Increasing Incidence and Prevalence of World Health Organization Groups 1 to 4 Pulmonary Hypertension

A Population-Based Cohort Study in Ontario, Canada

See Editorial by Mathai and Ryan

BACKGROUND: The World Health Organization recognizes 5 groups of pulmonary hypertension (PH), categorized by pathogenesis or comorbidity: 1-pulmonary arterial hypertension 2-left-heart disease, 3-lung disease and hypoxia 4-chronic thromboembolic disease, and 5-miscellaneous. The epidemiology of PH, apart from group 1, is largely unknown.

METHODS AND RESULTS: We describe incidence, prevalence, comorbidities, mortality and prescribing patterns for groups 1 to 4 PH from 1993 to 2012. Case definitions are based on hospitalizations and emergency department visits, using the Institute for Clinical Evaluative Sciences data, which comprises linked databases of universal coverage health service records for Ontario residents. This cohort included 50 529 patients with PH. The annual incidence of adult PH increased from 2003 to 2012 from 24.1 to 28.7 cases/100 000 population and the annual prevalence from 1993 to 2012 from 99.8 to 127.3 cases/100 000 population, respectively. The most common form of adult PH was group 2, alone (34.2%) or combined with group 3 PH (29.3%). A diagnosis of PH increased the 1-year standardized mortality ratio 7.2-fold. Mortality in adults with PH was 13.0%, 36.4%, and 62.4%, at 30 days, 1 year, and 5 years, respectively. Mortality was highest in groups 2 and 3 and lowest in group 1. PH was present in only 3.6% of people with left heart disease, 0.7% with lung disease, and 1.4% with thromboembolic disease, suggesting that PH is a relatively rare complication of these common diseases. Children (age<16 years) accounted for 3.6% of the cohort. In children group 1 PH was most common (65.2%), and 5-year mortality was lower (21.4%) than in adults. Group 1–specific PH therapies were increasingly prescribed over time and paradoxically were often used in patients who seemed to have group 2, PH based on diagnostic codes indicating left heart disease.

CONCLUSIONS: The incidence and prevalence of adult PH are increasing. Groups 2 and 3 are the most common and lethal forms of PH. This study identifies an emerging epidemic of PH that likely has substantial adverse health and economic implications.

D. Thiwanka Wijeratne, MD
Katherine Lajkosz, MSc
Susan B. Brogly, PhD
M. Diane Lougheed, MD
Li Jiang, MSc
Ahmad Housin, MD
David Barber, MSc
Ana Johnson, PhD
Katharine M. Doliszny, PhD
Stephen L. Archer, MD

Correspondence to: Stephen L. Archer, MD, Department of Medicine, Queen's University, Etherington Hall, Room 3041, 94 Stuart St, Kingston, ON K7L 3N6, Canada. E-mail stephen.archer@queensu.ca

Key Words: hypertension, pulmonary ■ heart diseases ■ lung diseases ■ comorbidity ■ hypoxia ■ incidence ■ prevalence

WHAT IS KNOWN

- The World Health Organization recognizes 5 groups of pulmonary hypertension (PH), categorized by pathogenesis or comorbidity.
- The epidemiology of PH, apart from group 1 disease (pulmonary arterial hypertension), is largely unknown and most data derive from specialized registries and referral programs, rather than from the population.

WHAT THE STUDY ADDS

- The incidence and prevalence of PH (all groups) are increasing over time.
- The most common form of adult PH is group 2 PH, occurring in isolation or in combination with group 3 disease.
- A diagnosis of any form of PH increases 1-year standardized mortality ratio 7.2-fold.

The World Health Organization (WHO) defines pulmonary hypertension (PH) as a hemodynamic condition in which the resting mean pulmonary artery pressure is ≥25 mm Hg.[1] The diagnosis of PH cannot be reliably made by echocardiography alone, because it is defined by hemodynamic criteria that mandate right heart catheterization (RHC). Although in theory the definition of PH requires RHC, in practice PH is usually identified by Doppler ultrasound, using the velocity of the tricuspid regurgitation jet to estimate the right ventricular systolic pressure and thereby infer pulmonary artery pressure. The WHO recognizes 5 PH groups:1 group 1 PH due to pulmonary arterial hypertension (PAH); group 2 PH related to left heart disease; group 3 PH due to lung disease and hypoxia; group 4 due to chronic thromboembolic PH; and group 5 which is a heterogeneous collection of PH syndromes (including sickle cell disease and sarcoidosis).

There are 5 classes of approved medications for group 1 PH (calcium channel blockers [CCB], prostanoids, endothelin receptor antagonists [ETRA], phosphodiesterase-5 inhibitors [PDE5i], and soluble guanylate cyclase stimulator) and 1 for group 4 PH (soluble guanylate cyclase stimulator). The average annual healthcare costs associated with PH in the United States from 2004 to 2010 was US $100 000/group 1 PH patient, $35 000 of which consisted of pharmacy costs.[2] In 2012, drug therapy for group 1 PH in Canada incurred substantial, albeit lower, annual costs/patient (US $4569±1544).[3] There are no PH-targeted medications approved for PH groups 2 and 3, and therapy for these patients largely targets comorbid conditions, such as systemic hypertension or valvular heart disease. Medications for group 1 are expensive and may be ineffective (as in the case of ETRA) or harmful (as in the case of prostanoids) when used in group 2 patients.[4,5]

Most previous epidemiological studies have focused on adult PH patients with group 1 disease, including four American cohorts,[1,6–9] 5 European cohorts,[10–14] 2 Chinese cohorts,[15,16] and 1 Australian cohort.[17] These studies were largely conducted in specialized group 1 referral centers and included patients in whom PH was diagnosed by echocardiography or RHC. Only 2 studies included information on groups other than group 1.[10,17] A population-based Australian study of 10 000 patients identified by echocardiography[17] found that group 2 PH was the most common and lethal form. A Spanish study[10] of group 1 (866 PAH) and group 4 (162 chronic thromboembolic PH) patients noted 1-, 3-, and 5-year survival rates of 87%, 75%, and 65%, respectively, with no intergroup differences. The few epidemiological studies of PH performed in Canada have not been population-based and have focused on small cohorts of group 1 patients.[18,19]

We conducted a population-based cohort study in Ontario to estimate the incidence, prevalence, mortality, and prescribing patterns in WHO PH groups 1 to 4 during the period from 1993 to 2012. To our knowledge, this is the first population-based study to comprehensively describe the epidemiology of PH in adults and children.

METHODS

The Institute for Clinical Evaluative Sciences (ICES) data were used, which comprise databases of universal coverage health service records for Ontario residents who have Ontario Health Insurance Plan (OHIP) coverage. OHIP covers most physician and hospital services. Drug dispensing coverage for patients aged 65 years and over was obtained from the Ontario Drug Benefit Database. Hospitalization data were obtained from the Canadian Institute for Health Information Discharge Abstract Database, (CIHI-DAD) database and the National Ambulatory Care Reporting System (CIHI-NACRS) database for outpatient emergency department visits. Demographic information including mortality was obtained from the registered persons database. Databases were linked using unique individual identifiers and analyzed at the ICES. The authors declare that all supporting data are available within the article and its online supplementary files. The data set from this study is held securely in coded form at the ICES. Although data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at http://www.ices.on.ca/DAS. The full data set creation plan is available from the authors on request.

The study cohort consisted of Ontario residents with a primary or secondary PH diagnosis between January 1, 1993 and December 31, 2012. They were identified from hospitalizations (CIHI-DAD) and emergency department visits (CIHI-NACRS) using *International Classification of Diseases*, Ninth Revision (Code 416.0, 416.1, 416.8, 416.9) or *International Classification of Diseases*, Tenth Revision (Codes I27.0, I27.1, I27.2, I27.8, I27.9). This strategy was also used to identify comorbidities. Patients missing information on sex or age were excluded from the cohort.

Patients with PH were classified into the 4 WHO PH groups based on diagnoses in the 5 years before their index date (using CIHI-DAD or CIHI-NACRS). Diagnostic codes for left heart disease, lung disease, and venous thromboembolism were used to identify patients in groups 2, 3, and 4, respectively (Table I in the Data Supplement for *International Classification of Diseases*, Ninth Revision and Tenth Revision codes). Group 5 PH (miscellaneous) was not studied because its heterogeneity precludes accurate identification in these databases. Patients were eligible to be included in multiple PH groups, except for group 1, because group 1 PH, by definition, should lack the diagnostic codes for the comorbidities that promote WHO group 2 to 4 PH. It is acknowledged that a clinician might code a group 1 patient as having some element of left heart or lung disease although ascribing the observed PH to PAH.

Four independent data abstractors validated our diagnostic algorithm. They were given a list of 20 diagnoses, including a mix of PH and systemic hypertension cases. The PH diagnoses were identified and coded with 100% specificity. Furthermore 100 random patients with a diagnosis of PH as captured through the database were case validated using hospital chart abstraction. We were able to verify the diagnosis of PH in all but 3 patients. The PH group inferred by our diagnostic algorithm was further verified by chart abstraction in the 97 patients who had a verified diagnosis of PH. The algorithm was consistent with the chart abstraction assignment to PH subgroups in 63/97 patients with 65% specificity. As a surrogate to the diagnosis of PH, we explored the use of RHC in our incidence cohort using OHIP procedure codes G297 and Z439. The Johns Hopkins Aggregated Diagnosis Groups was used to measure disease morbidity burden.[20] Socioeconomic status was determined using Canada Census data on neighborhood income quintiles. The prevalence of PH in Ontario was estimated for December 31, 2002 and 2012. In sensitivity analyses, the study period (January 1, 1993, to December 31, 2012) was divided into 2 equal time periods to examine temporal trends.

Patients were considered prevalent cases if they had a diagnosis of PH before the specified date and were Ontario residents on the specified date. The denominator used to calculate prevalence was comprised of all Ontario residents who had OHIP coverage on December 31st of the specified year and a date of last healthcare contact within the previous 7 years. Analysis was conducted for pediatric (defined as <16 years of age) and adult cohorts. To see how common PH was in patients with known risk factors, we determined the prevalence of PH among patients with the following comorbidities (left heart disease, lung disease, and thromboembolic disease) for the period December 31, 2002, to December 31, 2012.

A patient was considered to have incident PH if they had no diagnosis of PH in the 10 years before the first PH diagnosis. Annual incidence rates were calculated from 2003 to 2012. The denominator consisted of living Ontario residents with active OHIP coverage with a date of last healthcare contact within the previous 7 years. Incidence rates were stratified by age, PH group, and sex. A trend analysis for incidence rates was performed using a general additive model to determine any trends while accounting for nonlinearity. Crude 30-day, 1-year, and 5-year mortality after incident PH diagnosis were calculated by year and stratified by age, sex, and PH group. Time to death (or date of last contact) was estimated for incident PH. Standardized mortality ratios (SMRs) were calculated for 2003 and 2011 using the 2007 Canadian population as the standard (Data Supplement).[21]

Prescriptions for CCB, ETRA, PDE5i, and prostanoids were identified for patients who were 65 years of age and over between 2003 and 2012. A PH-specific limited-use code for PDE5i allowed definition of prescription indication. The number of days for which a medication was prescribed was determined, both for monotherapy or combination therapy (Data Supplement). The average number of days prescribed/100 patients/calendar year was determined as the total number of days prescribed divided by the number of prevalent patients for that year×100. The percentage of PH patients on different classes of medication was also calculated. Patients were considered to have been dispensed a medication if they were prescribed a medication from that class provided it was dispensed for a minimum cumulative duration of 30 days.

All analyses were performed at ICES using SAS software, version 9.2. Paired *t* tests or ANOVA was performed to compare between groups. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre in Toronto, Canada, and Queen's University Health Sciences Research Ethics Board.

RESULTS

From January 1, 1993, to December 31, 2012, 50 529 patients with PH were identified. Their mean age was 68.5 (±18.5) years and 54.5% were female (Table 1). Age, sex, and Aggregated Diagnosis Groups data for adult and pediatric PH are shown in Table 1. The frequency of WHO groups within the adult PH population was group 2 (68.5%), group 3 (47.0%), and group 4 (9.0%). Many adult patients (35.4%) belonged to more than 1 group, with the most frequent overlap diagnosis being groups 2 and 3 (29.3%; Figure I in the Data Supplement). PH patients with no diagnosis of left heart disease, lung disease, or chronic thromboembolic PH were identified as group 1 (13.8%). Group 1 patients were younger and had lower Aggregated Diagnosis Groups scores than other groups (Table 1). Among those WHO groups that have recognized subgroups, the leading etiologies in adults were group 1-idiopathic PH (50.4%), group 2-systolic or diastolic left ventricular dysfunction (86.8%) and group 3-COPD (chronic obstructive pulmonary disease) (83%; Table II in the Data Supplement). In children, group 1 PH was most common (65.2% [n=1 1198]; Table 1) and 78.6% of cases were idiopathic (Table II in the Data Supplement). However, 21.4% of children (n=394) had group 2 PH (Table 1).

Annual PH prevalence increased from 87.6 to 114.9 cases/100 000 population between 2002 and 2012 (Table 2). In 2012, the mean age of all prevalent PH cases was 59.6 (±23.8) years, 57.3% were female, and 43.6% were in the 2 lowest-income quintiles. In the adult PH cohort, PH prevalence increased over this period (99.8/100 000 to 127.3/100 000), primarily driven by

Table 1. Description of Ontario Adults and Children With Incident Pulmonary Hypertension Diagnosed in 1993 to 2012

	General Population*	All PH	Group 1	Group 2	Group 3	Group 4
All	12 187 218	50 529	7903	33 768	23 189	4425
Number						
% of PH population†			15.6	66.8	45.9	8.8
Female sex, %	50.8	54.5	59.7	54.1	49.9	59.4
Mean age at index date (SD)‡	37.3 (22.0)	68.5 (18.9)	55.4 (28.0)	72.1 (14.9)	71.4 (14.2)	67.4 (17.0)
Mean total ADG score (SD)	8.4 (4.4)	14.3 (4.2)	12.7 (4.6)	14.8 (4.1)	15.1 (4.0)	15.7 (4.1)
Mean major ADG score (SD)	1.0 (1.2)	3.7 (1.5)	3.3 (1.4)	3.8 (1.5)	3.9 (1.5)	4.3 (1.4)
<16 y	2 484 107	1837	1 198	394	295	65
Number						
% of PH population†			65.2	21.4	16.1	3.5
Female sex, %	48.7	46.9	45.9	52	48.8	43.1
Mean age at index date (SD)‡	7.8 (4.5)	1.4 (3.4)	1.2 (3.3)	1.7 (3.5)	1.9 (3.7)	1.8 (3.4)
Mean total ADG score (SD)	6.9 (3.3)	8.9 (4.5)	7.5 (3.8)	11.9 (4.0)	12.1 (4.7)	13.2 (4.2)
Mean major ADG score (SD)	0.6 (0.8)	3.0 (1.1)	2.7 (0.9)	3.5 (1.2)	3.5 (1.1)	4.1 (1.1)
≥16 y	9 703 111	48 692	6705	33 374	22 894	4360
Number						
% of PH population†			13.8	68.5	47	9
Female sex, %	51.3	54.8	62.1	54.1	49.9	59.6
Mean age at index date (SD)‡	44.8 (17.9)	71.0 (14.0)	65.1 (17.4)	72.9 (12.8)	72.3 (11.9)	68.3 (15.1)
Mean total ADG score (SD)	8.8 (5.6)	14.5 (4.1)	13.7 (4.0)	14.8 (4.0)	15.1 (4.0)	15.7 (4.0)
Mean major ADG score (SD)	1.2 (1.3)	3.7 (1.5)	3.3 (1.5)	3.8 (1.5)	3.9 (1.5)	4.3 (1.4)

Percentage values in a row may add to more than 100% because patients may be classified as belonging to more than 1 World Health Organization group. ADG indicates the Johns Hopkins Aggregated Diagnosis Groups; and PH, pulmonary hypertension.

*The reference date for the general population is January 1, 2003.

†Percentage of patients in age group belonging to group.

‡Index Date-date of first PH diagnosis between 1993 and 2012.

increases in group 2 PH (Table 2). The prevalence of pediatric PH in Ontario also increased over this period, from 39.6/100 000 population to 57.9/100 000 population.

The percentage of the general population of Ontario with a predisposing factor for development of PH was left heart disease (2.2%), lung disease (6%), and thromboembolic disease (1%) in 2012 (Table III in the Data Supplement). However, a diagnosis of PH was present in only 3.6% of people with left heart disease, 0.7% of those with lung disease, and 1.4% of those with thromboembolic disease patients. Fewer of these at risk patients had a PH diagnosis in 2012 versus 2002 (Table III in the Data Supplement).

For the entire PH cohort, the annual incidence of PH increased significantly from 19.8 to 24.1 patients per 100 000 population between 2003 and 2012. This increase was predominantly noted over the 2008 to 2011 time period (Figure 1A; Figure II in the Data Supplement; Table IV in the Data Supplement). This increase was also evident in the adult cohort (Figure 1B). The female predominance of the PH cohort was consistent over time. Group 2 accounted for over 75% of all new PH cases. The incidence of adult group 2 increased from 17.1 to 20.5/cases/100 000/year over the study period. In the incident cohort 11 272 of the 27 577 (40.9%) patients had a record of RHC. Almost 40% of these patients belonged to group 1.

For the entire PH population, crude mortality rates at 30 days, 1 year, and 5 years were 12.8%, 35.9%, and 61.5%, respectively. These rates were stable over the study period (Figure III in the Data Supplement). Group 1 patients had lower mortality rates than patients in other groups (Table V in the Data Supplement; Figure 2A). Similar mortality rates were observed for the adult-only PH cohort (Figure 2B). In children, the crude mortality rates at 30 days, 1 year, and 5 years were 6.4%, 16.8%, and 21.4% respectively (Table V in the Data Supplement). There was a 10-fold increase in the risk of death (SMR=9.9; 95% CI, 9.6–10.2) in the 1-year risk of death for patients diagnosed in 2003 compared with the general Canadian population. The 1-year SMR had declined by 2011, however, a PH diagnosis still conferred a 7.2-fold increase in the 1-year risk of death (SMR=7.2; 95% CI, 7.0–7.4). Group 1 patients had the

Table 2. Description of Ontario Patients With Prevalent Pulmonary Hypertension in 2002 and 2012

	<16 y			≥16 y			Total		
	2002	2012	*P* Value	2002	2012	*P* Value	2002	2012	*P* Value
Number	986	1404		9710	14108		10696	15512	
Prevalence per 100000 population*	39.6	57.9	<0.001	99.8	127.3	<0.001	87.6	114.9	<0.001
Age in years	0.7 (2.5)	1.8 (3.0)	<0.001	66.2 (14.7)	65.4 (15.8)	<0.001	60.2 (23.6)	59.6 (23.8)	0.07
Female sex, %	43.4%	46.4%	0.152	56.6%	58.2%	0.01	55.3%	57.2%	0.003
Summation of all ADG components	7.1 (3.5)	8.6 (4.7)	<0.001	13.8 (4.1)	14.1 (4.1)	<0.001	13.2 (4.5)	13.6 (4.5)	<0.001
Summation of major ADG components	2.7 (0.8)	2.9 (1.0)	<0.001	3.6 (1.4)	3.5 (1.5)	<0.001	3.3 (1.4)	3.4 (1.5)	<0.001
Income quintile, %			0.978			0.006			0.008
0th–20th	25.9%	24.9%		22.8%	22.2%		23.1%	22.4%	
20th–40th	20.0%	20.2%		22.9%	21.3%		22.6%	21.2%	
40th–60th	18.5%	18.7%		19.5%	19.9%		19.4%	19.7%	
60th–80th	20.7%	20.5%		17.4%	18.5%		17.7%	18.6%	
80th–100th	14.2%	14.7%		17.0%	17.7%		16.8%	17.5%	
PH group prevalence per 100000 population									
Group 1	31.3	39.7	<0.001	20.0	26.8	<0.001	22.3	29.1	<0.001
Group 2	5.4	11.5	<0.001	62.7	79.6	<0.001	51.0	67.4	<0.001
Group 3	2.9	8.0	<0.001	35.7	42.6	<0.001	29.0	36.4	<0.001
Group 4	0.7	1.9	<0.001	7.4	14.4	<0.001	6.0	12.1	<0.001

Values are mean±SD unless otherwise indicated. *P* values report differences in prevalence, age etc between 2002 and 2012 for each age group. Statistical comparisons were conducted using the student *t* test for continuous variables, and the χ^2 test for categorical variables. ADG indicates the Johns Hopkins Aggregated Diagnosis Groups; and PH, pulmonary hypertension.

*The denominator used for prevalence calculations is the number of people alive in Ontario on December 31st of that year with healthcare contact in the previous 7 years.

lowest SMR and experienced the largest reduction in SMR over time [(2003, SMR=9.1; 95% CI, 8.0–10.2) versus (2011, SMR=5.0; 95% CI, 4.4–5.6; Table 3)]. Based on RHC, 1-year mortality in patients with group 1 who had a RHC was 11.7%.

Prescription data were available for the 29137 PH patients who were 65 years or older (57.5% of the PH cohort). Prescription of CCB, ETRA, PDE5i, and prostanoids occurred in all groups (Figure 3A and 3B) and increased over time (Figure 3B). The most common combination used was CCB plus ETRA, followed by CCBs plus PDE5i. From 2003 to 2012 the largest dispensing of ETRA (based on number of total days prescribed) were to group 1>group 2>group 3 patients (total days prescribed 96088>70929>49507), respectively (Figure 3A). Similarly, PDE5i were consumed by group 2>group 1>group 3 patients (total days prescribed 39472>36355>23358), respectively. Prescriptions for CCB plateaued in 2008 (Figure 3B), whereas the prescriptions for ETRA and PDE5i continued to increase through the study period. Over 40% of group 1 patients and 34.2% of group 2 patients were dispensed CCBs. Although the percentage was small, ETRA, PDE5i usage was distributed across all PH groups (Table 4). Of those group 1 patients, 65 years or older who had a RHC, the use of PH-specific therapy (ETRA, PDE5i, and prostanoids) was 17.2%.

Almost as many patients qualified for a combination diagnosis of group 2+3 PH (9155) as had isolated group 2 (9956) or isolated group 3 (3641) PH (Table VI in the Data Supplement). Approximately 51% of group 2+3 were females. The group 2+3 cohort were older 74.4 (±11.6) years. Their comorbidity scores were also greater (major Aggregated Diagnosis Groups score 4.2 [1.5]) compared with isolated group 2 (3.8 [±1.5]) or group 3 PH (3.8 [±1.5]; Table VI in the Data Supplement). In the incidence cohort, survival of group 2+3 patients was worse than isolated group 2 or 3 patients (Figure IV in the Data Supplement). The SMR for group 2+3 was higher than for isolated group 2 patients (Table VII in the Data Supplement).

DISCUSSION

This is the first population-based study to describe the epidemiology of PH in adults and children. There are 5 important findings. First, the incidence and prevalence of PH in adults increased significantly over the past 2 decades, driven primarily by increases in WHO group 2. Second, any diagnosis of PH, regardless of WHO group, portended an adverse impact, with the worst outcomes observed in adults with groups 2 and 3 PH. Although the increase in SMR declined in the second decade of this study it remains high with any diagnosis

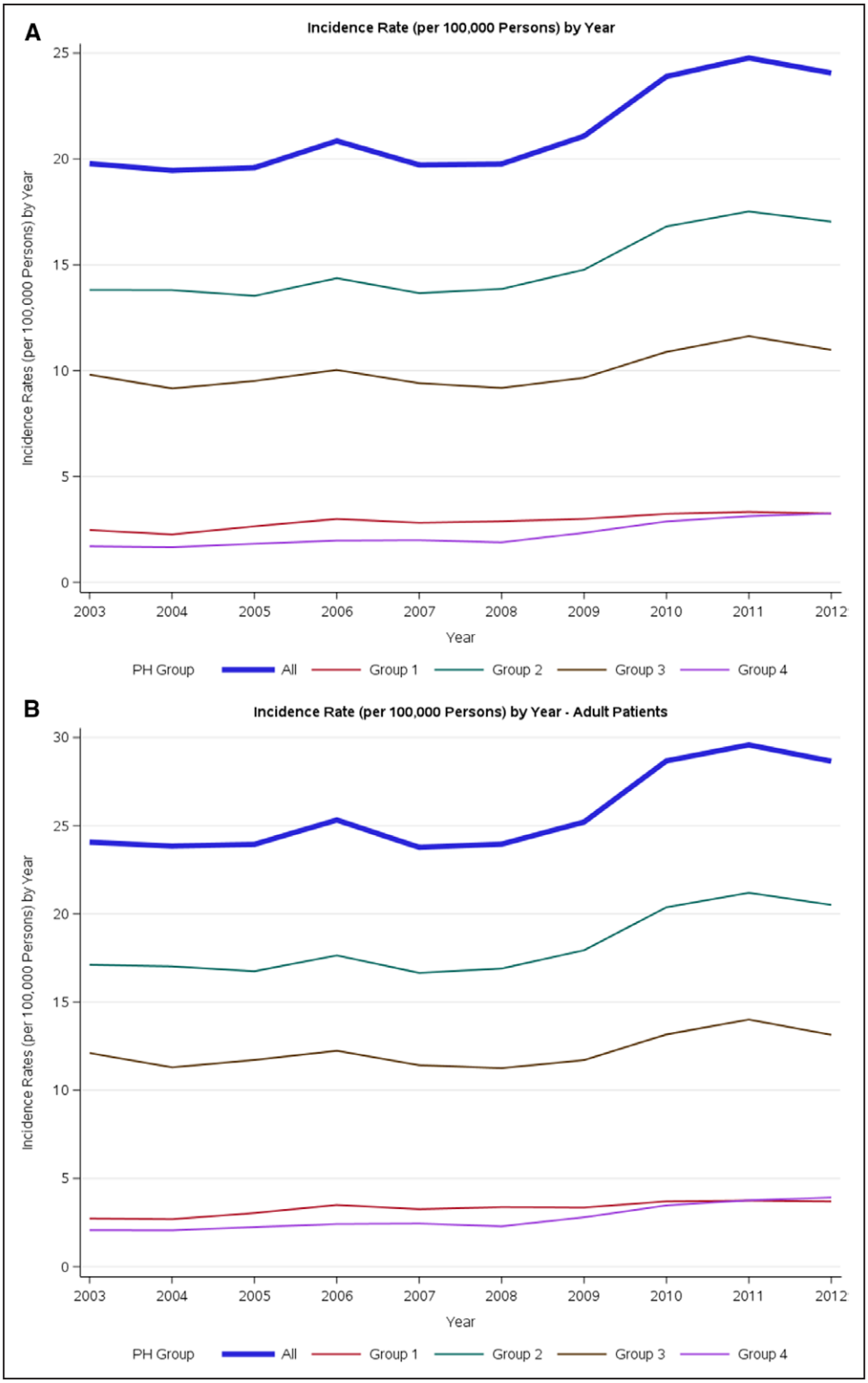


Figure 1. Incidence rates of Ontario patients with pulmonary hypertension (PH) per 100 000 persons by year. **A**, Overall. **B**, Adults. **C**, Pediatric (next page).

of PH conferring over a 7-fold increase in adjusted mortality (Table 3). Third, a substantial cohort of PH patients qualified for inclusion in more than 1 PH Group (usually group 2 and 3). This overlap is not surprising in light of common risk factors for left heart disease and COPD, notably cigarette smoking. Individuals with criteria for inclusion in both groups 2 and 3 were older with more comorbidities than those in the isolated group 2 or 3 and had a worse prognosis (Table VI in the Data Supplement). Fourth, substantial departure from prescribing

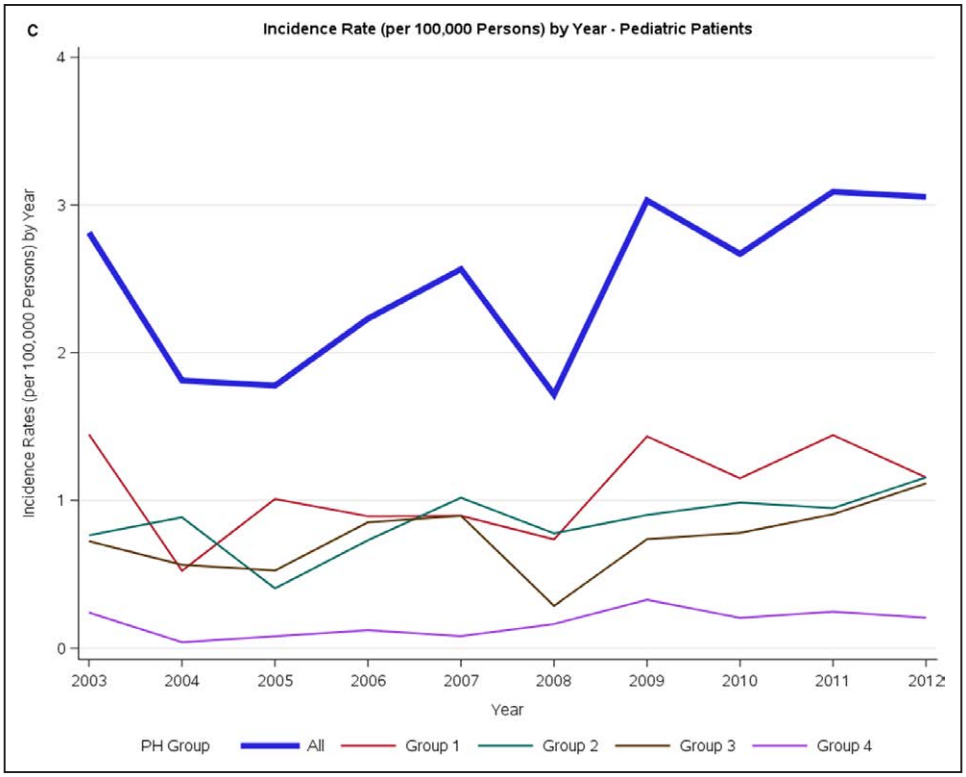


Figure 1, Continued.

guidelines was noted, including high rates of CCB use in group 1 PH and the use of group 1–specific therapeutic agents (ETRA and PDE5i) in groups 2 and 3 PH (Figure 3A). Fifth, pediatric PH was much less common and had better survival than adult disease. The predominant type of pediatric PH is PAH (group 1; Table II in the Data Supplement).

Between 2003 and 2012 the annual incidence of PH increased, with the greatest increase being in group 2 (Figure 1A). In Ontario in 2012, over 15 000 patients were living with a diagnosis of PH (Table 2). The temporal increase in incidence was most pronounced from 2008 to 2011 and may be related to increased rates of diagnosis related to improved disease awareness, increased treatment options, and the greater availability of less invasive diagnostic techniques. The annual incidence of group 1 PH increased from 2.5 to 3.2 patients per 100 000 population between 2003 and 2012. The fact that we captured primary or secondary diagnoses of PH patients at a population level and included both admitted patients and those seen in the emergency department may explain the somewhat higher rates of group 1 disease in our study versus reports from cohorts that only capture patients from referral centers. The range of reported incidences for group 1 PH (0.07/100 000 to 0.37/100 000[6,10,12–14]) in these referral center cohorts is up to 5- to 10-fold less than in our study, although in the same range as our findings.

PH, when considered in its totality (ie, including group 1 to 4 patients) is not rare; occurring at 7.9% of the incidence of congestive heart failure (306.1/100 000 people)[22] and 2.9% of the incidence of COPD (820/100 000 people)[23] in Ontario. Compared with the general population, PH patients are older, more often female and have more comorbidities (Table 1). We suspect that the rise in PH prevalence relates in part to the ubiquitous availability of Doppler echocardiography, which permits noninvasive quantification of pulmonary artery pressure. However, in addition to improved noninvasive detection, it is likely the true incidence and prevalence of PH are increasing. The most common isolated form of PH was group 2, followed by group 3 PH. The high burden of heart failure, especially diastolic left ventricular dysfunction[24] in our aging population likely underlies much of the increased prevalence of PH and will likely lead to continued growth in the absolute and relative importance of group 2 PH. However, PH is still a relatively rare complication in patients identified based solely on the presence of a predisposing comorbidities, such as COPD (<5%; Table III in the Data Supplement). It is interesting to note that between 2002 and 2012 fewer patients with risk factors for PH in fact developed PH, likely indicating early detection and better control of comorbid conditions including left heart disease, COPD, and thromboembolic disease. We interpret this as indicating a complex interplay of factors that

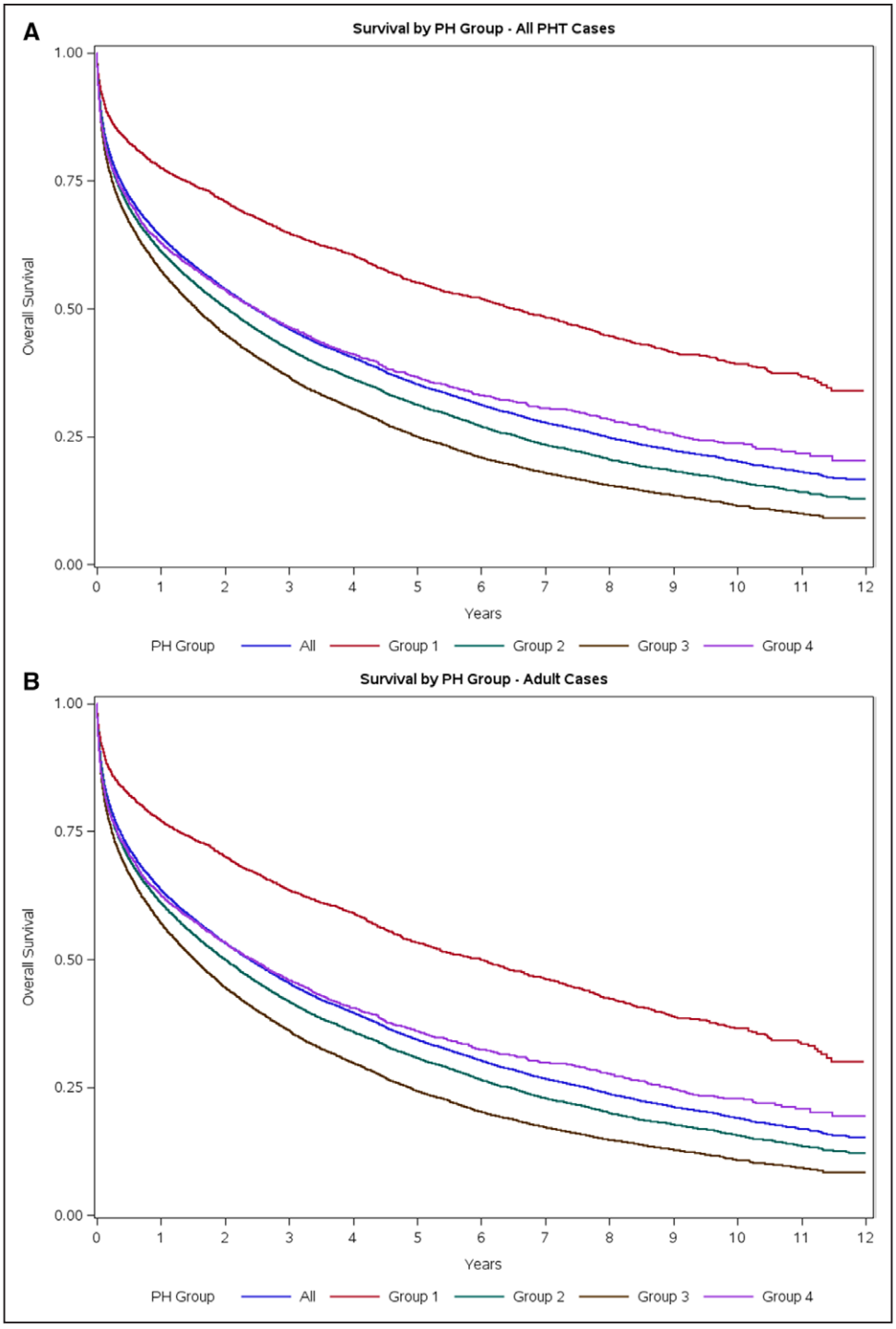


Figure 2. Survival of Ontario patients with pulmonary hypertension (PH).
A, Overall. **B**, Adults. **C**, Pediatric (next page).

determine whether a patient with left heart disease or chronic lung disease will develop PH. It is likely PH becomes significant in left heart disease only when left atrial pressures increase substantially and other factors, such as endothelial dysfunction, are present. Likewise, in COPD it is probable that PH only becomes manifest when disease is severe with significant hypoxia and loss of arteriolar and capillary bed volume.

Consistent with real-world clinical practice, it was often difficult to definitively categorize patients with concomitant heart and lung disease into a single WHO group based on diagnostic codes. Patients who had comorbidities that qualified them to be counted in both groups 2 and 3 accounted for over 9000 patients (20.5% of the entire PH cohort). This groups 2+3 cohort is older with more comorbidities than the relevant isolated PH

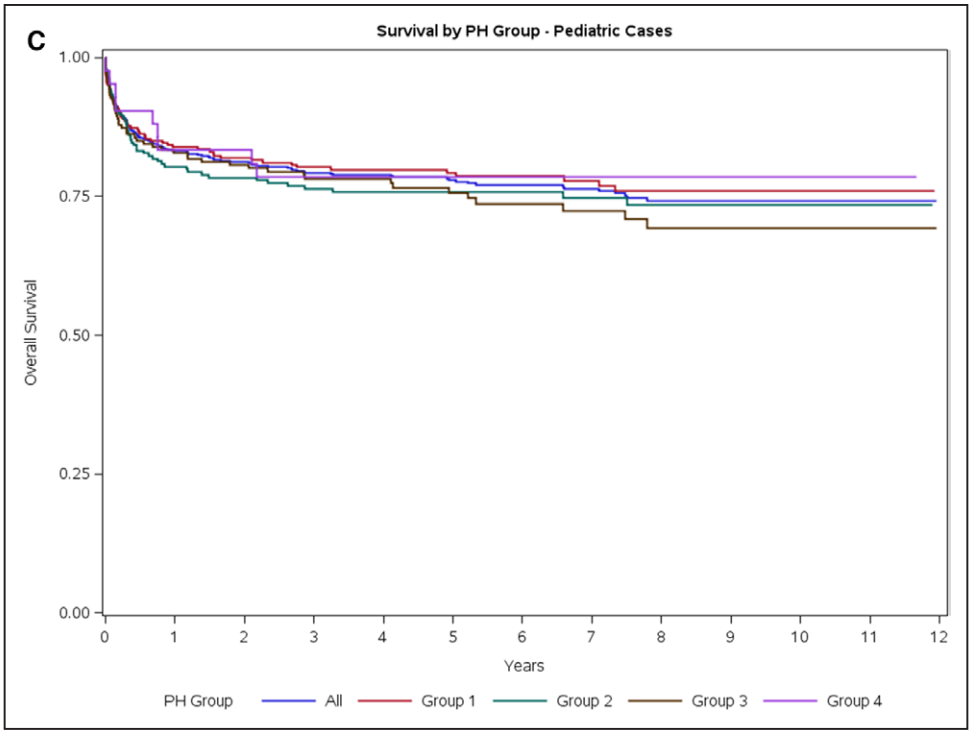


Figure 2 Continued.

Groups (Table VI in the Data Supplement). Accordingly, their survival is worse than their counterparts with isolated group 2 or 3 disease (Figure IV in the Data Supplement). This overlap group merits further consideration. Although most therapeutic focus is on group 1 and group 4 PH they account for only 13.8% and 9.0% of the adult cohort, respectively. Thus, an approach to the public health burden of PH will require an increased focus on patients with group 2 and 3 disease.

Little is known about the epidemiology of children with PH. We identified 1837 children with PH, representing 3.6% of all PH cases. In children, group 1 PH is the most common form of disease. Children have substantially better 5-year survival than adults. These data begin to fill the void in understanding the epidemiology of pediatric PH that was identified in the first scientific statement on PH in children.[25]

Table 3. Standardized Mortality Ratios for Ontario Patients With Incident Pulmonary Hypertension Diagnosed in 2003 and 2012 Compared With the Age- and Sex-Matched Canadian Population

Group	Year			
	2003		2011	
	SMR	95% Confidence Interval	SMR	95% Confidence Interval
All PH	9.9	(9.6–10.2)	7.2	(7.0–7.4)
Group 1	9.1	(8.0–10.2)	5.0	(4.4–5.6)
Group 2	9.4	(9.0–9.8)	7.1	(6.8–7.3)
Group 3	11.1	(10.6–11.6)	8.9	(8.6–9.3)
Group 4	12.6	(11.2–14.1)	8.4	(7.7–9.1)

PH indicates pulmonary hypertension; and SMR, standardized mortality ratio.

In previous studies, the calculated 1-year mortality of group 1 PH was 8% to 33%.[6–13,15–17] This variability is dependent on the period of study, the type of patient and expertise of the center. At a population level our study noted a 1-year mortality rate in adults of 22.9%, which is congruent with previous literature. Mortality was lower in group 1 than in all other WHO groups (Figure 2A). This better survival may reflect the natural history of group 1 disease, the increasing use of group 1–specific pharmacological treatments, the relative paucity of comorbidities in group 1 (Table 1) and the fact that group 1 patients are approximately a decade younger than other groups. We noted a generalized temporal decline in SMR in all groups over the study period after adjustment for age and sex (Table 3), similar to trends in PAH registries.[26]

PH, like COPD, heart disease, diabetes mellitus, and hypertension,[27] is more prevalent in low-income quintiles. The disparity in PH patients between the top 2 and bottom 2 income quintiles was 7.5% in our study. Patients with lower income have higher prevalence of smoking, inactivity, and obesity.[27] Although the basis for the increase in PH in those with low socioeconomic status was not explored it likely relates to disease factors such as smoking, obesity, and hypertension. It is unlikely that the effect of income is because of impaired access, because healthcare access is relatively uniform across income groups in Ontario, Canada.[27]

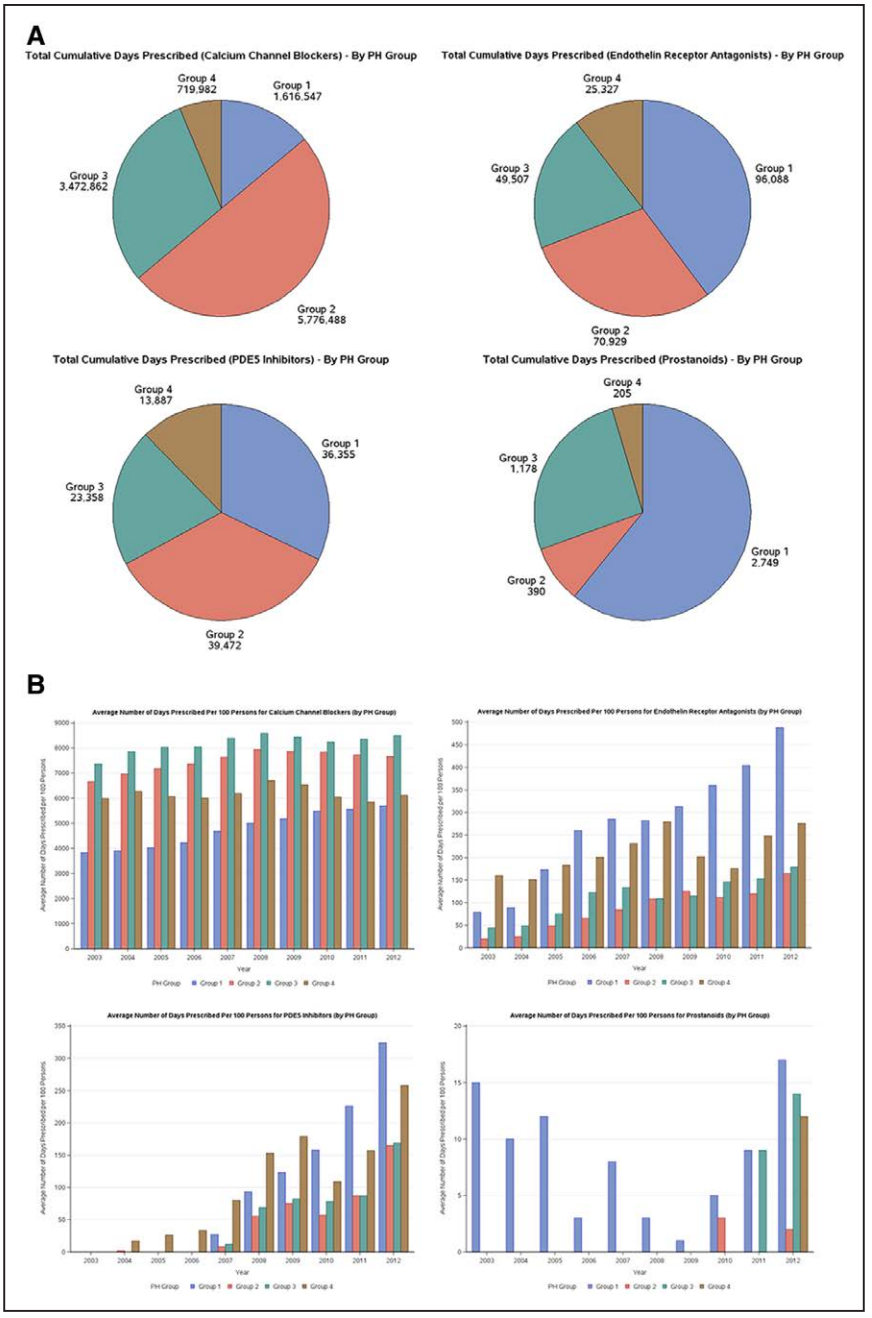


Figure 3. A, Cumulative number of days pulmonary hypertension (PH) medications were dispensed to Ontario patients with PH (2003–2012).
Cumulative number of days PH medications were dispensed. **B**, Average number of days PH medications were dispensed per 100 Ontario patients.

There are several strengths and limitations of our study. This is the largest PH study to date, including over 50 000 individuals. It is the first population-based study to describe the epidemiology of PH in adults and children. In a population study such as this we cannot determine whether there is a true change in disease incidence and prevalence versus better case ascertainment because of some combination of enhanced disease awareness by practitioners and increased utilization of cardiac ultrasound (which enhances disease detection in the population). Although PH codes are intended to be specific, it is possible that patients with other diagnoses may be misclassified as having PH leading to over or underestimation of rates. The lack of specificity of our diagnostic algorithm because of the absence of data about RHC and reliance predominantly on echocardiograms is a limitation.[28]

Although we could not case-validate for such a large study the veracity of the diagnostic code approach we used was validated by noting that a diagnosis of any form of PH conferred up to a 10-fold increase in SMR.

Table 4. Percentage of Patients 65 and Older With Pulmonary Hypertension in Ontario by Medication Use

Class	All PH	Group 1	Group 2	Group 3	Group 4
Calcium channel blockers	35.9	43.8	34.2	35.1	33.3
Endothelin receptor antagonists	1.1	3.6	0.7	0.8	1.2
PDE5 inhibitors	0.7	2.3	0.4	0.4	1
Prostanoids	<0.1	0.1	<0.1	<0.1	<0.1

The denominators used for the percentage calculations are PH patients in each group. PH indicates pulmonary hypertension.

This is important because if the PH we captured was physiologically insignificant and solely because of an echo surveillance bias one would not have expected a diagnosis of PH to have conferred the observed dramatic risk of mortality. Also over 40% of incident PH patients we captured had a RHC and of those 40% were identified as group 1. Over 17% of group 1 patients who had a RHC were dispensed PH-specific therapies. These findings support the specificity of identifying PH patients using administrative codes. Furthermore, the incidence, prevalence, and mortality rates noted for group 1 PH in our study are in line with those in the literature obtained from standard registries. A second limitation is that information on medication dispensing was limited to PH patients aged 65 years and over who obtain their medication through a government funded program. We were also unable to differentiate whether the indication for CCB use was PH versus systemic hypertension. However, the capture of PDE5i usage in PH was indication-specific and distinct from its use in erectile dysfunction. Although we acknowledge that the current WHO PH classification does not recognize combined comorbidities as drivers of PH (ie, the group 2 and 3 patients) we suspect that it is this multiple-hit pathophysiology (such as the combination of systemic hypertension and sleep apnea) that renders this patient subset vulnerable to developing PH. Supporting the validity of recognizing combined group 2 and 3 disease, this cohort had a particularly poor prognosis. Even in registries, such as Registry to Evaluate Early And Long-term Pulmonary Arterial Hypertension Disease Management, created in specialized group 1 PH-focused studies, where all patients are assessed and classified by a PH expert physician, multiple comorbidities, including COPD and sleep apnea, are common.[29] A limitation of our study is our inability to quantify severity of the comorbidities or attribute primary causality to one versus another of the major identified comorbidities. The fact that a comorbidity (COPD versus left heart disease) was sufficiently severe to merit diagnostic coding suggests that it was deemed physiologically relevant by the physician.

The rising incidence and prevalence of PH has several implications for health policy and practice. In terms of policy there should be a greater focus on prevention and treatment of groups 2 and 3 patients, because they are the most rapidly growing cohort and have the highest standardized mortality ratios. The substantial use of PH-specific therapies, approved solely for use in WHO group 1, notably ETRA and PDE5i, in the large and growing cohorts of WHO group 2 and 3 patients, suggests a departure from treatment guidelines is occurring. An alternative explanation is that the prescribing physician considered the left heart disease and lung disease minor and thus treated the patient as a group 1 patient, despite acknowledging the comorbidity with a diagnostic code. If this occurred, the patients would have been coded as a group 2 or group 3 PH patient, respectively in our study, potentially creating the appearance of off-label application of group 1–specific drugs in other PH groups. Conversely, if an echocardiogram led to a diagnosis of PH in a patient deemed either too well or too ill to merit investigation with RHC or therapy and if no comorbidity was noted, the case would be classified as group 1 PH. This would lead to underestimation of the use of PAH-targeted therapy. In our study, where severity of the comorbid condition and the proportion of the PH that should be attributed to a comorbidity cannot be ascertained, this may have led to overestimation of the off-label use of PH-targeted therapies in our study. However, in this case it would suggest practicing physicians are choosing to ignore left heart and lung disease in group 1 PH, which is inconsistent with guidelines. Education for prescribers may be worthwhile considering the cost and potential toxicity of off-label prescription of group 1 PH-targeted therapeutics.

ACKNOWLEDGMENTS

This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). We wish to acknowledge the administrative support rendered by Ms. Susan Roland from ICES and assistance with proof reading by Dr Nishardi Wijeratne from Queen's University, Kingston, Ontario. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and information compiled and provided by Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the author, and not necessarily those of CIHI. We wish to acknowledge the superb clinical care of our pulmonary hypertension (PH) patients at Kingston Health Sciences Centre at Queen's University, by Dr Christine D'Arsigny. We also thank our PH clinic patients for their inspiration of this study and input to study design based on the questions they posed in clinic.

SOURCES OF FUNDING

Dr. Archer and this research are supported by a Canadian Institute of Health Research Foundation Grant, NIH-RO1-HL071115, 1RC1HL099462, a Tier 1 Canada Research Chair in Mitochondrial Dynamics, the William J. Henderson Foundation, and the CIHR Vascular Network and the Canadian Vascular Network-Bayer Research Fellowship Award.

DISCLOSURES

None.

AFFILIATIONS

From the Department of Medicine (D.T.W., M.D.L., A.H., D.B., K.M.D., S.L.A.), Institute for Clinical Evaluative Sciences Queen's (D.T.W., K.L., S.B.B., M.D.L., L.J., A.J.), Department of Surgery (S.B.B.), and Department of Public Health Sciences (M.D.L., A.J.), Queen's University, Kingston, ON, Canada.

FOOTNOTES

Received June 20, 2017; accepted December 22, 2017.

The Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.117.003973/-/DC1.

Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org.

REFERENCES

1. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl):D34–D41. doi: 10.1016/j.jacc.2013.10.029.
2. Sikirica M, Iorga SR, Bancroft T, Potash J. The economic burden of pulmonary arterial hypertension (PAH) in the US on payers and patients. *BMC Health Serv Res*. 2014;14:676. doi: 10.1186/s12913-014-0676-0.
3. Vaid HM, Camacho X, Granton JT, Mamdani MM, Yao Z, Singh S, Juurlink DN, Gomes T. The characteristics of treated pulmonary arterial hypertension patients in Ontario. *Can Respir J*. 2016;2016:6279250. doi: 10.1155/2016/6279250.
4. Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, Darius H, Schulman K, Zannad F, Handberg-Thurmond E, Harrell FE Jr, Wheeler W, Soler-Soler J, Swedberg K. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). *Am Heart J*. 1997;134:44–54.
5. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E; RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309:1268–1277. doi: 10.1001/jama.2013.2024.
6. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, Giles S, Feldkircher K, Miller DP, McGoon MD. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest*. 2010;137:376–387. doi: 10.1378/chest.09-1140.
7. Kane GC, Maradit-Kremers H, Slusser JP, Scott CG, Frantz RP, McGoon MD. Integration of clinical and hemodynamic parameters in the prediction of long-term survival in patients with pulmonary arterial hypertension. *Chest*. 2011;139:1285–1293. doi: 10.1378/chest.10-1293.
8. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med*. 1987;107:216–223.
9. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982-2006. *Eur Respir J*. 2007;30:1103–1110. doi: 10.1183/09031936.00042107.
10. Escribano-Subias P, Blanco I, López-Meseguer M, Lopez-Guarch CJ, Roman A, Morales P, Castillo-Palma MJ, Segovia J, Gómez-Sanchez MA, Barberà JA; REHAP Investigators. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. *Eur Respir J*. 2012;40:596–603. doi: 10.1183/09031936.00101211.
11. Hoeper MM, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, Grunig E, Staehler G, Rosenkranz S, Halank M, Held M, Grohé C, Lange TJ, Behr J, Klose H, Wilkens H, Filusch A, Germann M, Ewert R, Seyfarth HJ, Olsson KM, Opitz CF, Gaine SP, Vizza CD, Vonk-Noordegraaf A, Kaemmerer H, Gibbs JS, Pittrow D. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol*. 2013;168:871–880. doi: 10.1016/j.ijcard.2012.10.026.
12. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med*. 2006;173:1023–1030. doi: 10.1164/rccm.200510-1668OC.
13. Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JS, Howard LS, Pepke-Zaba J, Sheares KK, Corris PA, Fisher AJ, Lordan JL, Gaine S, Coghlan JG, Wort SJ, Gatzoulis MA, Peacock AJ. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. *Am J Respir Crit Care Med*. 2012;186:790–796. doi: 10.1164/rccm.201203-0383OC.
14. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. *Eur Respir J*. 2007;30:104–109. doi: 10.1183/09031936.00092306.
15. Jing ZC, Xu XQ, Han ZY, Wu Y, Deng KW, Wang H, Wang ZW, Cheng XS, Xu B, Hu SS, Hui RT, Yang YJ. Registry and survival study in Chinese patients with idiopathic and familial pulmonary arterial hypertension. *Chest*. 2007;132:373–379. doi: 10.1378/chest.06-2913.
16. Zhang R, Dai LZ, Xie WP, Yu ZX, Wu BX, Pan L, Yuan P, Jiang X, He J, Humbert M, Jing ZC. Survival of Chinese patients with pulmonary arterial hypertension in the modern treatment era. *Chest*. 2011;140:301–309. doi: 10.1378/chest.10-2327.
17. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, Gabbay E. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. *Heart*. 2012;98:1805–1811. doi: 10.1136/heartjnl-2012-301992.
18. Pope JE, Lee P, Baron M, Dunne J, Smith D, Docherty PS, Bookman A, Abu-Hakima M. Prevalence of elevated pulmonary arterial pressures measured by echocardiography in a multicenter study of patients with systemic sclerosis. *J Rheumatol*. 2005;32:1273–1278.
19. Shimony A, Fox BD, Langleben D, Rudski LG. Incidence and significance of pericardial effusion in patients with pulmonary arterial hypertension. *Can J Cardiol*. 2013;29:678–682. doi: 10.1016/j.cjca.2012.04.009.
20. Austin PC, van Walraven C, Wodchis WP, Newman A, Anderson GM. Using the Johns Hopkins Aggregated Diagnosis Groups (ADGs) to predict mortality in a general adult population cohort in Ontario, Canada. *Med Care*. 2011;49:932–939. doi: 10.1097/MLR.0b013e318215d5e2.
21. Statistics Canada. Deaths and Mortality Rates, by Age Group and Sex, Canada, Provinces and Territories. http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=1020504. Accessed December 26, 2017.
22. Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE, Tu JV. Trends in the incidence and outcomes of heart failure in Ontario, Canada: 1997 to 2007. *CMAJ*. 2012;184:E765–E773. doi: 10.1503/cmaj.111958.
23. Statistics Canada. Population Aged 35 and Over Who Reported Being Diagnosed by a Health Professional With Chronic Bronchitis, Emphysema or Chronic Obstructive Pulmonary Disease (COPD). Table 105–0501 - Health Indicator Profile, Annual Estimates, by Age Group and Sex, Canada, Provinces, Territories, Health Regions (2013 Boundaries) and Peer Groups, Occasional, CANSIM (Database). http://www5.statcan.gc.ca/cansim/a26?lang=eng&retrLang=eng&id=1050501&&pattern=&stByVal=1&p1=1&p2=-1&tabMode=dataTable&csid=#F81. Accessed December 26, 2017.
24. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation*. 2009;119:2663–2670. doi: 10.1161/CIRCULATIONAHA.108.838698.

25. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, Stenmark KR, Steinhorn R, Thébaud B, Fineman JR, Kuehne T, Feinstein JA, Friedberg MK, Earing M, Barst RJ, Keller RL, Kinsella JP, Mullen M, Deterding R, Kulik T, Mallory G, Humpl T, Wessel DL; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132:2037–2099. doi: 10.1161/CIR.0000000000000329.
26. McGoon MD, Benza RL, Escribano-Subias P, Jiang X, Miller DP, Peacock AJ, Pepke-Zaba J, Pulido T, Rich S, Rosenkranz S, Suissa S, Humbert M. Pulmonary arterial hypertension: epidemiology and registries. *J Am Coll Cardiol*. 2013;62(25 suppl):D51–D59. doi: 10.1016/j.jacc.2013.10.023.
27. Health Quality Ontario. Income and Health: Opportunities to Achieve Health Equity in Ontario. http://www.hqontario.ca/Portals/0/documents/system-performance/health-equity-report-en.pdf. Accessed December 26, 2017.
28. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med*. 2009;179:615–621. doi: 10.1164/rccm.200811-1691OC.
29. Poms AD, Turner M, Farber HW, Meltzer LA, McGoon MD. Comorbid conditions and outcomes in patients with pulmonary arterial hypertension: a REVEAL registry analysis. *Chest*. 2013;144:169–176. doi: 10.1378/chest.11-3241.

Increasing Incidence and Prevalence of World Health Organization Groups 1 to 4 Pulmonary Hypertension: A Population-Based Cohort Study in Ontario, Canada

D. Thiwanka Wijeratne, Katherine Lajkosz, Susan B. Brogly, M. Diane Lougheed, Li Jiang, Ahmad Housin, David Barber, Ana Johnson, Katharine M. Doliszny and Stephen L. Archer

Circ Cardiovasc Qual Outcomes. 2018;11:
doi: 10.1161/CIRCOUTCOMES.117.003973
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7705. Online ISSN: 1941-7713

Increasing Incidence and Prevalence of WHO Groups 1-4 Pulmonary Hypertension: *A*
Population-Based Cohort Study in Ontario, Canada.

Thiwanka D Wijeratne MD, assistant professor[1,2], Katherine Lajkosz MSc, research analyst[2], Susan B. Brogly PhD, assistant professor[2,3], M. Diane Lougheed MD, professor [1,2,4], Li Jiang MSc, epidemiologist[2], Ahmad Housin MD Medical resident[1], David Barber MSc, research analyst[1], Ana Johnson PhD, associate professor [2,4], Katharine M Doliszny PhD, research assistant[1], Stephen L Archer MD, professor [1]

[1]Department of Medicine, Queen's University, Kingston, Ontario, Canada
[2]Institute for Clinical Evaluative Sciences Queen's, Queen's University, Kingston, Ontario
[3]Department of Surgery, Queen's University, Kingston, Ontario, Canada
[4]Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada

SUPPLEMENTAL MATERIAL

Table of Contents

Standardized Mortality Ratio (SMR)

To determine the impact of PH on mortality we calculated a gender and age-adjusted Standardized Mortality Ratios (SMRs) for two years of our study, 2003 and 2011 using the 2007 Canadian population as the standard population, as described below and in. For PH patients diagnosed in 2003, the observed number of deaths occurring in the 12 months following diagnosis was determined by gender and age. The expected number of deaths in each gender-age category was estimated by multiplying the number of PH patients in each gender-age category in 2003 by the death rate for the respective gender-age category, The observed number of deaths for 2003 was then summed across gender-age categories and then divided by the sum of the expected number of deaths to determine the SMR. The 95% confidence interval for the SMR was calculated using the gamma distribution. This same approach was used for PH cases diagnosed in 2011 and for WHO PH groups.

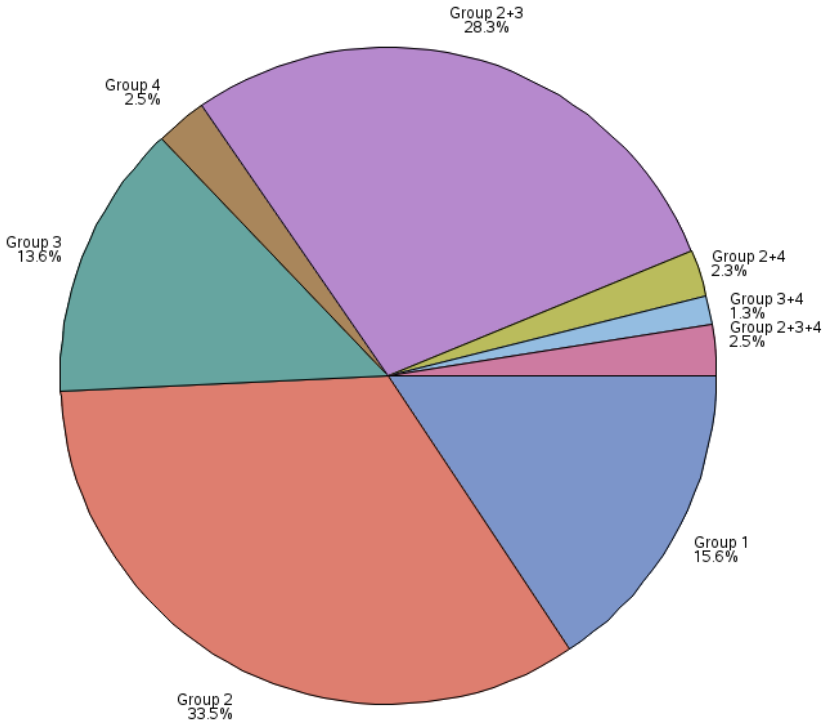
Calculation of Usage of PH Medication:

Medications were considered to be taken in combination if their prescription start and end dates (calculated by adding the number of days supplied to the start date) overlapped by ≥ 7 days. For medication combinations the number of total days supplied was calculated by adding the number of overlapping days in the prescriptions of the two combined medications. The total number of days supplied by calendar year was also determined.

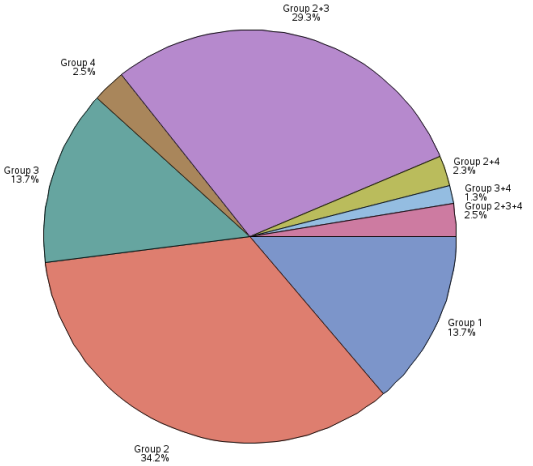
Table S1: Among patients with PH, codes used to describe their comorbidities

Group	ICD-9	ICD-10	OHIP
Group 1	4160, 695.4, 710.0, 710.1, 710.2, 710.3, 710.4, 710.8, 710.9, 714.0, 042, 043, 044, 572.3, 571.2, 571.5, 571.6, 746.84, 746.89, 746.9, V136, 745.4, 745.5, 745.9, 74710, 74711, 74720, 74721, 74722, 74729	I27.0, M32, M33, M34, M35, M05, J99.0, J99.1, B24, K70-K77, Q21, Q25.0, B65	710, 714, 042, 043, 044, 571, 745, 746, 747
Group 2	428.0, 428.1, 428.9, 394.0, 394.1, 394.2, 394.9, 396.0, 396.1, 396.2, 396.3, 396.8, 396.9, 424.0, 746.5, 746.6, 395.0, 395.1, 395.2, 395.9, 424.1, 746.3, 746.4, 425	I50, Q23, I05, I06, I08.0, I34, I35, I39.0, I39.1, I25.5, I25.6, I25.8, I25.9, O99.4, O90.3, I42.0, I42.1, I42.2, I42.5, I42.6, I42.7, I42.8, I42.9, I43.0, I43.1, I43.2, I43.8	-
Group 3	492.0, 492.8, 518.1, 277.00, 277.01, 518.2, 490, 491.0, 491.1, 491.2, 491.8, 491.9, 496, 5163, 18.1, 500, 502, 503, 505, 515, 748.5, 551.3, 552.3, 553.3, 780.51, 780.53	J40-J44, E84, J60-J70, J82, J84, P27.1, Q79.0, G47.30, G47.31, G47.38, I26, I80.2, 180.3, 182.2	-
Group 4	415.1, 673.80, 673.81, 673.82, 673.83, 673.84, 453.2, 453.8, 453.9	I26, I80.2, I80.3, I82.2	-

All PH patients



Patients ≥ 16 years



Patients <16 years

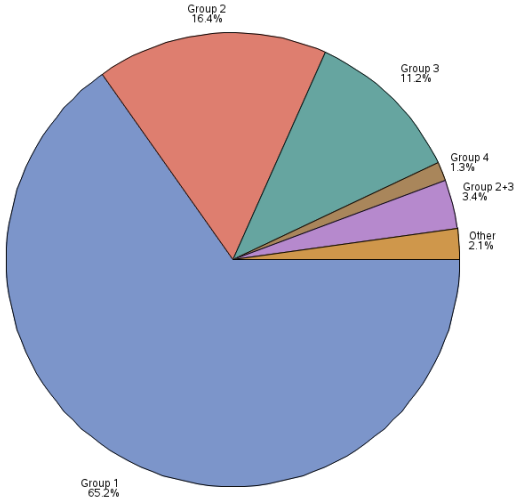


Figure S1: Multiple etiologies of Pulmonary Hypertension

Table S2: Comorbidities of Pulmonary Hypertension Patients by WHO Group Classification

	<16 years	>= 16 years	Total
All Group 1*	N = 1,198	N = 6,705	N = 7,903
Idiopathic PH (%)	78.6	50.4	54.7
Connective Tissue Diseases (%)	0.0	6.4	5.4
Congenital Heart Diseases (%)	41.8	6.1	11.5
All Group 2 (Left Heart Disease) *	N = 394	N = 33,374	N = 33,768
Diastolic/Systolic Dysfunction (%)	67.5	86.8	86.5
Mitral/Aortic Valve Disease (%)	43.9	37.1	37.2
Cardiomyopathy (%)	9.6	16.5	16.4
All Group 3 (Lung Disease/Hypoxia)*	N = 295	N = 22,894	N = 23,189
COPD (%)	12.9	83.0	82.1
Interstitial Lung Disease (%)	81.4	24.2	24.9
Sleep-Disordered Breathing (%)	12.5	10.1	10.1
Group 4: CTEPH	N = 65	N = 4,360	N = 4,425

* = denominator within each group
Abbreviations: PH- pulmonary hypertension; COPD – Chronic Obstructive Pulmonary Disease CTEPH- Chronic Thromboembolic Pulmonary Hypertension

Table S3: Prevalence of PH in Adults with Comorbid Conditions

	2002		2012	
Comorbid Conditions	**Prevalence in General Population**	**Prevalence of PH**	**Prevalence in General Population**	**Prevalence of PH**
	Number (%)*	Number (%)*	Number (%)*	Number (%)*
Left Heart Disease	212,675 (1.9%)	12,763 (6.0%)	246,852 (2.2%)	8,805 (3.6%)
Diastolic/Systolic Dysfunction	167,068 (1.5%)	10,839 (6.5%)	152,906 (1.4%)	6,760 (4.4%)
Mitral/Aortic Valve Disease	69,739 (0.6%)	5,354 (7.7%)	78,760 (0.7%)	4,008 (5.1%)
Cardiomyopathy	51,659 (0.5%)	2,347 (4.5%)	74,892 (0.7%)	1,669 (2.2%)
Lung disease/Hypoxia	367,866 (3.3%)	8,693 (2.4%)	663,855 (6.0%)	4,691 (0.7%)
COPD	248,046 (2.2%)	7,496 (3.0%)	513,503 (4.6%)	3,613 (0.7%)
Interstitial Lung Disease	157,663 (1.4%)	1,945 (1.2%)	131,360 (1.2%)	0,874 (0.7%)
Thromboembolic disease	56,343 (0.5%)	1,576 (2.8%)	112,880 (1.0%)	1,557 (1.4%)

***** The % under the column "Prevalence in General Population" refers to the % of patients with the diagnosis of interest among the population in Ontario ≥16 years of age. The % under column "Prevalence of PH" refers to the % of patients with PH among those who have the diagnosis of interest.
Abbreviations: PH- pulmonary hypertension; COPD – Chronic Obstructive Pulmonary Disease
Note - For each group, % PH cohorts were compared between 2002 and 2012. All comparisons showed a statistically significant change in the percentage of PH cohorts between years ($p < 0.001$)

Table S4: Trend Analysis of Incidence Rates (2003-2012)

	PH Group									
	All		1		2		3		4	
Group	**Mean Estimate**	**P-Value**	**Mean Estimate**	**P-Value**	**Mean Estimate**	**P-Value**	**Mean Estimate**	**P-Value**	**Mean Estimate**	**P-Value**
All Patients	1.029	<.0001	1.037	0.0014	1.030	<.0001	1.021	0.0011	1.086	<.0001
Adults	1.025	<.0001	1.035	0.0022	1.027	0.0001	1.017	0.0025	1.083	<.0001
Pediatrics	1.041	0.0329	1.031	0.1996	1.051	0.0896	1.054	0.0904	1.078	0.2154
Females	1.030	0.0001	1.038	0.0036	1.031	0.0003	1.024	0.0023	1.086	0.0002
Males	1.027	0.0004	1.035	0.0141	1.029	0.0005	1.017	0.0118	1.087	0.0004

Mean Estimate = average change in incidence between 2003-2012 (e.g. a mean estimate of 1.026 means the average increase in incidence between 2003-2012 was 2.6%)
Trend analysis was done using general additive model

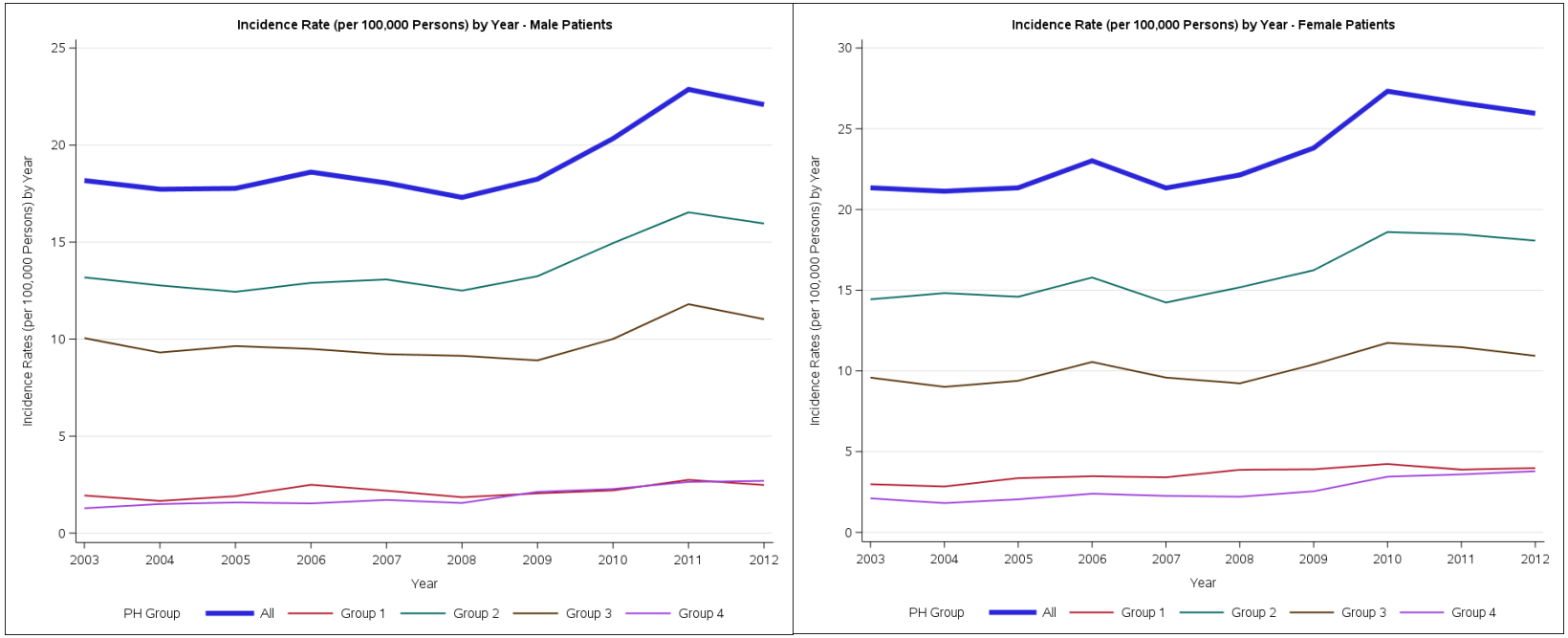


Figure S2: Incident rates of Pulmonary Hypertension per 100,000 persons by year (by gender)

Table S5: Crude Mortality Rate (per 100) by Group of PH and by Age group

All PH patients															
Year	**30 Day**					**1 Year**					**5 Year**				
	All	**1**	**2**	**3**	**4**	**All**	**1**	**2**	**3**	**4**	**All**	**1**	**2**	**3**	**4**
2003	14.0	13.4	13.7	15.5	11.9	35.9	23.0	38.0	41.9	36.2	64.2	44.9	67.7	74.9	59.5
2004	11.4	8.2	11.4	13.4	10.6	33.5	21.3	35.2	39.8	30.0	63.1	48.2	65.2	74.3	57
2005	13.7	10.8	14.2	15.2	11.8	35.1	24.0	36.9	40.1	31.9	65.1	42.6	68.9	75.9	61.6
2006	12.4	7.1	12.8	14.8	20.7	35.5	21.0	37.9	42.0	44.2	64.4	42.0	68.7	73.5	69.7
2007	13.7	9.4	14.0	17.3	16.4	36.9	26.6	39.1	42.9	34.4	64.0	47.6	67.7	74.6	62.5
2008	13.5	8.6	14.5	16.4	16.3	38.2	25.1	41.4	46.1	41.2	65.7	49.2	69.4	75.8	62.9
2009	12.7	7.6	13.5	16.2	14.3	35.0	21.4	38.6	41.3	36.5	64.0	41.7	68.9	74.4	63.2
2010	12.8	6.5	13.9	15.8	12.6	37.2	22.8	40.8	44.1	36.7	63.5	44.5	68.1	72.6	61.2
2011	11.7	6.3	12.8	13.6	14.1	34.2	17.3	37.8	40.2	36.4	55.2	32.8	59.7	64.4	56.9
2012	12.8	7.3	13.7	16.3	14.8	37.4	22.8	40.9	46.0	40.8	50.1	30.6	54.8	59.6	50.8
Overall	12.8	8.3	13.4	15.4	14.4	35.9	22.4	38.8	42.5	37.2	61.5	41.9	65.5	71.5	59.8
Patients ≥ 16 years															
Year	**30 Day**					**1 Year**					**5 Year**				
	All	**1**	**2**	**3**	**4**	**All**	**1**	**2**	**3**	**4**	**All**	**1**	**2**	**3**	**4**
2003	14.1	14.1	13.7	15.6	12.3	36.7	24.5	38.3	42.2	37.3	65.6	48.7	68.3	75.7	61.3
2004	11.5	8.2	11.5	13.6	10.7	33.9	21.9	35.5	40.2	30.1	63.9	49.4	65.7	75.0	57.3
2005	13.7	11.0	14.2	15.3	11.9	35.4	24.4	37.0	40.4	32.2	65.9	43.8	69.2	76.5	62.1
2006	12.4	7.0	12.8	14.8	21.0	35.7	20.9	37.9	42.1	44.8	65.1	42.9	68.9	74.2	70.2
2007	13.9	9.7	14.2	17.5	16.5	37.4	27.4	39.5	43.4	34.6	65.0	49.9	68.3	75.4	63.0
2008	13.7	8.7	14.6	16.5	16.6	38.6	25.8	41.6	46.2	41.5	66.5	50.8	69.9	76.1	63.5
2009	13.0	8.1	13.6	16.3	14.7	35.6	22.9	38.8	41.7	37.1	65.3	45.0	69.5	75.2	64.5
2010	12.9	6.7	13.9	15.9	12.5	37.6	22.9	41.0	44.5	37.0	64.4	46.1	68.6	73.3	61.4
2011	11.8	6.1	12.9	13.7	14.3	34.4	16.8	37.9	40.4	36.7	55.9	33.4	60.0	64.9	57.5
2012	12.9	7.1	13.9	16.5	14.7	37.9	22.9	41.3	46.7	40.6	50.8	31.0	55.2	60.4	50.7
Overall	13.0	8.4	13.5	15.6	14.5	36.4	22.9	39.0	42.8	37.5	62.4	43.5	66.0	72.2	60.4
Patients < 16 years															
Year	**30 Day**					**1 Year**					**5 Year**				
	All	**1**	**2**	**3**	**4**	**All**	**1**	**2**	**3**	**4**	**All**	**1**	**2**	**3**	**4**
2003	8.6	8.3	10.5	11.1	0	11.4	11.1	10.5	16.7	0	15.7	16.7	10.5	22.2	0
2004	4.4	7.7	4.5	0	0	11.1	7.7	18.2	7.1	0	22.2	23.1	22.7	21.4	0

2005	9.1	8.0	10.0	7.7	0	18.2	20.0	20.0	7.7	0	25.0	28.0	20.0	15.4	0
2006	10.9	9.1	16.7	14.3	0	27.3	22.7	38.9	33.3	0	30.9	27.3	44.4	33.3	33.3
2007	3.2	4.5	0	4.5	0	15.9	13.6	16	18.2	0	22.2	13.6	28.0	31.8	0
2008	4.8	5.6	5.3	0	0	11.9	11.1	15.8	14.3	25	19.0	16.7	21.1	28.6	25.0
2009	4.1	2.9	4.5	5.6	0	13.5	5.7	22.7	16.7	12.5	16.2	8.6	22.7	22.2	12.5
2010	6.2	3.6	8.3	10.5	20.0	16.9	21.4	16.7	10.5	20.0	20.0	21.4	20.8	15.8	40.0
2011	6.7	8.6	4.3	4.5	0	24	22.9	26.1	27.3	16.7	25.3	25.7	26.1	27.3	16.7
2012	6.8	10.7	3.6	7.4	20.0	16.2	21.4	14.3	11.1	60.0	20.3	25.0	21.4	14.8	60.0
Overall	6.4	6.9	6.2	7.2	4.8	16.8	16.0	19.5	17.1	16.7	21.4	20.2	23.8	23.2	21.4

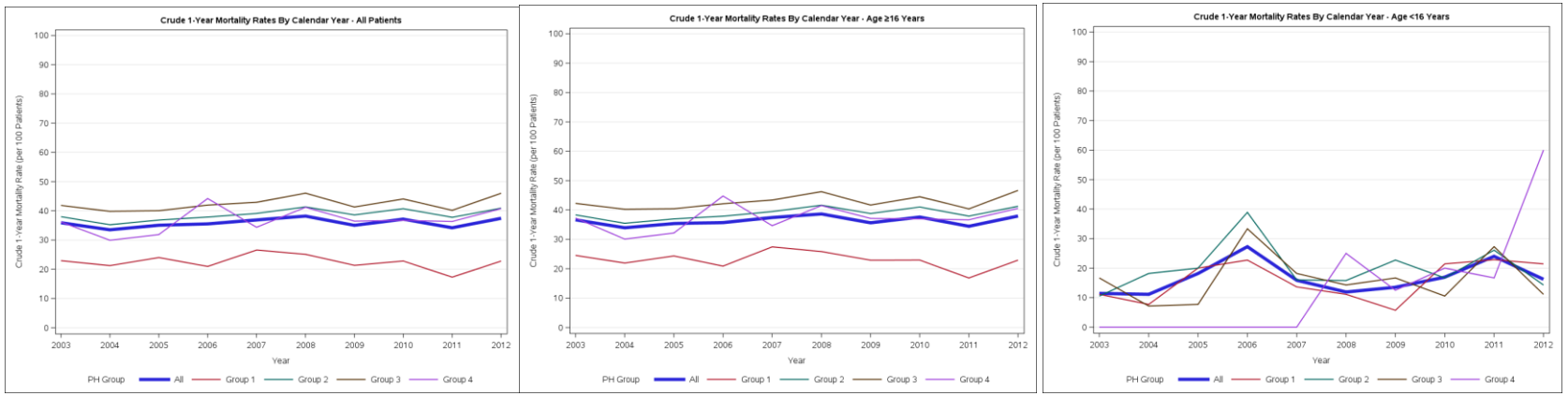


Figure S3: Crude 1 year mortality rate by calendar year for patients with Pulmonary Hypertension

Table S6: Description of Group 2/3 adult PH Patients with/without Combination Diagnoses (Group 2+3)

	Group 2	Group 3	Group 2+3	p value
	N = 9,956	N = 3,641	N = 9,155	
Female Gender (%)	58.2%	53.4%	51.1%	<0.001
Mean age at index date* (SD)	73.7 (14.0)	69.3 (13.2)	74.4 (11.6)	<0.001
Mean total ADG Score (SD)	14.6 (4.0)	15.0 (3.9)	16.1 (3.8)	<0.001
Mean major ADG Score (SD)	3.8 (1.5)	3.8 (1.5)	4.2 (1.5)	<0.001

Abbreviations: PH- pulmonary hypertension; SD- standard deviation; ADG- the Johns Hopkins Aggregated Diagnosis Groups
Statistical comparisons conducted using one way ANOVA test

Table S7: Standardized Mortality Ratios (2003/2011) for Group 2/3 adult PH patients with/without combination diagnoses (Group 2+3)

Year	Group	SMR	95% Confidence Interval
2003	Group 2	8.4	(7.4, 9.4)
	Group 3	13.3	(11.2, 15.5)
	Group 2+3	10.4	(9.3, 11.5)
2011	Group 2	5.9	(5.3, 6.5)
	Group 3	10.5	(8.8, 12.1)
	Group 2+3	8.5	(7.8, 9.3)

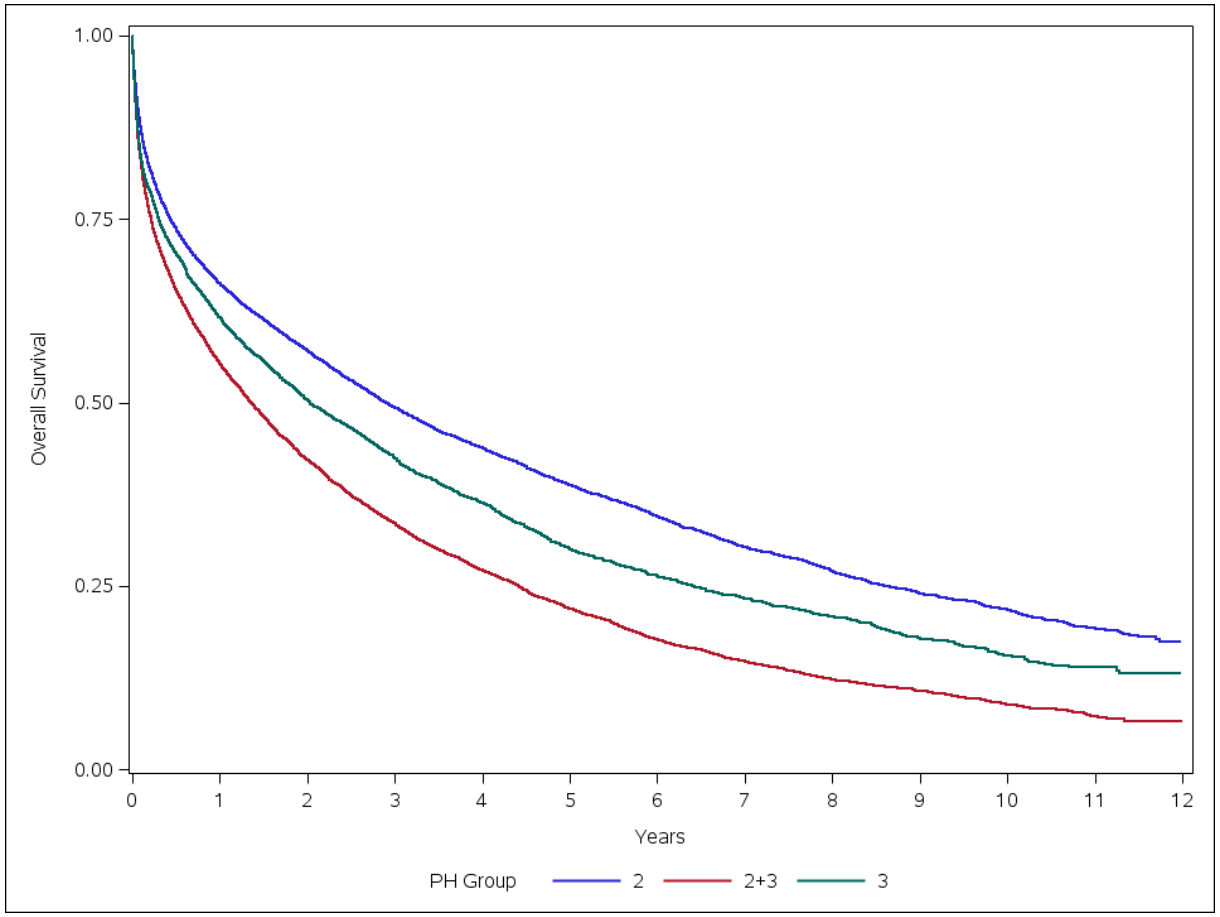


Figure S4: Survival of Group 2/3 adult PH patients with/without combination diagnoses