

expensive and should only be initiated by physicians in specialist centres who have expertise in dealing with PAH.

The drugs used for general treatment include well-known and frequently used agents such as warfarin (aiming for an international normalised ratio (INR) of 2.0–2.5), diuretics and oxygen. The role of these agents is to try to minimise any further deleterious effects of the sluggish pulmonary circulation and to treat hypoxia and any right-heart failure.

There are four main disease-targeted drug groups: the calcium-channel blockers, prostanoids, endothelin-receptor antagonists and phosphodiesterase inhibitors.

Calcium-channel blockers
Prior to the more modern treatments for PAH becoming available, most patients received some form of oral calcium-channel blocker such as high-dose nifedipine or diltiazem. It is now clear that only those patients who respond favourably to a vasoreactivity test performed at right-heart catheterisation will gain any benefit from these treatments. This test involves administration of a short-acting vasodilator, then measuring the haemodynamic response. In our centre, this is performed routinely at catheterisation using inhaled nitric oxide, and a positive response is defined as a decrease in the mean pulmonary artery pressure of at least 10mmHg to a value less than 40mmHg, accompanied by an increased or unchanged cardiac output.

Recent evidence suggests that only approximately 10% of patients with idiopathic PAH will be vasoreactive, and of these, only 50% or so will respond to a calcium-channel blocker.$^5$ However, those that do improve on this treatment, have a much better outcome compared with those who do not. The doses used are often higher in than in systemic hypertension and as a result, side-effects are often encountered, including peripheral oedema and systemic hypotension. Close follow-up of these patients is warranted, and if they do not improve functional class by three to six months then they should be started on additional therapy.

Prostanoids
These are prostacyclin (PGI$_2$) analogues that have both pulmonary vasodilatory and antiproliferative effects. The ones in clinical use are epoprostenol and iloprost. A third prostacyclin analogue, treprostinil, is not discussed here as it is not currently licensed for use in the UK.

Epoprostenol This is a short-acting sodium salt of PGI$_2$ that has been shown in studies to improve haemodynamics, six-minute walks and also survival. In what was the first prospective randomised trial of treatment in PAH, an improvement was shown in patients’ six-minute walk distance (by an average of 50m) and importantly this was the only trial to have demonstrated improved survival in PAH.$^6$ Treatment with epoprostenol is generally reserved for the sickest patients with the poorest functional class.

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It is generally felt that inhaled prostanoids should be seen as an adjunctive therapy rather than monotherapy and should not be regarded as equivalent to continuous intravenous prostanoids.

Endothelin-receptor antagonists
Bosentan This is an orally active dual-receptor blocker (ET$_A$ and ET$_B$) of the endothelin system and is licensed for treat-
ment of patients with PAH. The pivotal trial for this agent was BREATHE-1, which was a large, multicentre, randomised, placebo-controlled trial to investigate the efficacy of bosentan in patients with idiopathic or connective tissue-related PAH. It demonstrated improvement in functional ability and six-minute walk distance by a mean of 44m. In addition, the EARLY trial looked at the use of bosentan in patients with WHO functional class II disease (see Table 1) and used the change in pulmonary vascular resistance (PVR) as the primary endpoint. The trial showed that bosentan slowed the deterioration in PVR and also suggested an improvement in the six-minute walk distance. These results have led the way to the initiation of treatment at an earlier stage.

In trials, the main side-effects of bosentan included flushing and peripheral oedema. However, the most significant problem was that of hepatic dysfunction leading to elevated transaminases in 10–12% of patients, which reversed upon withdrawal of the drug. Consequently, patients require monthly liver function tests while on bosentan treatment. It is also teratogenic, so contraception advice is mandatory. The liver toxicity effect of the endothelin-receptor antagonist class remains important, especially when we consider the idiosyncratic reaction in a few patients that led to severe hepatic necrosis and the withdrawal of the endothelin-receptor antagonist sitaxentan from the market.

**Ambrisentan** This is a selective ETₐ-receptor blocker that has more recently been approved for use in PAH. It is orally active and is administered once daily. It seems to be well tolerated with a low incidence of liver abnormalities.

**Macitentan** This is another dual ETₐ and ET₉-receptor blocker licensed for treatment of patients with PAH. It is an oral agent, and was shown in the SERAPHIN trial to reduce the composite endpoint of morbidity and mortality, as well as improving haemodynamics at right-heart catheterisation and improving six-minute walk distance.

<table>
<thead>
<tr>
<th>PAH drug</th>
<th>Mechanism</th>
<th>Interacting drug</th>
<th>Interaction</th>
</tr>
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<tbody>
<tr>
<td>Bosentan</td>
<td>CYP3A4 inducer</td>
<td>sildenafil</td>
<td>sildenafil levels fall 50%; bosentan levels increase 50%</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 substrate</td>
<td>ciclosporin</td>
<td>ciclosporin levels fall 50%; bosentan levels increase 4-fold; combination contraindicated</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 substrate</td>
<td>erythromycin</td>
<td>bosentan levels increased</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 substrate</td>
<td>ketoconazole,itraconazole</td>
<td>bosentan levels increased</td>
</tr>
<tr>
<td></td>
<td>CYP2C9 inducer</td>
<td>HMG CoA reductase inhibitors</td>
<td>simvastatin levels reduced 50%; similar effects likely with atorvastatin</td>
</tr>
<tr>
<td></td>
<td>CYP2C9 inducer</td>
<td>warfarin</td>
<td>increases warfarin metabolism, may need to adjust warfarin dose</td>
</tr>
<tr>
<td></td>
<td>CYP2C9 and CYP3A4 inhibitor</td>
<td>omeprazole</td>
<td>leads to higher levels of bosentan</td>
</tr>
<tr>
<td></td>
<td>CYP2C9 and CYP3A4 inducer</td>
<td>hormonal contraceptives</td>
<td>hormone levels decreased, contraception unreliable</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>CYP3A4 substrate</td>
<td>bosentan</td>
<td>sildenafil levels fall 50%; bosentan levels increase 50%</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 substrate</td>
<td>HMG CoA reductase inhibitors</td>
<td>may increase simvastatin/atorvastatin levels through competition for metabolism</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 substrate</td>
<td>HIV protease inhibitors</td>
<td>ritonavir and saquinavir increase sildenafil levels</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 substrate</td>
<td>erythromycin</td>
<td>sildenafil levels increased</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 substrate</td>
<td>ketoconazole</td>
<td>sildenafil levels increased</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 substrate</td>
<td>cimetidine</td>
<td>sildenafil levels increased</td>
</tr>
<tr>
<td></td>
<td>CYP2C9 and CYP3A4 inhibitor</td>
<td>omeprazole</td>
<td>leads to higher levels of sildenafil</td>
</tr>
<tr>
<td>cGMP</td>
<td>nitroprusside, nitrates</td>
<td>profound systemic hypotension</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Significant drug interactions with bosentan and sildenafil
It has been one of the first agents that has been shown to be effective in patients already on disease-targeted therapy.\(^9\)

**Phosphodiesterase inhibitors**

**Sildenafil** This is a specific phosphodiesterase type-5 (PDE5) inhibitor that was originally licensed for erectile dysfunction. However, uncontrolled case reports suggested that patients with PAH benefited from sildenafil. This was confirmed in the SUPER trial, which demonstrated improvement in distance walked in six minutes (up to 50m), functional class and reduction in mean pulmonary artery pressure with sildenafil compared with placebo.\(^{10}\) An extension study showed that this benefit was maintained up to at least 12 months.

Sildenafil is generally well tolerated. Side-effects include flushing, epistaxis, heartburn and headache. There is a potential interaction with bosentan in the route of metabolism (see section below on combination therapy) and the drug exacerbates hypotension caused by nitrates, so should be avoided in patients receiving nitrates.

**Tadalafil**, another PDE5 inhibitor, has also shown efficacy in the treatment of PAH in a multicentre study, and is an alternative agent to sildenafil with the advantage of being once daily (sildenafil is dosed three times daily).

**Soluble guanylate cyclase stimulators**

**Riociguat** is a soluble guanylate cyclase stimulator, and currently the only drug of this class available. It directly stimulates guanylate cyclase, and has a synergistic action with endogenous nitric oxide. In the PATENT-1 study, riociguat use increased the distance covered in the six-minute walk test (primary endpoint), as well as decreasing morbidity, improving haemodynamics at right-heart catheterisation and reducing NTproBNP levels (secondary endpoints).\(^{11}\) Adverse effects include bleeding, dyspepsia/reflux, acute kidney injury, elevation in liver enzymes and hypotension.

Riociguat is also the first licensed agent for use in patients with inoperable chronic thromboembolic pulmonary hypertension, including for those who are unfit for pulmonary endarterectomy surgery and those who have persistent elevated pulmonary arterial pressure thereafter. In the CHEST trial, it increased exercise capacity in this group of patients.\(^{12}\)

**Prostacyclin-receptor agonists**

**Selexipag** is an oral selective prostacyclin-receptor agonist. It targets the same receptor as PGI\(_2\), but is structurally different. In the GRIPHON trial, selexipag was shown to improve morbidity from PAH.\(^{13}\) It is contraindicated in patients with significant left-heart disease, in pregnancy, breastfeeding and in those on dialysis. Despite being more selective, the prostanoïd side-effect profile remains – headache, jaw pain and gastrointestinal upset. This agent was recently licensed in the UK for PAH and may offer an alternative prostanoïd therapy for those patients who are unable to tolerate the parenteral forms.

**Combination therapy**

The therapies currently available for the treatment of PAH improve symptoms and can improve functional class, although with monotherapy this is usually achieved in less than 50% of patients. However, they do not offer a cure and patients still deteriorate on targeted therapies. Our understanding of the pathobiology of PAH is increasing, with the three main biological pathways involved being identified as nitric oxide, endothelin and prostacyclin.

The rationale of using the different classes of drugs to target different pathological pathways in the same patient seems logical and has beneficial effects in other cardiovascular and oncological diseases. Moreover, some patients develop tolerance to their initial treatment and it therefore loses efficacy. For example, it is well known that tachyphylaxis can develop in patients on prostanoïds, and increasing the dose leads to a higher incidence of side-effects. This provides another reason for using multiple therapies as it may allow the use of lower doses of one agent when combined with a second.

Previously, the role of combination therapy was reserved for patients who were failing on monotherapy, although the definition of when treatment is failing is also yet to be fully clarified. However, it is now recognised that earlier combination therapy is efficacious. The AMBITION trial showed that upfront combination therapy with a PDE5 inhibitor and endothelin-receptor antagonist in patients who were treatment naive led to a greater reduction in PAH-related morbidity/mortality.\(^{14}\) In addition, the SERAPHIN study confirmed that sequential combination therapy provides added benefit to patients already on established therapy. However, whether all combinations are equally effective is unclear and there are pharmacokinetic interactions that need to be considered. For example, sildenafil can lead to increased plasma levels of bosentan, and similarly bosentan can lead to reduced plasma levels of sildenafil. Therefore if these drugs are given in combination, reducing the dosage of bosentan is often advisable. Table 2 outlines some important drug interactions. It seems likely that use of combination therapy will increase in the coming years.

**Role of primary care**

The GP will undoubtedly be the first doctor that the patient will present to, and early recognition of PAH is essential to successful management. Unfortunately, the lack of specific pathognomonic symptoms means that diagnosis is often delayed. The initial referral for anyone with suspected pulmonary hypertension is usually to the local cardiologist or respiratory team. It is from these specialists that the patient is referred on to the specialist centre dealing with the diagnosis and management of pulmonary hypertension. In the UK, there are seven nationally designated centres that deal with pulmonary hypertension. These centres will diagnose the patient with noninvasive and invasive tests (such as right-heart catheterisation) and initiate management with disease-specific medication, if appropriate.

The GP also has an essential role to play in the ongoing care of patients with PAH. As the majority of patients will not live near their pulmonary hypertension specialist centre, any medical deterioration will often be seen first by the GP. Discussion with the pulmonary hypertension centre about any patient’s condition is essential before therapies are either stopped or
introduced. Sudden withdrawal of disease-targeted treatment can lead to a rebound worsening of PAH, and many of these agents have potential interactions with commonly prescribed medications such as proton-pump inhibitors and statins.

Perhaps one of the most important roles of the GP is in the safety monitoring of PAH drugs; this mainly concerns the endothelin-receptor antagonists. Guidelines require that while on an endothelin-receptor antagonist, the patient has monthly liver function and haemoglobin tests. Again, any abnormality should be discussed with the pulmonary hypertension centre, but as a general guide, any increase in transaminases more than three times the upper limit of normal is an indication for stopping.

PAH is a chronic disease that will lead to changes in patients’ social circumstances and living arrangements. There may be a need for oxygen, which should be arranged by referral to the local clinical oxygen service. Patients may benefit from aids at home, such as a stairlift, and the early involvement of social services and community health services will be helpful. PAH is often progressive and shortens life. Thus, the early involvement of palliative care services is recommended. This will require a multidisciplinary approach.

**Conclusion**
The diagnosis and management of PAH has undergone a dramatic transformation over the last two decades. Newer therapies developed on the background of a greater understanding of the molecular pathogenesis of the condition have entered routine clinical practice and have improved patient survival and wellbeing. Moreover, a large number of experimental studies are continuing, and there is great hope that it will not be long before more treatments are made available that potentially offer a cure for this disease.

**References**

**Declaration of interests**
Dr Church has received consultancy fees from Actelion, MSD and GSK.

Dr Ricketts is a specialty registrar in respiratory medicine at Glasgow Royal Infirmary, and Dr Church is a consultant and honorary senior clinical lecturer in the Division of Cardiovascular and Medical Sciences, University of Glasgow.