



A global view of pulmonary hypertension

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Pulmonary hypertension is a substantial global health issue. All age groups are affected with rapidly growing importance in elderly people, particularly in countries with ageing populations. Present estimates suggest a pulmonary hypertension prevalence of about 1% of the global population, which increases up to 10% in individuals aged more than 65 years. In almost all parts of the world, left-sided heart and lung diseases have become the most frequent causes of pulmonary hypertension. About 80% of affected patients live in developing countries, where pulmonary hypertension is frequently associated with congenital heart disease and various infectious disorders, including schistosomiasis, HIV, and rheumatic heart disease. These forms of pulmonary hypertension occur predominantly in those younger than 65 years. Independently of the underlying disease, the development of pulmonary hypertension is associated with clinical deterioration and a substantially increased mortality risk. Global research efforts are needed to establish preventive strategies and treatments for the various types of pulmonary hypertension.

Introduction

Pulmonary hypertension is defined by a mean pulmonary artery pressure at rest of 25 mm Hg or more, measured by right heart catheterisation.¹ According to pulmonary artery wedge pressure (PAWP), pulmonary hypertension can be subclassified as precapillary (PAWP \leq 15 mm Hg) or postcapillary (PAWP >15 mm Hg). Based on pathophysiological, clinical, and therapeutic considerations, pulmonary hypertension is divided into five groups: pulmonary arterial hypertension; pulmonary hypertension due to left-sided heart disease; pulmonary hypertension due to lung disease or hypoxia; chronic thromboembolic pulmonary hypertension; and pulmonary hypertension with unclear or multifactorial mechanisms (figure 1).

Although pulmonary hypertension has long been recognised to complicate many common diseases, especially left-sided heart disease and lung disease, most

researchers, clinicians, and the pharmaceutical industry have focused on certain forms of pulmonary hypertension, mainly pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Both entities are rare, leading to the belief that pulmonary hypertension in general is a rare condition. More recently, evidence suggests that pulmonary hypertension complicates various common diseases in which the development of pulmonary hypertension is almost invariably associated with aggravation of clinical symptoms and increased mortality. Additionally, the increasing age of populations worldwide is leading to a marked change in the distribution and phenotypes of patients presenting with pulmonary hypertension. A population-based study³ of 3381 participants in Rotterdam, Netherlands, reported echocardiographic signs suggestive of pulmonary hypertension in 2.6% of the overall population. The prevalence of echocardiographic signs of possible pulmonary hypertension was higher in older individuals (8.3% in those older than 85 years compared with 0.8% in those aged between 65 years and 70 years). We summarise the global incidence and prevalence of pulmonary hypertension and derive implications for health-care providers, policy makers, and future research strategies.

Group 1—pulmonary arterial hypertension

The pulmonary arterial hypertension group (figure 1) comprises patients with precapillary pulmonary hypertension due to distinct underlying disorders who share a similar pulmonary angioproliferative vasculopathy that predominantly affects the precapillary arterioles.⁴ The ensuing rise in the pulmonary vascular resistance leads to increased right ventricular afterload. Without effective therapeutic interventions, patients with pulmonary arterial hypertension eventually die from right heart failure.⁵

Idiopathic, heritable, or drug-induced, and associated with connective tissue disease or associated with portal pulmonary arterial hypertension

Most contemporary pulmonary arterial hypertension registries (table 1) have been established in Europe and

Key messages

- Pulmonary hypertension is becoming an increasingly common global health issue
- Pulmonary arterial hypertension, especially the idiopathic form, although still a rare disease with an incidence of 2–5 per million adults, is increasingly being diagnosed in elderly people
- Globally, left-sided heart failure, particularly heart failure with preserved ejection fraction, is becoming a leading cause of pulmonary hypertension, probably affecting 5–10% of individuals aged 65 years or older
- Lung disease, especially chronic obstructive pulmonary disease, is another leading cause of pulmonary hypertension in all parts of the world
- Schistosomiasis, HIV infection, post-streptococcal rheumatic heart disease, and sickle cell disease are frequent causes of pulmonary hypertension in countries where these diseases are still endemic
- The development of pulmonary hypertension is almost invariably associated with worsening symptoms and increased mortality, independent of the underlying disease

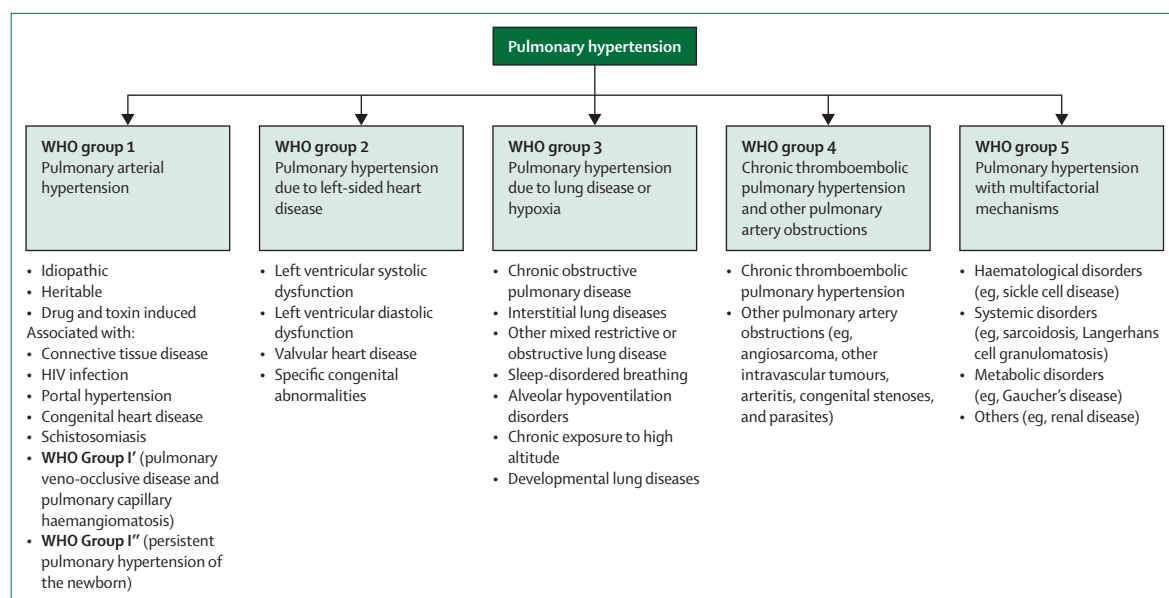


Figure 1: Classification of pulmonary hypertension*

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the USA. At least for idiopathic or heritable pulmonary arterial hypertension, global variation is small between ethnicities and environmental factors such as urbanisation and exposure to drugs or toxins. Genetic causes of heritable pulmonary arterial hypertension have been identified worldwide, germline mutations in the gene coding for bone morphogenetic protein receptor type II (*BMPR2*) cause up to 80% of cases of familial disease and 20% of cases of sporadic disease.²⁷

The reported incidence of pulmonary arterial hypertension in the developed world is 1.1–7.6 per million adults per year; the prevalence of pulmonary arterial hypertension is 6.6–26.0 per million adults.^{10,12,18} Pulmonary arterial hypertension has generally been thought to affect predominantly younger individuals, mostly females.⁶ This consideration is particularly true for heritable pulmonary arterial hypertension, which affects twice as many females as males before the age of 50 years.²⁸ Moreover, female sex is a risk factor for pulmonary arterial hypertension, yet females have better survival than males.²⁹

Since pulmonary arterial hypertension has been deemed to be a disease affecting mostly young people, some registries restrict inclusion to patients 65–70 years or younger.^{10,11} More recent data from the USA and Europe suggest,^{17,21,23,30} however, that pulmonary arterial hypertension is now frequently diagnosed in older patients, ie, those 65 years and older, who often present with cardiovascular comorbidities. In the 2014 UK National Audit on Pulmonary Hypertension, the median age at the time of diagnosis of pulmonary arterial hypertension was 60 years and 29% of the patients were 70 years or older.²² In Germany in 2014, the mean age of

patients newly diagnosed with idiopathic pulmonary arterial hypertension was 65 years.²¹ Older age has been identified as an independent risk factor for mortality in patients with pulmonary arterial hypertension.^{19,31,30} In developing countries, the average age of patients with idiopathic pulmonary arterial hypertension is younger than 40 years.^{23,24,32} These discrepancies are probably due to several factors, including differences in the overall population age between developed countries and developing countries, and presumably higher disease awareness as well as easier access to experienced diagnostic facilities in developed countries.

In most pulmonary arterial hypertension registries from the USA and Europe, idiopathic pulmonary arterial hypertension was the most common subtype (50–60% of all cases), followed by pulmonary arterial hypertension associated with connective tissue disease, pulmonary arterial hypertension associated with congenital heart disease, and pulmonary arterial hypertension associated with portal hypertension (portopulmonary hypertension).^{12,14,18,33} In patients with pulmonary arterial hypertension associated with connective tissue disease, systemic lupus erythematosus is the most common subtype in southeast Asia,^{24,34} whereas systemic sclerosis is the predominant underlying disease in the rest of the world.^{8,10,12,14,35} Portopulmonary hypertension is rare, even in areas where viral hepatitis is endemic.^{36–38}

The crude estimate for the global incidence of pulmonary arterial hypertension (including only idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension associated with connective tissue disease, and portopulmonary hypertension) is about 5 million adults per year and a prevalence of about

	Year of inclusion	Number of participants	Proportion of females (%)	Age (years)	Estimated incidence in the population (per million)	Estimated prevalence in the population (per million)	1 year survival by incident patients (%)	3 year survival by incident patients (%)
National Institutes of Health ^{6,7}	1981–85	187	59%	36 (15)	68%	48%
Chicago registry ⁸	1982–2006	578	77%	48 (14)	85%	..
Columbia University registry ⁹	1994–2002	84	81%	42 (14)	87%	75%
Scottish morbidity records ¹⁰	1986–2001	374	70%	52 (12)	7.6	26.0
The International Primary Pulmonary Hypertension study, Belgium ¹¹	1992–94	24	1.7
French registry ^{12,13}	2002 and 2003	674	65%	50 (15)	2.4	15.0	89%	55%
REVEAL ^{14–17}	2006 and 2007	2967	80%	50 (14)	2.0	10.6	91%	75%
Spanish registry ¹⁸	1998–2008	886	71%	45 (17)	3.7	16.0	89%	77%
UK and Ireland registry ¹⁹	2001–09	482	70%	50 (17)	1.1	6.6	93%	73%
Danish registry ²⁰	2000–12	134	58%	50 (21)	86%	73%
German registry ²¹	2014	1754	62%	65 (16)	3.9	25.9	92%	68%
UK National Audit 2014 ²²	2004–14	2940	65%	Female: 60 (-), male: 58 (-)	86%	63%
Chinese registry ²³	1999–2004	72	71%	36 (12)	68%	39%
Chinese registry ²⁴	2007–09	276	70%	33 (15)	92%	75%
Brazilian registry ²⁵	2008–13	178	77%	46 (15)	93%	74%
Saudi Arabian registry ²⁶	2009–12	107	63%	36 (9)	72%	57%

Data are mean (SD). *Inclusion age was restricted to 16–65 years. †Inclusion age was restricted to 18–70 year. ‡Inclusion age was 18 years or older. §Inclusion age older than 3 months, only 16% of the patients were incident. ¶Inclusion age in inclusion criteria not stated. ||Only idiopathic, heritable, and drug-associated pulmonary arterial hypertension.

Table 1: Data for the epidemiology and outcomes of pulmonary arterial hypertension reported from registries of various countries

15 per million adults. Hence, these disorders might affect about 35 000–100 000 individuals worldwide. Of note, these numbers do not include pulmonary arterial hypertension associated with congenital heart disease, schistosomiasis, and HIV infection, which play a prominent part in some areas of the world.

Pulmonary arterial hypertension associated with congenital heart disease

Congenital heart disease affects 0.8% of newborns, with some geographical variation.³⁹ With increasing survival, the prevalence of congenital heart disease is now about 0.5 per 1000 adults, and 4–6% of these patients develop pulmonary arterial hypertension.^{40,41} On the basis of these numbers, the estimated global prevalence of pulmonary arterial hypertension due to congenital heart disease is about 25 people per million in the general population. Patients with pulmonary arterial hypertension associated with congenital heart disease tend to have a better survival than patients with idiopathic pulmonary arterial hypertension.¹⁵ However, compared with patients with congenital heart disease without pulmonary arterial hypertension, patients with

congenital heart disease and pulmonary arterial hypertension are more symptomatic and have at least a doubled mortality risk.^{42,43}

Pulmonary arterial hypertension associated with infectious diseases

Present estimates suggest that more than 200 million people worldwide are infected with species of *Schistosoma*.⁴⁴ More than 85% of these patients live in Brazil and sub-Saharan Africa where the prevalence of infected individuals can exceed 50% in local populations.^{45,46} In Brazil, about 20–30% of patients treated in pulmonary hypertension clinics are infected with *Schistosoma mansoni*.^{25,47} Pulmonary arterial hypertension develops predominantly in patients with the hepatosplenic manifestation of the disease, which occurs in 4–8% of the patients with chronic schistosomiasis.^{44,48} A study from Brazil⁴⁷ reported a prevalence of pulmonary arterial hypertension of 4.6% in patients with hepatosplenic schistosomiasis. Mortality in patients with schistosomiasis-associated pulmonary arterial hypertension is similar to mortality in patients with idiopathic pulmonary arterial hypertension.⁴⁹ More

than 270 000 people have been estimated to be affected by schistosomiasis-associated pulmonary arterial hypertension worldwide.^{47,50,51} This number might grossly overestimate the true prevalence of schistosomiasis-associated pulmonary arterial hypertension because reliable data are not available for Africa (predominantly *Schistosoma mansoni* and *Schistosoma haematobium* species) and southeast Asia (predominantly *Schistosoma japonicum* species). In these parts of the world, schistosomiasis might be much less frequently associated with pulmonary arterial hypertension than in Brazil but robust evidence is absent.⁵²

The prevalence of pulmonary arterial hypertension in patients living with HIV infection is about 0.5% in Switzerland and France.^{53,54} In Europe and the Americas, HIV is a rare cause of pulmonary arterial hypertension, accounting for less than 10% of the patients enrolled in contemporary pulmonary arterial hypertension registries.^{12,14,18,25} Worldwide, about 30 million individuals are infected with HIV.⁵⁵ If 0.5% of these patients develop pulmonary arterial hypertension, the global prevalence of pulmonary arterial hypertension due to HIV infection would be about 150 000 cases, possibly making HIV the most common infectious cause of pulmonary arterial hypertension. The greatest burden of HIV lies in sub-Saharan Africa where more than 20 million people were affected in 2013, and HIV prevalence exceeded 10% in some areas.⁵⁵ Here, the prevalence of pulmonary arterial hypertension due to HIV might be up to 0.5 per 1000 individuals—ie, 20–50 times higher than the prevalence of all pulmonary arterial hypertension subtypes together in the developed world. However, these numbers are hypothetical and are not yet supported by published data.

Group 2—pulmonary hypertension due to left-sided heart disease

In 2013, the Global Burden of Disease Study reported 61.7 million cases of heart failure worldwide, which represented almost a doubling since 1990.⁵⁶ The leading causes of heart failure were ischaemic heart disease and hypertensive heart disease, followed by myocarditis, cardiomyopathies, and rheumatic heart disease.⁵⁶

On the basis of estimates from the Framingham Heart Study,⁵⁷ the lifetime risk of heart failure is about 20% in men and women living in the USA. Both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction affect predominantly elderly people.^{58–60} In Europe and the USA, more than 80% of patients with heart failure are 65 years of age and older.⁶¹ Over the past 30 years, survival has improved for patients with heart failure and reduced ejection fraction but not for patients with heart failure and preserved ejection fraction.^{58,62–64} The number of elderly patients diagnosed with heart failure is steadily growing, which is due not only to the rapid global rise in the number of people older than 65 years, but also due to the increasing

physician awareness of the disease, especially with respect to heart failure with preserved ejection fraction.^{57,63,65}

Postcapillary pulmonary hypertension, either isolated or combined with a precapillary component,^{2,66} is a frequent complication of heart failure with preserved ejection fraction or with reduced ejection fraction, affecting at least 50% of these patients (table 2). In both populations, the development of pulmonary hypertension is associated with right ventricular dysfunction and at least a doubled mortality risk (table 2).^{59,60,67,71,77}

The pandemic of left-sided heart disease is not confined to high-income countries but has already reached most parts of Asia, Africa, and Latin America.^{78,79} Recent studies from sub-Saharan Africa^{80–85} showed that patients admitted to the hospital for treatment of heart failure were younger than patients in the developed world but risk factors and underlying diseases were becoming similar, with hypertension being the most frequent underlying cause. Data from the Heart of Soweto Cohort⁸⁶ suggest that pulmonary hypertension might be common in Africans living in an urban environment. From 5328 de-novo presentations to a single tertiary referral centre in South Africa, 2505 cases presented with heart failure and 697 (28%) were noted to have echocardiographic signs suggestive of pulmonary hypertension.⁸⁶ Apart from concurrent left-sided heart disease (213 [31%] of 697 cases), several contributors to pulmonary hypertension were noted, including 179 (26%) cases of tuberculosis or chronic obstructive pulmonary disease (COPD) and 141 cases (20%) of suspected pulmonary arterial hypertension. In these cohorts, the presence of echocardiographic signs suggestive of pulmonary hypertension was a strong and independent predictor of mortality.^{80,87}

Aortic stenosis

The prevalence of aortic stenosis increases with age. In a population-based study from Norway,⁸⁸ the prevalence of aortic stenosis was 1.3% in individuals aged 60–69 years and 9.8% in those who were 80–90 years old. The prevalence of severe aortic stenosis needing surgery was about 2% in the 80–90 year olds.⁸⁸ Based on Medicare data,⁸⁹ the adjusted incidence rates of patients 75–84 years old undergoing aortic valve replacement surgery increased from 125 per 100 000 in 1999 to 168 per 100 000 in 2011; the respective adjusted incidence rates of patients 85 years or older undergoing aortic valve replacement surgery increased from 48 per 100 000 in 1999 to 91 per 100 000 in 2011, indicating aortic stenosis is becoming an increasingly relevant problem, particularly in ageing populations.

Several studies indicate that 50–70% of patients with severe aortic stenosis develop pulmonary hypertension and that the presence of pulmonary hypertension is associated with about a doubled increase in mortality risk (table 2).^{70,72–76}

Overall, the left-sided heart diseases described previously affect mainly elderly people with a lifetime risk in ageing populations of 20% or higher. Based on the

	Year of inclusion	Number of participants	Proportion of females (%)	Age (years)	Predominant population	Proportion with pulmonary hypertension (%)	Effect of pulmonary hypertension on survival
Ghio et al; Italy ⁶⁷	1992–98	379	15%	51 (10)	Heart failure with reduced ejection fraction (left ventricular ejection fraction <35%)	62% by right heart catheter†	10% increase in risk of death with each 5 mm Hg increase in PAPm (p<0.001)
Grigioni et al; Italy ⁶⁸	1996–2003	196	27%	54 (9)	Heart failure with reduced ejection fraction (left ventricular ejection fraction 18–36%)	..	Pulmonary hypertension at time of diagnosis associated with a relative risk of 2.3 for acute heart failure or death (p<0.001)
Miller et al; Rochester, MN, USA ⁶⁹	2002–08	463	27%	57 (13)	Heart failure with reduced ejection fraction	73% by right heart catheter	Pulmonary hypertension at time of diagnosis associated with a hazard ratio of 2.3 for death (p<0.001), particularly in patients with a precapillary component
Gerges et al; Austria ⁷⁰	1996–2003	2351	..	63 (13)	Heart failure with preserved ejection fraction and heart failure with reduced ejection fraction	46% by right heart catheter (PAPm ≥25 mm Hg)	Presence of pulmonary hypertension associated with significantly worse survival, p<0.001, particularly in patients with combined precapillary and postcapillary pulmonary hypertension
Lam et al; Olmsted County, MN, USA ⁵⁹	2003–05	244	55%	76 (13)	Heart failure with preserved ejection fraction (left ventricular ejection fraction ≥50%)	PAPs >35 mm Hg by echocardiography, in 83% of the patients	Hazard ratio 1.3 per 10 mm Hg increase in PAPs (p<0.001)
Bursi et al; Olmsted County, MN, USA ⁷¹	2003–10	1049	51%	76 (13)	Heart failure with preserved ejection fraction and heart failure with reduced ejection fraction	PAPs >35 mm Hg by echocardiography in 79% of the patients	PAPs significantly associated with mortality (p<0.001)
Kjaergaard et al; Denmark ⁶⁰	..	388	40%	75 (66–82)	Heart failure with preserved ejection fraction and heart failure with reduced ejection fraction	PAPs ≥39 mm Hg by echocardiography in 49% of the patients	9% increase in mortality per 5 mm Hg increase in PAPs (p<0.001)
Barbash et al; Washington, DC, USA ⁷²	2007–13	415	53%	84 (8)	Aortic stenosis, patients undergoing transcatheter aortic valve replacement	PAPs >50 mm Hg by echocardiography in 59% of the patients, 35% had signs of right ventricular failure	30 day mortality 14.5% in patients with PAPs >50 mm Hg vs 7.4% in patients with PAPs ≤50 mm Hg (p=0.02); 1 year mortality 30.8% in patients with PAPs >50 mm Hg vs 21% in patients with PAPs ≤50 mm Hg (p=0.02)
Cam et al; Cleveland, OH, USA ⁷³	2004–09	317	47%	PAPm >25 mm Hg, 71 (12), PAPm>35 mm Hg, 75 (10)	Aortic stenosis, right heart catheter before aortic valve replacement	PAPm >25 mm Hg in 47% of the patients; PAPm >35 mm Hg in 11% of the patients	..
Roselli et al; Cleveland, OH, USA ⁷⁴	1996–2010	2385	45%	74 (10)	Aortic stenosis, echo assessment of pulmonary hypertension before aortic valve replacement	74% echocardiography signs of pulmonary hypertension, 50% of patients had PAPs 35–50 mm Hg; 24% of patients had PAPs >50 mm Hg	5 year survival, 85% for PAPs <35 mm Hg, 77% for PAPs 35–50 mm Hg, 62% for PAPs >50 mm Hg (p<0.001)
Ben-Dor et al; Washington, DC, USA ⁷⁵	2007–09	509	About 25%	About 82 (..)	Aortic stenosis	68% had signs of pulmonary hypertension by echocardiography, 34% of patients had PAPs 40–59 mm Hg; another 34% of patients had PAPs ≥60 mm Hg	In a median follow-up of 202 days, mortality was 21.7% in PAPs <40 mm Hg, 39.3% in PAPs 40–49 mm, and 49.1% in PAPs ≥50 mm Hg in the (p<0.001)
O'Sullivan et al; Switzerland ⁷⁶	2007–12	433	55%	82 (5)	Aortic stenosis	PAPm ≥25 mm Hg in 75% of the patients	Higher 1 year mortality in patients with pulmonary hypertension, especially for combined precapillary and postcapillary disease compared with no pulmonary hypertension; hazard ratio 3.28; p=0.005

Data are mean (SD) or median (IQR). *Patients assessed for heart transplant. †Pulmonary hypertension was defined as PAPm >20 mm Hg. PAPm=mean pulmonary artery pressure. PAPs=systolic pulmonary artery pressure.

Table 2: Studies assessing the prevalence and effect of pulmonary hypertension in heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, and valvular heart disease by country and institution

data in table 2, the lifetime risk of developing pulmonary hypertension due to left-sided heart disease may be 10% or higher. About 600 million people on the planet are

>65 years old.⁹⁰ Hence, pulmonary hypertension due to left-sided heart disease might affect 30 million individuals older than 65 years old worldwide.

Rheumatic heart disease

Post-streptococcal rheumatic fever has become rare in developed countries but remains a leading cause of heart disease in the developing world, estimated to affect about 15 million individuals worldwide.⁹¹ The Global Rheumatic Heart Disease Registry,⁹² a prospective, international, multicentre, hospital-based study of characteristics, management, and outcome of rheumatic heart disease that enrolled 3323 participants from low-income and middle-income countries, showed that rheumatic heart disease affects predominantly young women, causes multivalvular disease and is associated with high rates of complications, such as heart failure. Echocardiographic signs suggestive of pulmonary hypertension were reported in 28·8% of these patients.⁹²

In a study from southern India, the age-adjusted prevalence of rheumatic heart disease was 9·7 per 1000 and the mean age of the affected patients was 33 years.⁹³ Echocardiographic signs suggestive of pulmonary hypertension were noted in 52% of these patients.⁹³ Similar numbers were reported from Africa, where 53% of patients with newly diagnosed rheumatic heart disease presented with echocardiographic signs of pulmonary hypertension.⁹⁴ Pulmonary hypertension and right ventricular failure have independent, incremental prognostic value and frequently exclude candidacy for surgery in patients with advanced rheumatic heart valve disease.⁹⁵ Additionally, pulmonary hypertension complicates pregnancy in women with operated or not operated rheumatic heart disease contributing to increased maternal and fetal mortality.⁹⁶

These data indicate that rheumatic heart disease is a major cause of pulmonary hypertension in some parts of the world, probably affecting between 3 million and 4 million individuals worldwide. However, these numbers need to be interpreted with caution because they are based almost entirely on echocardiographic assessments.

Group 3—pulmonary hypertension due to lung disease or hypoxia

Chronic obstructive pulmonary disease

COPD is the most common non-infectious lung disease worldwide.⁹⁷ According to the Burden of Obstructive Lung Disease Initiative,⁹⁸ the global prevalence of COPD GOLD stage II or higher is about 10% in adults 40 years or older and about 20% in adults 70 years or older.⁹⁹ Similar numbers have been reported from other studies implemented in Latin America, the Middle East, Africa, and Asia.^{100–103} A systematic review and meta-analysis of epidemiological studies of COPD published between 1990 and 2004 calculated a global pooled COPD prevalence in adults 40 years and older of 9–10% (GOLD \geq stage II, 5·5%), which increased to 14·2% in individuals aged 65 years or more.¹⁰⁴

The prevalence of pulmonary hypertension in patients with COPD is difficult to estimate as most right heart catheter-based data come from highly

selected populations of patients with advanced disease referred for evaluation of lung volume reduction surgery or lung transplantation. In these patient populations, the prevalence of pulmonary hypertension ranged from 30% to 50% (table 3).^{106,111,112,116} Some of the available population-based studies were completed more than 10 years ago and defined pulmonary hypertension as a mean pulmonary artery pressure of more than 20 mm Hg.^{105,106,113–115} The reported estimates of pulmonary hypertension prevalence (defined by a mean pulmonary artery pressure \geq 25 mm Hg) in patients with COPD has ranged from 18% to 50% (table 3).^{107–110,111,112,116} Pulmonary hypertension is usually mild in this patient population. The proportion of patients with COPD and more severe pulmonary hypertension indicated by a mean pulmonary artery pressure of 35 mm Hg or more, ranges from 2% to 14% (table 3).^{106,108,110,112–114,116} Severe pulmonary hypertension in patients with COPD is often associated with other potential causes, such as left-sided heart disease or chronic thromboembolic disease.¹¹³

Irrespective of the populations under study, the presence of pulmonary hypertension was associated with more severe symptoms, reduced exercise capacity, and more frequent hospital admissions than in patients without pulmonary hypertension. Mortality was about twice as high in patients with COPD and pulmonary hypertension as in patients with COPD and normal pulmonary artery pressure, even when adjusted for other variables known to affect outcome, such as lung function variables, blood gases, or age (table 3).^{105,113,115,116}

Assuming a global COPD prevalence (disease severity stage II or higher) of 10% in the 2·5 billion adults that are 40 years or older and estimating a pulmonary hypertension prevalence of 10% in these patients,¹¹⁷ about 25 million individuals aged 40 years or older might be affected worldwide by pulmonary hypertension due to COPD. Again, these numbers have to be interpreted with caution as they are based on assumptions rather than population-based studies.

Interstitial lung disease

Among the interstitial lung diseases, idiopathic pulmonary fibrosis is by far the most widely studied, including idiopathic pulmonary fibrosis with the presence of pulmonary hypertension. The reported prevalence of idiopathic pulmonary fibrosis ranges from 2·9 per 100 000 in Japan to 500 per 100 000 in the USA.^{118–120} Idiopathic pulmonary fibrosis occurs predominantly in individuals older than 60 years and the global prevalence is increasing.^{120–122}

Estimating the global prevalence of pulmonary hypertension in patients with idiopathic pulmonary fibrosis is hampered by similar restrictions to patients with COPD. Most catheter-based studies have been done in patients with advanced disease referred for evaluation of lung transplantation. In these studies, the prevalence

	Year of inclusion	Number of participants	Proportion of females (%)	Age (years)	Lung function: FEV ₁ /FVC, or predicted FEV ₁ (%)	Arterial blood gases: PaO ₂ , PaCO ₂ (mm Hg)	Patients with pulmonary hypertension (%)	Effect of pulmonary hypertension on survival
Weitzenblum et al; France ¹⁰⁵	1968–72	175	1%	60 (range 36–82)	FEV ₁ /FVC 40% (11%)	63 (10), 40 (6)	PAPm >20 mm Hg in 35.4%, PAPm >30 mm Hg in 9.7%	4 year survival 71.8% when PAPm <20 mm Hg vs 49.4% when PAPm >20 mm Hg (p<0.01)
Scharf et al; USA ¹⁰⁶	..	120	39%	66 (6), evaluation for lung volume reduction surgery	Predicted FEV ₁ 27% (7%)	66 (10), 42 (6)	PAPm >20 mm Hg in 91%, PAPm >35 mm Hg in 5%	..
Sims et al; USA ¹⁰⁷	1991–2003	362	53%	56 (5), evaluation for transplantation	Predicted FEV ₁ 20% (5%)	62 (12), 51 (10) pulmonary hypertension group	PAPm ≥25 mm Hg and PAWP ≤15 mm Hg in 23%	..
Minai et al; USA ¹⁰⁸	..	797	35%	67 (6)	Predicted FEV ₁ 26% (7%) (pulmonary hypertension group)	61 (9), 43 (6) pulmonary hypertension group	PAPm ≥25 mm Hg in 38%, severe pulmonary hypertension in 2.2%*	..
Cuttica et al; USA ¹⁰⁹	1997–2006	4930	54%	56 (6), pulmonary hypertension group, evaluation for transplantation	Predicted FEV ₁ 22% (10%)	..	PAPm ≥25 mm Hg and PAWP ≤15 mm Hg in 30%	Adjusted hazard ratio for death associated with the presence of pulmonary hypertension 1.27 (95% CI 1.04–1.55)
Portillo et al; Spain ¹¹⁰	..	139	4%	63 (8)	Predicted FEV ₁ 41% (16%)	69 (12), 40 (6)	PAPm ≥25 mm Hg in 18%, PAPm ≥35 mm Hg in 3%	..
Vizza et al; Italy ¹¹¹	1993–1995	168	62%	54 (6), evaluation for transplantation	Predicted FEV ₁ 20% (6%)	59 (12), 46 (11)	PAPm ≥25 mm Hg in about 50%	..
Thabut et al; France ¹¹²	1988–2002	215	21.4%	55 (..), evaluation for transplantation or LVRS	Predicted FEV ₁ 24.3% (..)	66 (13), 41 (7) lung volume reduction surgery cohort	PAPm >25 mm Hg in 50.2%, PAPm >35 mm Hg in 13.5%	..
Chauat et al; France ^{113,114}	1990–2002	998	10%	67 (62–68)	Predicted FEV ₁ 50% (44–56)	46 (41–53), 32 (28–37)	PAPm >20 mm Hg in about 50%, PAPm ≥35 mm Hg in 5.8%, PAPm ≥40 mm Hg in 1%	3 year survival about 88% in patients with PAPm <20 mm Hg vs about 38% in patients with PAPm ≥40 mm Hg (p<0.01)
Oswald-Mammosser et al; France ¹¹⁵	1976–1992	84	10.7%	63 (..)	FEV ₁ /FVC 36% (11%)	52 (5), 45 (8)	PAPm >20 mm Hg in 77%, PAPm >30 mm Hg in 37%	5 year survival 62.2% when PAPm ≤25 mm Hg vs 36.3% when PAPm >25 mm Hg (p<0.001)
Andersen et al; Denmark ¹¹⁶	1991–2010	409	61%	54 (7), evaluation for transplantation	Predicted FEV 23% (7%)	63 (12), 49 (11) pulmonary hypertension group	PAPm ≥25 mm Hg in 35.7%, PAPm ≥35 mm Hg in 3.9%, PAPm ≥40 mm Hg in 1.5%	5 year survival 63% when PAPm <25 mm Hg vs 37% when PAPm ≥25 mm Hg (p=0.016)

Data are mean (SD) or median (IQR). FEV₁=forced expiratory volume in the first second. FVC=forced vital capacity. PaO₂=partial pressure of oxygen in arterial blood. PaCO₂=partial pressure of carbon dioxide in arterial blood. PAPm=mean pulmonary arterial pressure. PAWP=pulmonary arterial wedge pressure. *Severe pulmonary was defined by a PAPm ≥35 mm Hg or a PAPm ≥25 mm Hg with pulmonary vascular resistance >480 dyn·s·cm⁻⁵ or cardiac index <2 L/min per m².

Table 3: Right heart catheter-based studies on pulmonary hypertension in patients with chronic obstructive pulmonary disease

of pulmonary hypertension in patients with idiopathic pulmonary fibrosis ranged from 29% to 77% (table 4).^{123,125,126,127} In two cohorts of patients with idiopathic pulmonary fibrosis from Japan,^{128,129} the prevalence of pulmonary hypertension was 8% and 15%. In a clinical trial with ambrisentan in patients with idiopathic pulmonary fibrosis with mild or moderate lung volume restriction, the prevalence of precapillary pulmonary hypertension was 14% and 5% of patients had postcapillary pulmonary hypertension.¹³¹

Cross-sectional studies might, however, underestimate the true lifetime risk of pulmonary hypertension in this

patient population. This theory is supported by the work of Nathan and colleagues¹²⁷ who completed a longitudinal assessment of pulmonary hypertension in patients with idiopathic pulmonary fibrosis listed for lung transplantation. At the time of admission to the waiting list, 39% of the patients had pulmonary hypertension. An average of 8 months later, at the time of transplant, this figure had risen to 86%.¹²⁷ By contrast, no significant change was noted in the mean pulmonary artery pressure after 12 months in the clinical trial with ambrisentan in patients with mild or moderate lung volume restriction.¹³¹

	Year of inclusion	Number of participants	Proportion of females (%)	Age (years)	Lung function: predicted FVC (%)	Arterial blood gases: PaO ₂ , PaCO ₂ (mm Hg)	Patients with pulmonary hypertension (%)	Effect of pulmonary hypertension on survival
Idiopathic pulmonary fibrosis								
Lettieri et al, USA ¹²³	1998–2004	79	36%*	55 (4)* transplantation evaluation	49% (11%)*	..	PAPm ≥25 mm Hg in 31.6%	1 year survival 95% in patients with PAPm <25 mm Hg vs 71% in patients with PAPm ≥25 mm Hg (p<0.001)
Patel et al, USA ¹²⁴	2004–05	376	PAPm ≥25 mm Hg and PAWP ≤15 mm Hg in 28%	..
Shorr et al, USA ¹²⁵	1995–2004	2525	37%*	53 (9) transplantation evaluation	48% (17%)*	.. (-), 41 (7)*	PAPm ≥25 mm Hg in 46.1%, PAPm >40 mm Hg in 9.1%	..
Rivera-Lebron et al, USA ¹²⁶	2005–10	135	27%	58 (7) transplantation evaluation	51% (15%)	..	PAPm ≥25 mm Hg and PAWP ≤15 mm Hg in 29%	Adjusted hazard ratio for each 10 mm Hg increase in PAPm, 1.3 (95% CI 1.0–1.8)
Nathan et al, USA ¹²⁷	2000–05	44	22%	57 (7) transplantation evaluation	50% (16%)	..	Baseline PAPm ≥25 mm Hg in 38.6%; in 86.4% pulmonary hypertension at time of transplantation	..
Hamada et al, Japan ¹²⁸	1991–2004	78	14%	63 (9)*	71% (20%)*	67 (12),* 37 (3)*	PAPm ≥25 mm Hg in 8.1%	5 year survival 62% with PAPm <17 mm Hg vs 17% with PAPm >17 mm Hg (p<0.001)
Kimura et al, Japan ¹²⁹	2001–09	101	16%	65 (8)	70% (20%)	80 (12), .. (-)	14.9% had a PAPm >25 mm Hg; 3.9% had a PAPm >35 mm Hg	3 year survival about 60% in patients with PAPm <25 mm Hg vs 20% in patients with PAPm ≥25 mm Hg (p<0.001)
Glaser et al, Germany ¹³⁰	2004–11	135	39%	64 (56–72)	56% (43–67%; (pulmonary hypertension group)	..	PAPm ≥25 mm Hg in 54%	Hazard ratio for death associated with the presence of pulmonary hypertension 1.07 (95% CI 1.04–1.11)
Raghu et al, ARTEMIS-IPF study (global) ¹³¹	2009–10	488	31%	68 (6)*	67% (12%)	..	PAPm ≥25 mm Hg and PAWP ≤15 mm Hg in 14%	..
Diffuse parenchymal lung disease								
Corte et al, UK ¹³²	1987–07	66	42%	57 (12) transplantation evaluation	68% (23%)	66 (17), 39 (7)	PAPm ≥25 mm Hg in 76%; PAPm ≥35 mm Hg in 42%	Odds ratio for mortality 3.0 when PAPm ≥25 mm Hg (p=0.18)
Various interstitial lung diseases								
Alhamad et al, Saudi Arabia ¹³³	2009–12	144	71%	59 (15)*	59% (20%)	..	PAPm ≥25 mm Hg in 29%	..
Data are mean (SD) or median (IQR). FVC=forced vital capacity. PaO ₂ =partial pressure of oxygen in arterial blood. PaCO ₂ =partial pressure of carbon dioxide in arterial blood. PAPm=mean pulmonary arterial pressure. PAWP=pulmonary artery wedge pressure. *Patients with pulmonary hypertension.								
Table 4: Right heart catheter-based studies on pulmonary hypertension in patients with interstitial lung disease								

Assuming an idiopathic pulmonary fibrosis prevalence of 500 per 100 000 individuals 65 years or older, as suggested by Raghu and colleagues,¹²⁰ and a conservative estimate of pulmonary hypertension of 10% among these patients, the global figure of patients affected by pulmonary hypertension due to idiopathic pulmonary fibrosis would be about 300 000 individuals older than 65 years. These assumptions do not include other forms of interstitial lung disease, which might also be complicated by the development of pulmonary hypertension.

The effect of pulmonary hypertension on the survival of patients with idiopathic pulmonary fibrosis is substantial.

Several studies have shown that the mortality risk was about three times higher in patients with idiopathic pulmonary fibrosis and pulmonary hypertension compared with patients with idiopathic pulmonary fibrosis without pulmonary hypertension.^{123,128,129}

Pulmonary hypertension due to high altitude

More than 140 million people live above 2500 m from sea level and are exposed to chronic hypoxia, particularly in the Andes and Himalayas.¹³⁴ Some of these individuals develop symptomatic pulmonary hypertension,^{135,136} but because of the scarcity of systematic studies, the

prevalence of pulmonary hypertension in people living at high altitude is difficult to estimate. The same is true for the clinical implications because pulmonary hypertension is a physiological result of exposure to chronic hypoxia, at least to some extent.^{137,138} Pulmonary hypertension proportional to hypoxaemia and haematocrit is a complication of chronic mountain sickness.¹³⁷ High altitude pulmonary hypertension might affect a substantial number of individuals but insufficient data are available to estimate its clinical burden.

Group 4—chronic thromboembolic pulmonary hypertension

In a detailed review on chronic thromboembolic pulmonary hypertension,¹³⁹ the incidence and prevalence of this disease are largely unknown. Studies in patients who survived an episode of acute pulmonary embolism have reported that 1.0–8.8% of them eventually developed chronic thromboembolic pulmonary hypertension.^{140–143} The higher estimates are likely to be an over-representation. In the USA, the annual incidence of acute pulmonary embolism is about 100 in 100 000 adults, increasing with age.¹⁴⁴ Individuals aged 25–35 years have a pulmonary embolism incidence of 30 per 100 000 per year, whereas the respective rates in individuals aged 70–79 years are 300–500 per 100 000 per year.¹⁴⁴ If 1% of these patients develop chronic thromboembolic pulmonary hypertension, the expected annual incidence would be at least one in 100 000 adults. In the USA, this number would result in about 2500 new cases per year. By contrast, the number of patients undergoing pulmonary endarterectomy (the preferred treatment for chronic thromboembolic pulmonary hypertension) in the USA is about ten times lower.¹⁴⁵

Estimates of the prevalence of chronic thromboembolic pulmonary hypertension are further restricted by the fact that about 25% of these patients have no history of acute pulmonary embolism.¹⁴⁶ Two pulmonary hypertension registries, one from Spain and one from the UK,^{18,147} have assessed the incidence of patients with an established diagnosis of chronic thromboembolic

pulmonary hypertension. These registries reported annual chronic thromboembolic pulmonary hypertension incidence rates of 0.9 per million in Spain and 1.75 per million in the UK—ie, about a tenth of that expected from the assumptions made previously in this Review (table 5).^{18,147} Recent data from Germany reported an annual chronic thromboembolic pulmonary hypertension incidence of 4.0 per million adults per year (Hoeper MM, unpublished data). The global prevalence of chronic thromboembolic pulmonary hypertension is difficult to calculate as many of these patients undergo pulmonary endarterectomy surgery (at least in developed countries), which is curative in many cases.^{145,146,148}

Group 5—pulmonary hypertension with unclear multifactorial mechanisms

Group 5 comprises various diseases that are often accompanied by pulmonary hypertension, which is characterised by unclear and multifactorial underlying mechanisms. One example is chronic renal failure, in which pulmonary hypertension is being increasingly recognised as an important medical issue. Echocardiography-based estimates of pulmonary hypertension prevalence in patients with end-stage renal disease range from 20% to 50%.^{149–151} The pathogenesis of pulmonary hypertension in these patients is complex. Most patients with end-stage renal disease have various comorbidities, including a high rate of systolic or diastolic heart failure. Anaemia, fluid overload, and arteriovenous fistulae might be additional factors contributing to the development of pulmonary hypertension.^{149,150}

Pulmonary hypertension is also identified in patients with systemic disorders such as sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, and neurofibromatosis, as well as in metabolic disorders such as Gaucher's disease or glycogen storage disease, and in patients with haemoglobinopathies.^{152–159} Although pulmonary hypertension is common in some of these diseases, most of them do not contribute substantially to the

	Year of inclusion	Number of participants (enrolled)	Proportion of females (%)	Age (years)	Estimated incidence (per 1 million adults)	Estimated prevalence (per 1 million adults)	1 year survival	3 year survival
Spanish registry ¹⁸	1998–2008	162	60%	61 (15)	0.9	3.2	93% (mostly prevalent patients)	75% (mostly prevalent patients)
UK ¹⁴⁷	2001–06	469	56%*	60 (14)*	1.75	..	82%*	70%*
Germany†	2014	272	49%	68 (–)	4.0
UK National Audit ^{22‡}	2009–14	684 (operated), 501 (non-operated)	53% (operated), 48% (non-operated)	69 (–; operated), 63 (–; non-operated)	..	2.2 (for all chronic thromboembolic pulmonary hypertension)	98% (operated), 88% (non-operated)	90% (operated), 70% (non-operated)

Data are mean (SD). *Nonsurgical cases. †Hoeper MM, unpublished data. ‡Participants were patients with chronic thromboembolic pulmonary hypertension who either had an operation or did not.

Table 5: Chronic thromboembolic pulmonary hypertension

global burden of pulmonary hypertension because of their rarity. An important exception is pulmonary hypertension associated with haemoglobinopathies.

Pulmonary hypertension associated with haemoglobinopathies

According to WHO estimates, 20–25 million individuals worldwide are affected by homozygous sickle cell disease, most of them living in sub-Saharan Africa, the Middle East, and India.^{160–163} Echocardiographic signs suggestive of pulmonary hypertension are reported in 20–40% of these patients.^{160,164,165} These numbers need to be interpreted with great caution as several studies reported that the positive predictive value of echocardiography is particularly low in this patient population.^{165–167} The prevalence of pulmonary hypertension in patients with sickle cell disease confirmed by right heart catheterisation was 6–10%,^{165–167} resulting in an estimated 1.0–2.5 million individuals affected by pulmonary hypertension due to sickle cell disease worldwide. Most of these patients show a unique haemodynamic profile with mildly elevated pulmonary artery pressures, elevated right-sided and left-sided filling pressures, high cardiac output, and a normal or mildly elevated pulmonary vascular resistance.^{165,168} Hence, pulmonary hypertension in patients with sickle cell disease most often presents in a state of high cardiac output failure rather than a state of low cardiac output as

usually encountered in patients with pulmonary arterial hypertension,¹⁶⁹ although a few patients do have low cardiac output.

The prevalence of pulmonary hypertension in patients with sickle cell disease increases with age and is associated with more pronounced anaemia, haemolysis, and renal dysfunction.^{164,165,167} Additionally, the presence of pulmonary hypertension in patients with sickle cell disease is associated with impaired functional capacity and an increased risk of death, which was reported to be at least twice as high as in patients with sickle cell disease without pulmonary hypertension.^{164–168,170}

Thalassaemia and spherocytosis are common haemoglobinopathies, but the associated risk of pulmonary hypertension is unclear. Echocardiographic signs suggestive of pulmonary hypertension have been reported in 10–79% of patients with β -thalassaemia,^{171,172} but the catheter-based pulmonary hypertension prevalence based on a multicentre cross-sectional study was 2.1%.¹⁷³ Some reports suggest that pulmonary hypertension is more common in patients with thalassaemia intermedia,^{173–175} although pulmonary hypertension seems rare in well transfused patients with thalassaemia major.^{176,177} Pulmonary hypertension seems to be rare in patients with spherocytosis and seems to be linked to splenectomy and subsequent pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension rather than to the underlying disease.^{178,179}

	Heart failure (associated pulmonary hypertension)	Moderate to severe chronic obstructive pulmonary disease* (associated pulmonary hypertension)	HIV (associated pulmonary hypertension)	Schistosomiasis (associated pulmonary hypertension)	Rheumatic heart disease (associated pulmonary hypertension)	Sickle cell disease (associated pulmonary hypertension)
Worldwide	61 million (30.0 million)	250 million (25 million)	30.0 million (150 000)	200 million (unclear, except for some countries in Latin America)	15.0 million (3.75 million)	20.0 million (2 million)
Europe, Australia, and New Zealand	8 million (4.0 million)	40 million (4 million)	1.0 million (5000)	Rare, only by travel and migration (rare)	Rare, except for the Indigenous populations of Australia and New Zealand (..)	100 000 (10 000)
North America	7 million (3.5 million)	30 million (3 million)	1.1 million (5500)	Rare, only by travel and migration (..)	Rare (..)	80 000 (8000)
Latin America and the Caribbean	5 million (2.5 million)	20 million (2 million)	1.6 million (8000)	10 million (13 000)	800 000 (200 000)	100 000 (10 000)
Asia including Oceania (except Australia and New Zealand)	30 million (15.0 million)	110 million (11 million)	6.0 million (30 000)	10 million (unclear, probably rare)	6.5 million (1.63 million)	7.5 million, mostly India (750 000, mostly India)
Africa (except northern Africa)	8 million (4.0 million)	30 million (3 million)	20.0 million (100 000)	170 million (unclear, probably rare)	6.5 million (1.3 million)	12.0 million (1.2 million)
Northern Africa and Middle East	5 million (2.5 million)	20 million (2 million)	0.4 million (2000)	10 million (unclear, probably rare)	1.0 million (250 000)	0.5 million (50 000)

*Moderate to severe was not used uniformly in all studies but usually refers to GOLD II–IV.

Table 6: Crude estimates of the global and regional numbers of patients with pulmonary hypertension associated with the most frequent underlying disorders

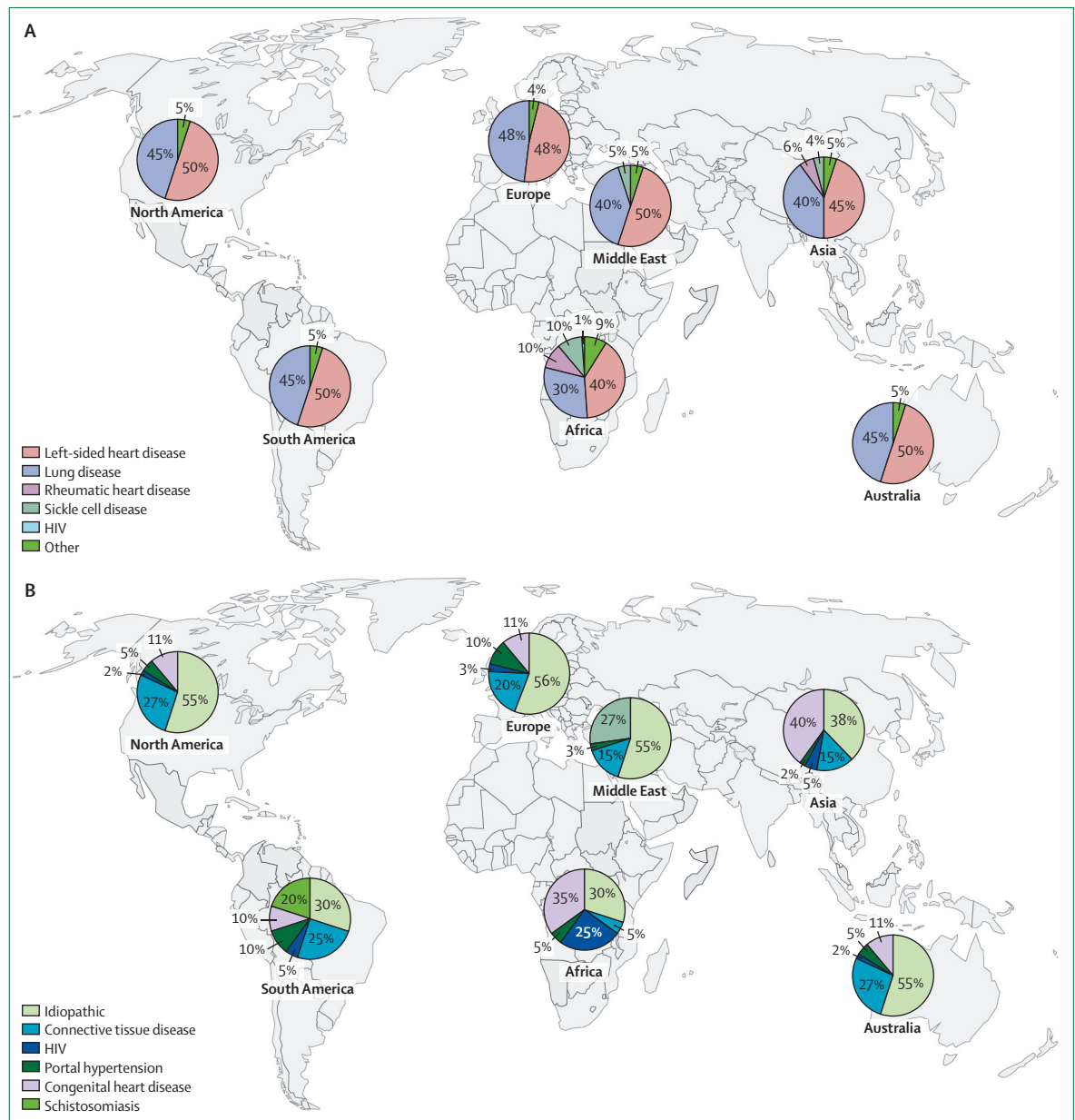


Figure 2: Estimated global distribution of the most prevalent forms of (A) pulmonary hypertension and (B) pulmonary arterial hypertension

Interpretation should be done with caution as most of the underlying evidence has been derived from populations at risk for pulmonary hypertension and echocardiography data rather than from population-based studies involving right heart catheterisation. Data from the developing world are particularly sparse. Additionally, variations exist within the world regions. In Latin America, for instance, schistosomiasis is highly prevalent in Brazil, Venezuela, and the Caribbean, but not in other countries. Schistosomiasis is also prevalent in sub-Saharan Africa and Southeast Asia, but there is almost no data on the association between schistosomiasis and pulmonary arterial hypertension from these areas. HIV is not evenly distributed in Africa and is particularly frequent in some areas of sub-Saharan Africa.

Limitations of studies of pulmonary hypertension

The epidemiology of pulmonary hypertension is much more difficult to study than the epidemiology of systemic hypertension because a reliable diagnosis requires right heart catheterisation, which is an invasive procedure. Therefore, large-scale population-based studies have to rely on echocardiography because invasive tests for epidemiological studies would be neither ethical nor

feasible. The interpretation of these data must take into account that echocardiography is not a reliable method to diagnose pulmonary hypertension.

Several catheter-based studies have been done in patients at risk for pulmonary arterial hypertension and in patients with left-sided heart disease and chronic lung disease. The results of these studies have been largely consistent, therefore confirming each other and also to a large extent, confirming studies on the basis of echocardiography,

indicating some reliability and reproducibility of the available data (tables 2–4). Patients assessed by right heart catheterisation represent those with symptoms or some indication for evaluation, so that there are very few true screening studies of pulmonary hypertension. Most studies come from academic centres offering advanced treatments, such as transplantation, so that the characteristics of the patients under study might not be generalisable to the population at large. Additionally, almost all studies on the prevalence of pulmonary hypertension were cross-sectional by design. Longitudinal studies are needed to assess the true lifetime risk of various disorders associated with pulmonary hypertension.

More uncertainties come from those types of pulmonary hypertension that occur predominantly in lesser-developed parts of the world, such as those reported in patients with schistosomiasis, HIV infection, rheumatic fever, or sickle cell disease. Any estimates of the incidence, prevalence, and effect of these forms of pulmonary hypertension have to be interpreted with great caution. The same is true for prevalence estimates of major diseases, such as left-sided heart failure and lung disease in the developing world, which are often based on clinical symptoms alone rather than on validated diagnostic tests.

Despite these uncertainties, a consistent finding of almost all studies was the observation that the development of pulmonary hypertension is associated with worsening symptoms and shortened survival, independent of the underlying disease. The causes and mechanisms leading to death are enigmatic. Whether pulmonary hypertension is causative for adverse outcomes in most heart and lung disease is not clear; attempts to treat pulmonary hypertension in these disorders have not resulted in clinical benefit. Therefore, patients might die with pulmonary hypertension rather than as a result of the disorder. In most of the diseases discussed in this Review, to what extent pulmonary hypertension and right heart failure contribute to excess mortality is unclear. Importantly, present pulmonary hypertension guidelines state that the use of pulmonary arterial hypertension approved treatments is not recommended in patients with pulmonary hypertension due to left-sided heart disease or lung disease.^{2,66}

Public health implications and conclusions

Pulmonary hypertension is an under-recognised global health issue and is by no means rare. In economically developed countries, left-sided heart disease and lung disease are by far the most common causes of pulmonary hypertension (table 6, figure 2). About 80% of patients with pulmonary hypertension live in the developing world, where heart disease and lung disease have become the most frequent causes of pulmonary hypertension, but other disorders such as schistosomiasis, rheumatic heart disease, HIV, or sickle cell disease continue to play an important part (table 6, figure 2). Hence, in industrialised countries, pulmonary hypertension affects

Search strategy and selection criteria

References for this Review were identified through searches of PubMed, until Aug 31, 2015, by use of various combinations of the terms “pulmonary hypertension”, “lung disease”, “heart failure”, “aortic stenosis”, “chronic obstructive lung disease”, “pulmonary fibrosis”, “left heart disease”, “renal disease”, human immunodeficiency virus”, “schistosomiasis”, “rheumatic heart disease”, “registry”, “high altitude”, “epidemiology”, “incidence”, “prevalence”, “mortality”, and “phenotype”. Relevant articles were identified by MMH and JSRG. These articles were retrieved in full and were reviewed for content. Additional relevant references cited in those articles were added, as were relevant references provided by the other authors. Articles published in English, French, Spanish, Portuguese, Chinese, and German were considered. All searches and data analyses were restricted to studies of adults. We focused primarily on studies with right heart catheterisation for the diagnosis of pulmonary hypertension but also considered studies in which the presence of pulmonary hypertension was estimated by echocardiography, especially in areas where a paucity of right heart catheterisation data was available and whenever large populations of more than 100 patients were studied.

mainly elderly people whereas mostly young people are diagnosed in the developing world. Preventive strategies and effective treatments have been or are being implemented for HIV infection, schistosomiasis, and rheumatic fever, which will affect the incidence of pulmonary hypertension associated with these disorders.

At the same time, an increase in the global prevalence of left-sided heart disease and lung disease will continue, and pulmonary hypertension associated with these disorders will be mainly driven by a worldwide increase in life expectancy. In 2015, about 600 million people globally were 65 years or older with a projected number of 700 million for 2020 and 1·6 billion for 2050.¹⁸⁰ For 2015, we estimate that up to 50–70 million individuals—almost 1% of all people—were affected by pulmonary hypertension worldwide. This figure is expected to rise continuously over the next few decades as the global population enlarges and ages. With increasing life expectancy, individuals who reach the age of 40 might have a lifetime risk of one in ten of developing pulmonary hypertension. This risk is similar to the one in ten lifetime risk of developing COPD,¹⁰⁴ or to the one in eight remaining lifetime risk for breast cancer in women of the same age.¹⁸¹

Globally, prevention strategies aimed at reducing smoking, particulate matter and household air pollution, hypertension, diabetes, and obesity will have a major role in reducing heart failure and lung disease, which might eventually contribute to reducing the prevalence of some forms of pulmonary hypertension.

Effective treatments have been developed for some of the rare forms of pulmonary hypertension, especially pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.^{139,182} No treatments directed at the pulmonary circulation have yet proven efficacious for most of the remaining much more frequent forms of pulmonary hypertension in which treatment is that of the underlying disease. Hence, clinical studies and registries are needed to further

elucidate the effect of pulmonary hypertension in the various conditions discussed in this Review and to establish whether preventive strategies and treatments targeting pulmonary hypertension will affect the morbidity and mortality that accompany this disorder.

Declaration of interests

RS received personal fees from Actelion, Bayer, GlaxoSmithKline, and Pfizer, outside of this Review. SMK received grants from NIH; non-financial support from American College of Chest Physicians and American Thoracic Society; personal fees from *European Respiratory Journal*; grants to his institution for continuing medical education from Actelion, United Therapeutics, Gilead, Merck, Lung Biotech, Ikaria, Pulmonary Hypertension Association, GeNO, and Bayer, outside of this Review; and grants to his institution for research from Actelion, Gilead, and GeNO, outside of this Review. MMH received personal fees from Actelion, Bayer, GlaxoSmithKline, and Pfizer. Z-CJ received personal fees from Actelion, Bayer, GlaxoSmithKline, and Pfizer. MH received grants and personal fees from Actelion, Bayer, GlaxoSmithKline, and Pfizer. JSRG received grants and personal fees from Actelion, Bayer, and GlaxoSmithKline, and United Therapeutics personal fees from Gilead, Novartis, and Pfizer, and grants from Amco, outside of this Review. KS-H and MI declare no competing interests.

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