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Early View

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Mortality Trends in Pulmonary Arterial Hypertension in Canada: A Temporal Analysis of Survival per ESC/ERS Guideline Era

Running Title: Temporal Changes in PAH survival in Canada

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Abstract

Introduction: The evolution in pulmonary arterial hypertension (PAH) management has been summarized in three iterations of the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines. No study has assessed whether changes in management, as reflected in the changing guidelines, has translated to improved long-term survival in PAH.

Methods: Mixed retrospective/prospective analysis of treatment naïve, incident PAH patients (n=392) diagnosed at three major centers in Canada from 2009-2021. Patients were divided into two groups based on their diagnosis date and in accordance with three ESC/ERS guideline iterations: 2009 and 2015. Overall survival was assessed based on date of diagnosis and initial treatment strategy (i.e. mono vs combination).

Results: In Canada, there was a shift towards more aggressive upfront management with combination therapy after the publication of the 2015 guidelines (10.4% and 30.8% in 2009-2015 patients, and 36.0% and 57.4% in 2016-2021 patients, for baseline and 2-year follow-up respectively). A key factor associated with combination therapy after 2015 was higher pulmonary vascular resistance (p=0.009). The 1, 3 and 5 year survival rates in Canada were 89.2%, 75.6%. and 56.0%, respectively. Despite changes in management, there was no improvement in long-term survival before and after publication of the 2015 ESC/ERS guideline (p=0.53).

Conclusions: There was an increase in the use of initial and sequential combination therapy in Canada after publication of the 2015 ESC/ERS guidelines, which was not associated with improved long-term survival. These data highlight the continued difficulties of managing this aggressive pulmonary disease in an era without a cure.

Introduction:

Pulmonary arterial hypertension (PAH) is a progressive pulmonary arteriopathy, which engenders elevations in pulmonary vascular resistance (PVR) and right ventricular (RV) strain.[1, 2] Right heart failure is a common sequel of PAH, and represents the leading cause of death in these patients. [3] Over the last 40 years, a number of national registries have yielded valuable epidemiological data on demographics, hemodynamics, prognostic factors, and real-world treatment approaches for patients with PAH. As these registries cumulatively span several decades, they offer unique insights into secular trends in PAH mortality.

The natural progression of the disease in the pre-treatment era of PAH was captured by the US National Institutes of Health (NIH) Primary Pulmonary Hypertension registry in the 1980s.[3] At this time, outcomes were grim with one and five-year survival rates of only 68% and 34%, respectively.[3] The advent of epoprostenol in the early 90s revolutionized treatment for these patients, conferring marked improvements in survival, with one and five-year survival rates of 88% and 47% (~14-20% absolute improvement) respectively.[4] Since the introduction of epoprostenol, 5 main classes of pharmaceutical agents have been approved for the treatment of PAH. PAH treatment options now include prostacyclin analogs/prostacyclin receptor agonists, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 (PDE5) inhibitors/activators of soluble guanylate cyclase, which target three aberrant pathways: prostacyclin, endothelial, and nitric oxide pathways, respectively. The primary mechanism of action for these therapies relate to vasodilation with subsequent improvement in symptoms and improve functional capacity, but their ability to prevent disease progression and improve survival remains less certain.[5]

The evolution in PAH management is reflected in several iterations of the American [6–8], Canadian [9], and European guidelines [10–12]. One of the most significant advancements in

PAH management was reflected in the 2015 joint European Society of Cardiology (ESC)/ European Respiratory Society (ERS) clinical guidelines which introduced the concept of initial risk-guided therapy.[10] Treatment algorithms were incorporated into these contemporary guidelines, illustrating an important shift towards more aggressive upfront management with combination therapy. These changes were subsequently endorsed by the 6th World Symposium on PH (WSPH 2018).[13] That is, for patients deemed 'high-risk', initial combination therapy including intravenous (IV) prostacyclin is recommended. Conversely, guidelines recommend 'low' or 'intermediate-risk' patients be treated with either initial monotherapy or dual oral combination therapy. To date, no study has evaluated whether these episodic changes in guideline treatment recommendations are followed by incremental improvements in long-term survival in a real world population.

There is a paucity of multicentre Canadian PAH outcomes data as the first prospective clinical Canadian registry was only recently initiated. As such, we have little insight into the changing landscape of PAH disease characteristics and mortality across Canada. Therefore, the aims of the present study were twofold, 1) to describe any temporal changes in demographics, disease characteristics, and management of PAH in Canada, and 2) to describe the secular trends in PAH mortality in Canada. We hypothesized that there would be increasing use of combination therapy and improvements in mortality following major PAH treatment guideline updates, particularly after 2015.

Methods

This study was approved by the Research Ethics Review Board at the University of Ottawa Heart Institute (20180423-01H), Calgary (REB20-0916), and Vancouver (H20-01322).

Canadian PAH Cohort

This analysis includes a cohort of treatment naïve WHO (World Health Organization) Group 1 PAH patients diagnosed at three major PAH centers in Canada: Ottawa, Ontario; Calgary, Alberta; and Vancouver, British Columbia. Group 1 PAH was ascertained by right heart catheterization in accordance with clinical guidelines at the time of diagnosis.[14] At diagnosis, patient demographics, disease characteristics, and hemodynamic data were recorded.
Patient PAH specific therapies were also documented, specifically whether they were placed on initial monotherapy (i.e. one PAH agent) or combination therapy (i.e. dual or triple therapy). A patient's initial therapy was defined as treatment up to three months post diagnosis. To determine temporal changes in management, patient's PAH therapy at 2-years post diagnosis, death or last clinical visit was recorded.

Ottawa:

Treatment naïve WHO Group 1 PAH patients who received their incident diagnosis at the University of Ottawa Heart Institute between January 2009 - October 30, 2017 were retrospectively identified. After October 30, 2017, patients were prospectively enrolled until August 20, 2021.

Calgary:

Patients diagnosed from January 2015 until April 2018 were retrospectively identified from a local right heart catheterization database. After April 2018 patients were enrolled prospectively in the Canadian Pulmonary Hypertension Registry using PAHTool® (INOVULTUS, Santa Maria da Feira, Portugal) until March 2021.

Vancouver:

Patients were prospectively enrolled in the Canadian Pulmonary Hypertension registry from January 1, 2017 until January 24, 2021.

Treatment Era:

Patients were divided into two groups according to their incident diagnosis date and in relation to iterations of the ESC or ESC/ERS PAH treatment guidelines: i) 2009 to 2015 (2009 update), ii) August 2015 to present (2015 update) (Table 1).

Statistical Analysis

Differences in demographics and disease characteristics between treatment eras were compared using ANOVA or a chi-square test where appropriate. The primary endpoint was transplant-free survival. All patients were followed until death, lung or heart-lung transplant, or their last clinical encounter; whichever occurred first. Patients were censored at the end of the follow-up period. Transplant-free survival was analyzed using the Kaplan-Meier method and differences between risk strata were assessed by the Log-Rank test.

To examine the impact of initial therapy on survival in patients diagnosed after 2015, a propensity score was first developed to account for the selection bias and nonrandomized treatment allocation of mono vs combination therapy. Specifically, this approach used a logistic regression model to summarize measured covariates that were predictors of this decision into a single composite score that represents a probability of a patient being treated with mono vs combination therapy. For this analysis, missing values of the covariates were imputed (multiple imputations) to ensure that propensity scores could be calculated for all patients. The distribution of the propensity scores derived from the multiple imputations were compared between patients who were placed on mono and combination therapy. A total of 14 demographic and clinical covariates that were associated with initial treatment strategy were entered into the propensity score model. Next, we used a multivariable Cox proportional hazards model to assess for the HR associated with combination therapy, as compared to patients initiated on mono therapy; this was adjusted for the propensity score, NYHA function class, PVR and ESC/ERS risk score. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute, NC), and graphics were created using the R statistical environment (R Development Core Team). Code is available upon request.

Results:

Demographic Characteristics at Diagnosis

We identified a cohort of 435 incident and treatment naïve WHO Group 1 PAH patients in three major cities across Canada: Ottawa (n=234), Calgary (n=111) and Vancouver (n=47). As expected, this cohort was comprised of predominantly idiopathic PAH (iPAH) and PAH associated with connective tissue disease (APAH-CTD) , at 58.4% and 30.4% respectively

(Table 2). At the time of diagnosis, patients had a mean age of 61.1±16.4 years, with the majority (64.0%) experiencing NYHA functional class III symptoms. The incident right heart catheterization revealed an average mPAP of 45.2±12.7 mm Hg, a RAP of 8.5±5.4 mm Hg, a PVR of 9.7±5.3 Woods units and a CI of 2.2 ±0.7 L/min/m^2.

Temporal Changes in Patient Demographics:

Patients were grouped relative to their diagnosis date and in accordance with publication of the respective ESC/ERS guideline iteration (i.e. 2009-2015, after 2015). Baseline demographics and co-morbidities were similar over the 12-year follow-up period (Table 2). After 2015, there was a slight decrease in the proportion of patients diagnosed with iPAH (64% in 2009 and 56% in 2015), with increasing proportions of drug/toxin-induced PAH and portopulmonary hypertension (table 2). RHC data also revealed a similar degree of PAH severity over this time period with no differences in mPAP, RAP, PVR or CI at diagnosis (Table 2).

Initial PAH Therapy

Therapeutic advancements in the past two decades have been summarized in multiple iterations of the ESC/ERS guidelines (Table 1). In the 2015 update, guidelines endorsed a switch from NYHA functional class to a risk-based therapeutic strategy. In our Canadian cohort of incident PAH patients, the functional classification and ESC/ERS risk status were similar over the course of the two guideline implementation periods (Figure 1B/D). As expected, patients presenting with advanced NYHA class (Figure 1A) or ESC/ERS risk-status (Figure 1C) had a higher risk of mortality ($p<0.001$).

Over time, there has been a transition to more aggressive upfront management with dual or even triple therapy for patients at elevated risk. Between 2009-2015, 85% of patients were treated with initial monotherapy (Figure 2A), with the majority being prescribed bosentan or tadalafil (Figure 2B). After 2015, 40.1% of patients who were not vasoreactive and qualified for treatment (NYHA II-IV) with PAH therapies were placed on initial combination therapy (Figure 2C). In patients with NYHA class III/IV symptoms 45.0% were placed on either initial dual or triple therapy (Figure 2C). The percentage of patients on combination therapy at 2-year follow-up further improved with only 30.8% of patients diagnosed from 2009-2015, to 57.4% in patients diagnosed after 2015 (Figure 2A). The demographics and disease characteristics of patients initiated on combination vs mono-therapy—and who were diagnosed after 2015—are illustrated in Supplemental Table 1. Patients placed on initial combination therapy were, on average, younger (57.8±16.6 vs 63.1±15.9 (p=0.013)) and tended to have a lower burden of co-morbidities like diabetes (mono=35.2% vs comb=20.8%, p=0.029), and atrial fibrillation (mono=21.4% vs comb=11.5%, p=0.08). Patients placed on combination therapy also had a higher proportion of patients with NYHA group III/IV symptoms (p=0.024) and had more severe hemodynamics (PVR: 11.9±5.8 vs. 8.4±4.4, p<0.0001; CI: 2.0±0.6 vs. 2.3±0.6, p=0.0027).

Survival:

The median follow-up was 2.91 years (IQR: 1.45, 4.58 years) with a maximum follow-up duration of 11.7 years. During this time period there were 143 deaths and 4 lung transplants. The 1, 3 and 5 year survival rates in our Canadian PAH cohort were 89.2% (95%CI: 86.2, 92.4), 75.6% (95%CI: 71.1, 80.4), and 56.0% (49.9, 62.8) respectively. In the overall population, there was no impact of diagnosis date on 1 or 5-year mortality rates (Figure 3). Specifically, 1-year

survival rates for patients diagnosed during the 2009 and 2015 guideline era were 88.8%, 89.5% respectively (p=0.87). Similarly, the 5-year survival rates were also not statistically different across these time periods (53.8% and 58.9% respectively (p=0.53)). In our cohort, age at diagnosis (p<0.0001, Supplemental Figure 1) and male sex (p=0.0035, Supplemental Figure 2) were associated with higher mortality risk. The lack of temporal improvement in survival across the two guideline iterations was consistent even when stratifying the cohort by age (Supplemental figure 1), sex (Supplemental Figure 2) and PAH subtype (Supplemental Figure 3).

Survival rates from historic and contemporary PAH registries were graphed in chronological order (Figure 4). In our Canadian PAH cohort, survival rates were comparable to other time-matched national registries. After the introduction of epoprostenol in the early 90s, 1-year survival rates appear to have plateaued for the subsequent 3 decades. The 3- and 5-year survival rates reached their zenith in the early 2000s, and seem to have similarly plateaued for the successive two decades.

Initial treatment strategy and survival:

In the overall population, there was no difference in 1-year (Figure 5A) or 5-year (Figure 5B) survival in patients who received upfront monotherapy (5yr, 52.7%) or dual therapy (5yr, 59.2%, p=0.32). There was also no difference in survival between patients on sequential combination therapy and patients placed on initial dual therapy (p=0.45, Supplemental Figure 4). In an exploratory analysis, there was an early signal that upfront triple therapy may confer a survival benefit (Figure 5); however, there was likely insufficient power to detect a difference (n=7). The largest trial in support of upfront combination therapy was the AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial, which compared

ambrisentan and tadalafil vs. either drug alone as monotherapy.[15] When the inclusion/exclusion criteria were applied to our Canadian cohort, only 41.8% would have qualified (Supplemental Figure 5). In our Canadian cohort, this trial would have preselected a group of patients with a more favorable prognosis (p=0.0002).

Multivariable Modelling

a) Overall population

There was no association between upfront combination therapy and better survival after adjusting for baseline ESC/ERS risk category (Dual vs Mono HR: 0.70, 95% CI 0.45,1.08, p=0.11).

b) Diagnosis date >2015: Logistic regression-derived propensity score

Logistic regression identified multiple factors as predictive of being treated with initial combination therapy in patients receiving a PAH diagnosed after 2015 (x^2=43.2, c index=0.75, Table 3). In the multivariable analysis, age at diagnosis (p=0.15), and PVR (p=0.0098) were associated with initial combination therapy. Of these variables, PVR (x^2=6.67, p=0.0098), and age at diagnosis (x^2=2.1, p=0.15) were the predominant factors associated with use of combination therapy (Table 3). The predicted likelihood of combination therapy for each individual patient was determined from this model and was entered into the Cox Proportional Hazards model as a propensity score to adjust for the lack of randomization (Table 4). In the Cox model, there was also no association between initial combination therapy and survival after adjusting for the propensity score, PVR and ESC risk score (HR=0.76 95%CI 0.40, 1.46).

Discussion:

Data derived from major historic and contemporary PAH registries demonstrate only modest improvements in short and long-term survival over the past few decades despite several guideline iterations and new drugs that target the three key pathways. This study investigated secular trends in mortality in patients with PAH in Canada, focusing on changes after the publication of the 2015 ESC/ERS-based guidelines. Major findings from our Canadian cohort were: 1) the demographics and pulmonary hemodynamics of PAH patients have been stable over the 12 year follow-up period, 2) a higher proportion of patients were treated with initial dual or triple therapy after publication of the 2015 ESC/ERS guidelines, 3) despite clear evolution in PAH management strategies, there was no parallel improvement in 1- or 5-year survival rates at three major PAH centres in Canada after publication of the 2015 guidelines, and 4) initial dual therapy was not associated with better transplant-free survival compared with initial monotherapy. Together, this body of work highlights the difficulties of managing this aggressive pulmonary vascular disease in an era without a cure.

To our knowledge, this is the first study to examine long-term survival before and after publication of the ESC/ERS 2015 PAH guidelines. A key finding from our study was an absence of improvement in survival despite clear efforts to comply with the prevailing guideline. These data add credence to our understanding that contemporary management does not target causative mechanisms and may fail to improve overall survival. Our data is supported by several other large national registries (Figure 4), which demonstrate little improvement in survival since the advent of epoprostenol in the early 90s. This is particularly relevant as intravenous epoprostenol is the only PAH therapy with a demonstrated survival benefit in a single randomised multicentre open-label trial conducted over 30 years ago.[16] There was low use of epoprostenol in initial

regimens in our cohort. However approximately 4% of patients in our study were receiving parenteral prostanoids by 2 years in all three time periods, which is slightly lower, but still comparable to rates of prostanoid use in other national registries.[17, 18] While combination therapy provides unquestionable clinical benefits to patients as demonstrated in several RCTs [19, 20, 15], the ultimate impact of sequential or upfront combination therapy on long-term survival remains to be established. To date, trials have historically used a combined clinical morbidity/mortality endpoint including a change in six minute walk distance, which yields equivocal prognostic utility.[21–23] Meta-analyses on these trials have consistently demonstrated an overall benefit of combination therapy on time to clinical worsening, but have produced conflicting reports on mortality.[19, 20] At this time it is unclear why survival has not improved at our Canada PAH centres, but our data does not preclude the possibility of improvements in cause-specific mortality from PAH. It is also possible that the lack of improvement was due to <50% of patients being placed on upfront combination therapy after 2015, but by two year follow-up 57% of these patients were on dual or even triple therapy. Thus, another interpretation is that sequential combination therapy strategies have similar benefits to upfront combination therapy with respect to long-term survival. The relatively low rate of initial combination therapy use may be potentially explained by the barriers and delays in access to reimbursement for combination therapy that were present at many Canadian PH centres until more recent years.

Sequential management with dual or triple therapy is now the reality for many patients who have an inadequate initial response to a single agent or eventual progression to RV failure. The AMBITION trial provided impetus for more aggressive upfront management with combination therapy that is now incorporated into clinical guidelines (Table 1). AMBITION

investigated the effect of upfront combination therapy with ambrisentan and tadalafil in treatment naïve patients compared to those receiving monotherapy on the composite endpoint of death, hospitalization, disease progression or unsatisfactory long-term clinical response.[15] Patients placed on upfront dual therapy had a 50% decrease in clinical failure events. Importantly, the primary endpoint was largely driven by a decrease in hospitalization for PAH in patients on combination therapy. In a *post hoc* analysis of the AMBITION trial data there was a suggestion that survival might be improved for patients who were receiving initial dual therapy, but this requires confirmation.[24] In our study, there was also no difference in survival between patients placed on initial mono versus dual therapy, even after adjusting for baseline mortality risk and disease severity. However, our results do corroborate recent evidence from the French PAH registry which found no difference in long-term survival between those treated with upfront mono or dual therapy in the overall cohort, although there was a small benefit with dual therapy in the subgroup who were intermediate risk at baseline.[25] It is also noteworthy that many modern PAH RCTs are biased towards selecting a more homogenous population of clinically stable patients without comorbidities. When we applied the AMBITION inclusion/exclusion criteria to the available data in our Canadian cohort, 57% were excluded. Excluded patients were more likely to present with co-morbid conditions which conferred a worse prognosis than patients satisfying the inclusion/exclusion criteria for AMBITION.

This Canadian cohort includes patients who were evaluated over an extended period of time over which management and treatment of PAH has changed. This enabled us to examine whether the evolution of treatment, as reflected in the changing guidelines, has translated to better long-term survival in Canada. The present analysis encompasses PAH patients from 3 major centers in Canada and represents the largest published Canadian PAH cohort to date.

However, there were a few limitations of this analysis. We recognize the limitations in retrospectively collecting data on patients between 2009-2017; however, the comparable survival in this group to other international registries argues against a major selection bias. In the present study, we collected data on initial upfront therapy (within 3 months after diagnosis). After the publication of the 2015 guidelines, the overall number of patients treated with initial combination therapy was still low, relative to their ESC/ERS risk assessment. While some patients after 2015 were only initiated on monotherapy, by the two year follow-up, 57% of these patients were escalated to dual or even triple therapy, in accordance with their perceived risk or clinical deterioration. Thus, while the use of initial combination therapy was lower than expected, sequential combination therapy was frequently used. We also acknowledge that the propensity score model we used does not account for these later sequential therapy decisions, nor does it fully eliminate the possibility of residual confounding, which can only be reduced by randomization of treatment strategy allocation. The secular trends in PAH survival in the PAH registries also need to be interpreted in the context of changing patient demographics. This is particularly relevant for comparisons with the NIH cohort which had a mean age at diagnosis that was markedly younger than in more contemporary cohorts.

Summary:

In summary, our study of incident PAH patients in Canada found that the evolution to a more aggressive initial treatment approach was not associated with incremental improvements in survival in recent years. This study supports the urgent need for new therapies that directly and selectively target disease mechanisms. Other factors such as earlier diagnosis of PAH and

personalization of existing drugs in different combinations continues to be an important area of investigation.

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Table I: ESC/ERS Guidelines for initial therapy for non-responders to acute vasoreactivity testing

	ESC/ERS Guideline			
	2004[12]	**2009**[11]		**2015**[10]
WHO-FC I	-	-		-
WHO-FC II		Monotherapy with: ERA; or PDE-5 Inhibitor	Low Risk	Initial Monotherapy; or initial combination therapy considered
WHO-FC III	Monotherapy with: ERA; or PDE-5 Inhibitor; or prostanoid; or i.v. Epoprostenol	Monotherapy with: ERA; or PDE-5 Inhibitor; or prostanoid	Intermediate Risk	
WHO-FC IV	Monotherapy with: i.v. Epoprostenol	Monotherapy with: i.v. Epoprostenol; or - Initial Combination therapy	High Risk	Initial combination including i.v. PCA
	Available PAH Specific Drugs			
PDE-5 inhibitors	Sildenafil	Sildenafil Tadalafil		Sildenafil Tadalafil Vardenafil*
sGC Stimulator	-	-		Riociguat
ERA	Bosentan Ambrisentan Sitaxentan	Bosentan Ambrisentan Sitaxentan		Bosentan Ambrisentan Macitentan
PCA	Epoprostenol Iloprost* Treprostinil Beraprost*	Epoprostenol Iloprost* Treprostinil Beraprost*		Epoprostenol Iloprost* Treprostinil Beraprost*
IP Receptor Agonist	-	-		Selexipag**

WHO= World Health Organization; Association; FC=Functional Class; PAH= pulmonary arterial hypertension; ERA= endothelin receptor antagonists; PDE-5= phosphodiesterase type 5 inhibitor; sGC= soluble guanylate cyclase; PCA= Prostacyclin analogues. * Drug not available in Canada. ** Selexipag received Health Canada approval in 2016.

Table II: Patient Demographic and Disease Characteristics separated by diagnosis date and in accordance with publication of the ESC/ERS guidelines.

	Total		ESC/ESC Clinical Guidelines		
			2009 Update (2009-2015) **(N=125)**	**2015 Update** (2015-2021) **(N=267)**	**p-value**
Variables	**(n=392)**	**% missing**			
Age (Years)	61.1±16.4	0%	61.5±16.1	60.9±16.5	**0.73**
BMI (kg/m^2)	29.2±8.3	0%	29.2±8.1	29.2±8.4	**0.98**
Sex (female)	260 (66.3)	0%	87 (69.6)	173 (64.8)	**0.35**
Diabetes	98 (28)	10.1%	33 (26.6)	65 (28.8)	**0.67**
Hypertension	168 (47.3)	9.4%	60 (48.4)	108 (46.8)	**0.77**
Coronary Artery Disease	61 (17.6)	11.7%	22 (17.9)	39 (17.5)	**0.93**
Atrial Fibrillation	62 (17.8)	11.0%	24 (19.4)	36 (16.9)	**0.56**
COPD	50 (14.5)	12.0%	22 (17.7)	28 (12.7)	**0.20**
Obstructive Sleep Apnea	65 (19.9)	16.6%	19 (15.3)	46 (22.8)	**0.10**
eGFR (mL/min/1.73m^2)	69.5±25.9	6.4%	68.1±27.8	70.1±24.8	**0.48**
Group 1 PAH Subgroups		0%			**0.054**
Idiopathic	229 (58.4)		80 (64.0)	149 (55.8)	
Connective Tissue Disease	119 (30.4)		33 (26.4)	86 (32.2)	
Congenital Heart Disease	24 (6.1)		10 (8)	14 (5.2)	
Drug/Toxin	12 (3.1)		0 (0)	12 (4.5)	
Portal Hypertension	7 (1.8)		2 (1.6)	5 (1.9)	
HIV Associated	1 (0.30)		0 (0)	1 (0.4)	
NYHA Class		0%			**0.31**
1	13 (3.3)		2 (1.6)	11 (4.1)	
2	100 (25.5)		35 (28.0)	65 (24.3)	
3	251 (64.0)		82 (65.6)	169 (63.3)	
4	28 (7.1)		6 (4.8)	22 (8.2)	
6MWD (m)	293.0±143.7	16.3%	263.4±130.6	309.5±148.3	**0.0052**
mRAP (mmHg)	8.5±5.4	1.8%	8.3±4.8	8.6±5.7	**0.85**
mPAP (mmHg)	45.2±12.7	1.4%	45.4±13.9	45.2±12.2	**0.85**
PVR (Woods Units)	9.7±5.3	5.4%	9.8±5.4	9.6±5.2	**0.77**
Cardiac Index (L· min^{-1} ·m^{-2})	2.2±0.7	4.8%	2.2±0.7	2.2±0.7	**0.88**

Data mean ±SD or count (%)

BMI= body mass index; 6MWD= 6-minute walk distance; NYHA= New York Heart Association; PAH= pulmonary arterial hypertension; eGFR= estimated glomerular filtration rate; mRAP= mean right atrial pressure; mPAP= mean pulmonary artery pressure; PVR= pulmonary vascular resistance.

Table III Propensity Score: Results of the logistic regression modelling for initial combination therapy. Overall Model x^2=43.2, c=0.75

Covariates	Beta Coefficient	x^2	p-value
Intercept	0.82	0.13	0.72
BMI	0.010	0.19	0.66
Age at Diagnosis	-0.019	2.10	0.15
eGFR	-0.010	1.67	0.20
6MWD	0.0013	0.69	0.41
Cardiac Index	0.043	0.014	0.91
mPAP	-0.027	1.54	0.22
PVR	0.18	6.76	0.0098
SBP	-0.0063	0.69	0.41
NYHA Class (I/II Ref)			
NYHA III	0.022	0.009	0.92
NYHA IV	0.58	2.20	0.14
Diabetes	-0.20	1.19	0.28
Coronary Disease	-0.049	0.054	0.82
Male Sex	0.055	0.097	0.76
RHF Symptoms	-0.12	0.42	0.51
PAH Etiology (iPAH vs Other 'Ref')	-0.15	0.82	0.36

BMI= body mass index; 6MWD= 6-minute walk distance; NYHA= New York Heart Association; eGFR= estimated glomerular filtration rate; mRAP= mean right atrial pressure; mPAP= mean pulmonary artery pressure; PVR= pulmonary vascular resistance; SBP, Systolic blood pressure; PAH, pulmonary arterial hypertension; iPAH, idiopathic pulmonary arterial hypertension; CTD, connective tissue disease; CHD, congenital head disease; RHF, right heart failure.

Table IV: Cox Proportional Hazard model for all-cause death.

Factor	x^2	p-value	Hazard Ratio (95%CI)
Model 1: Total cohort of PAH-specific therapy			
Combination vs Monotherapy	2.51	0.11	0.70 (0.45, 1.08)
ESC/ERS-risk assessment			
Intermediate Risk	11.40	0.0007	2.81 (1.54, 5.13)
High Risk	4.84	0.028	3.09 (1.13, 8.45)
Model 2: Diagnosis after 2015			
Combination vs Monotherapy	0.67	0.41	0.76 (0.40, 1.46)
ESC/ERS-risk assessment			
Intermediate Risk	4.21	0.040	2.25 (1.04, 4.87)
High Risk	4.72	0.029	4.28 (1.15, 15.89)
Propensity Score	0.91	0.34	0.32 (0.030, 3.38)
PVR	1.86×10^{-8}	0.99	1.00 (0.91, 1.10)

PVR, pulmonary vascular resistance.

Figures:

Figure 1. Kaplan-Meier cures for baseline NYHA (A) and ESC/ERS-based risk assessment (C), and the associating proportion of patients (B/D) per ESC/ERS guideline iteration.

Figure 2. Class of initial and follow-up PAH Therapy per ESC/ERS Guideline Iteration (A). This was further divided according to PAH-specific agents

Figure 3. ESC/ERS treatment era and survival in PAH patients. Both 1-year (A) and 5-year (B) survival was not different before and after publication of the 2015 guidelines.

Figure 4. Survival of incident patients in historic and contemporary PAH registries. 1, 3 and 5 year survival rates are displayed with registries placed in chronological order. Red Star indicates data from our Canadian PAH cohort of treatment naïve group 1 PAH patients. NIH, National Institutes of Health pulmonary hypertension registry[3]; USA [4]; FPHN, France pulmonary hypertension registry[26]; USA-PHC, pulmonary hypertension connection database[27]; Spanish REHAP, Registry of Pulmonary Arterial Hypertension[28], UK PAH registry[29]; REVEAL, Registry to Evaluate Early And Long-term PAH disease management [30], Swiss PAH Registry [31], COMPERA-European PAH Registry, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension[32]; Sweedish PAH registry [33]; EXPERT database, The Exposure Registry Riociguat in patients with pulmonary hypertension[34].

Figure 5. Survival and initial Drug Therapy. 1-year (A) and 5-year (B) survival according to initial treatment with a single agent (monotherapy), dual or triple therapy.

Supplemental Figure 1. Patient age and survival per treatment era. In the overall cohort, older age portends a worse prognosis (A). The mean age was not different between the treatment era with similar distributions (B). In PAH patients <60 (C) and >60 (D), there was no difference in survival before and after publication of the 2015 guidelines.

Supplemental Figure 2. Patient sex and survival per treatment era. In the overall cohort, males had a worse prognosis (A). In both males (B) and females (C), there was no difference in survival before and after publication of the 2015 guidelines.

Supplemental Figure 3. PAH subtype and survival. In iPAH (A) and CTD-aPAH (B), there was no difference in survival before and after publication of the 2015 guidelines.

Supplemental Figure 4. Survival and initial combination versus sequential combination therapy. There was no difference in survival in PAH patients initiated on dual therapy as compared to sequential combination therapy.

Supplemental Figure 5. The Ambition trial inclusion/exclusion criteria was applied to our Canadian Cohort. Canadian PAH patients who satisfied the Ambition inclusion/exclusion criteria had a more favorable prognosis (A/B).

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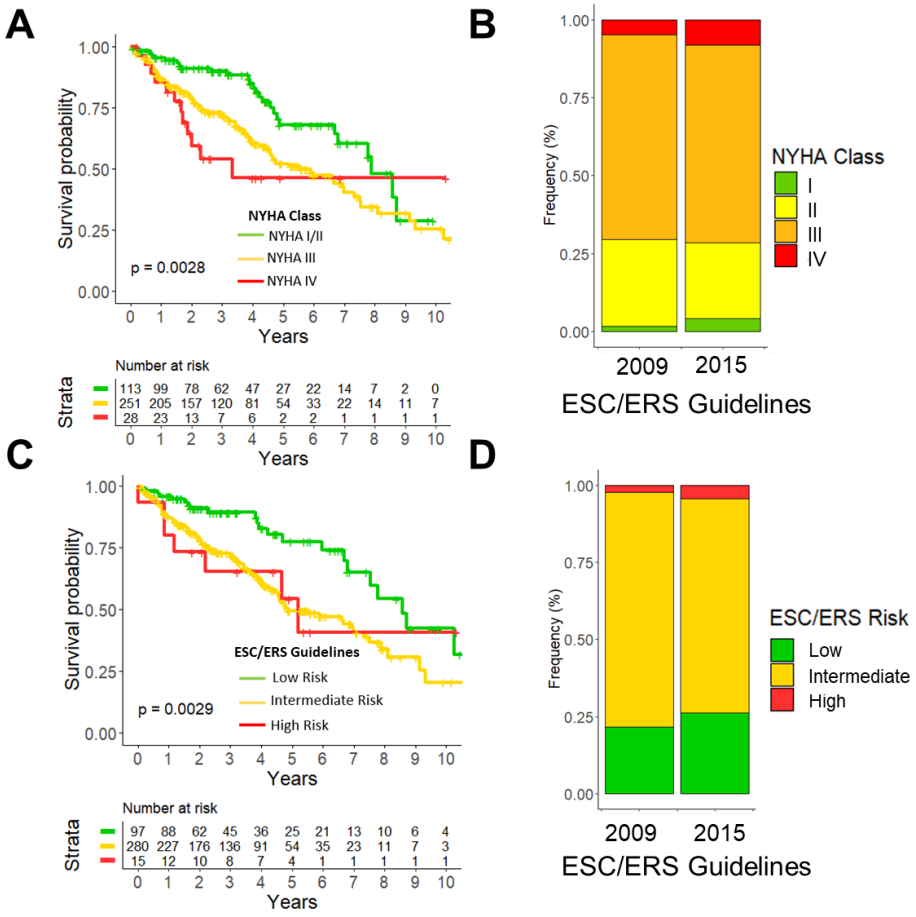

A
Survival probability
1.00
0.75
0.50
0.25
0.00
NYHA Class
NYHA I/II
NYHA III
NYHA IV
p = 0.0028
0 1 2 3 4 5 6 7 8 9 10
Years
Number at risk
Strata
113 99 78 62 47 27 22 14 7 2 0
251 205 157 120 81 54 33 22 14 11 7
28 23 13 7 6 2 2 1 1 1 1
0 1 2 3 4 5 6 7 8 9 10
Years
B
Frequency (%)
1.00
0.75
0.50
0.25
0.00
NYHA Class
I
II
III
IV
2009 2015
ESC/ERS Guidelines
C
Survival probability
1.00
0.75
0.50
0.25
0.00
ESC/ERS Guidelines
Low Risk
Intermediate Risk
High Risk
p = 0.0029
0 1 2 3 4 5 6 7 8 9 10
Years
Number at risk
Strata
97 88 62 45 36 25 21 13 10 6 4
280 227 176 136 91 54 35 23 11 7 3
15 12 10 8 7 4 1 1 1 1 1
0 1 2 3 4 5 6 7 8 9 10
Years
D
Frequency (%)
1.00
0.75
0.50
0.25
0.00
ESC/ERS Risk
Low
Intermediate
High
2009 2015
ESC/ERS Guidelines

Figure 1

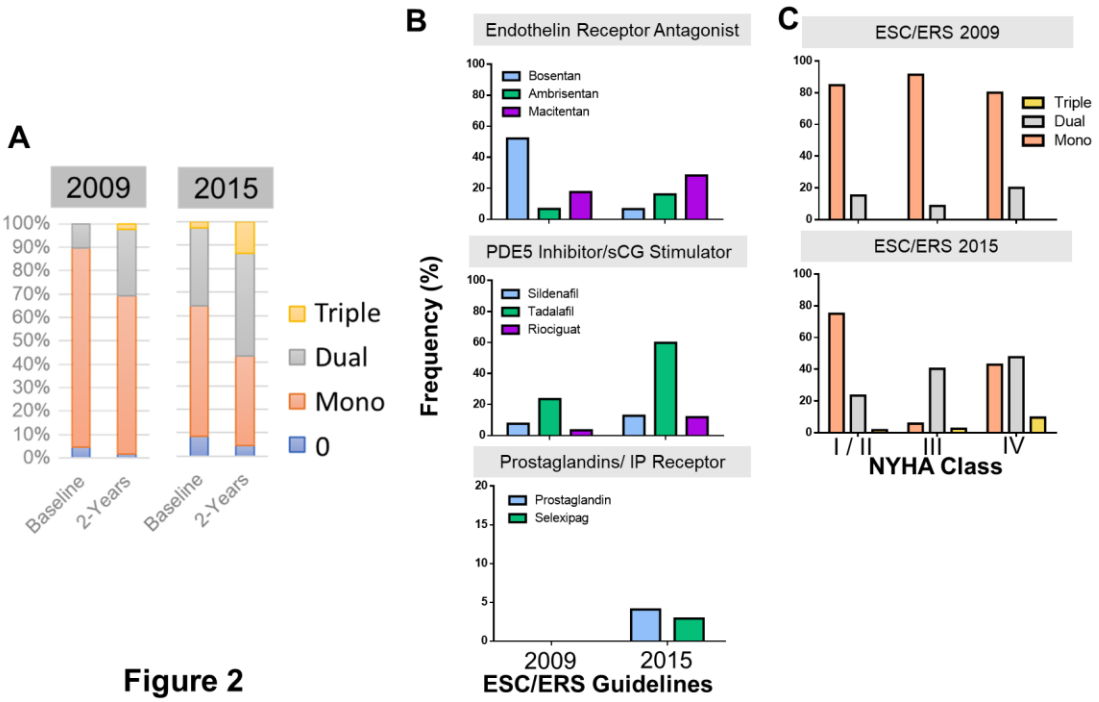

A
2009
2015
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Baseline
2-Years
Baseline
2-Years
Triple
Dual
Mono
0
B
Endothelin Receptor Antagonist
Bosentan
Ambrisentan
Macitentan
PDE5 Inhibitor/sCG Stimulator
Sildenafil
Tadalafil
Riociguat
Prostaglandins/ IP Receptor
Prostaglandin
Selexipag
Frequency (%)
2009
2015
ESC/ERS Guidelines
C
ESC/ERS 2009
ESC/ERS 2015
Triple
Dual
Mono
I / II
III
IV
NYHA Class

Figure 2

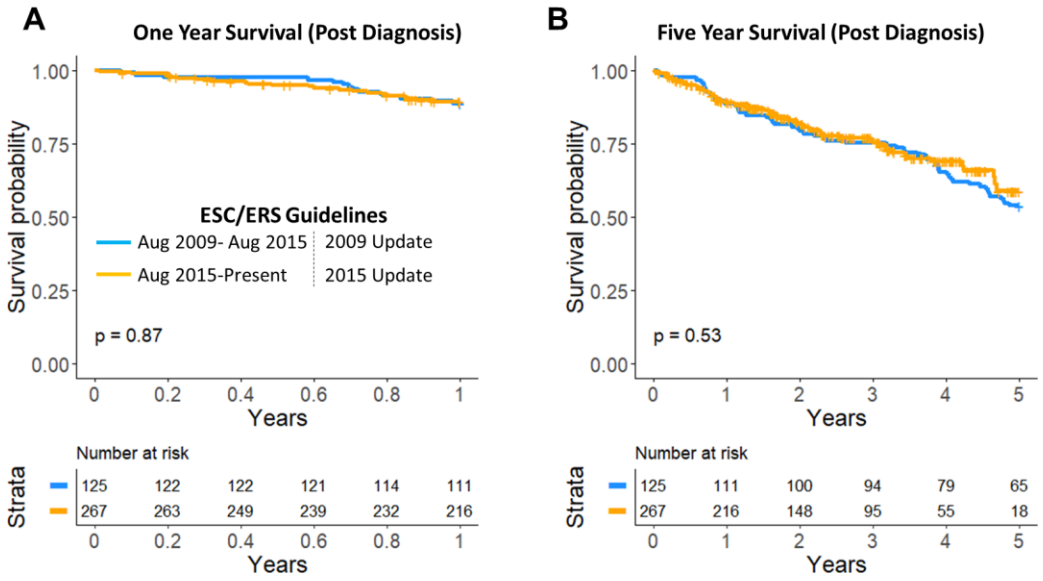

A
One Year Survival (Post Diagnosis)
Survival probability
1.00
0.75
0.50
0.25
0.00
ESC/ERS Guidelines
Aug 2009- Aug 2015
2009 Update
Aug 2015-Present
2015 Update
p = 0.87
0
0.2
0.4
0.6
0.8
1
Years
Number at risk
Strata
125 122 122 121 114 111
267 263 249 239 232 216
0
0.2
0.4
0.6
0.8
1
Years
B
Five Year Survival (Post Diagnosis)
Survival probability
1.00
0.75
0.50
0.25
0.00
p = 0.53
0
1
2
3
4
5
Years
Number at risk
Strata
125 111 100 94 79 65
267 216 148 95 55 18
0
1
2
3
4
5
Years

Figure 3

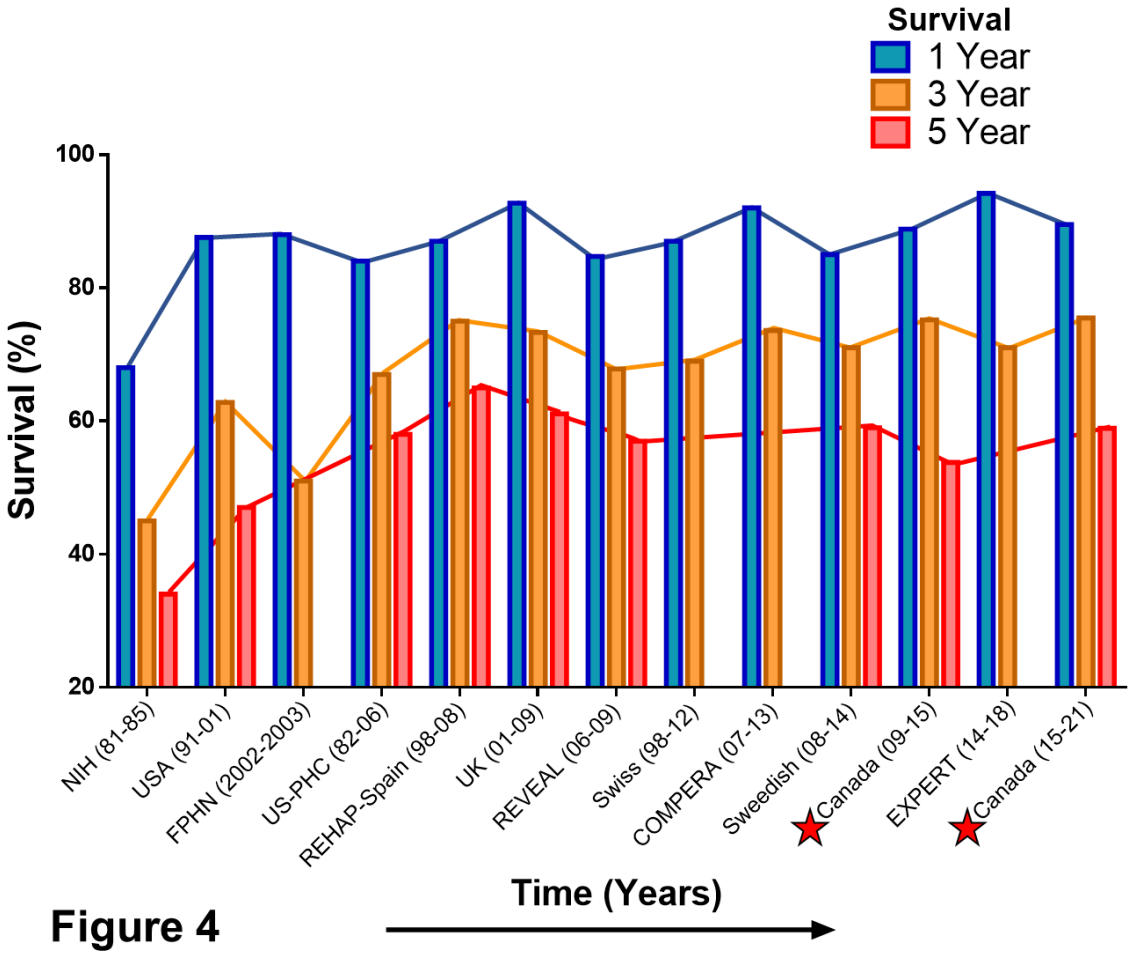

Survival
1 Year
3 Year
5 Year
100
80
60
40
20
Survival (%)
NIH (81-85)
USA (91-01)
FPHN (2002-2003)
US-PHC (82-06)
REHAP-Spain (98-08)
UK (01-09)
REVEAL (06-09)
Swiss (98-12)
COMPERA (07-13)
Sweedish (08-14)
Canada (09-15)
EXPERT (14-18)
Canada (15-21)
Time (Years)

Figure 4

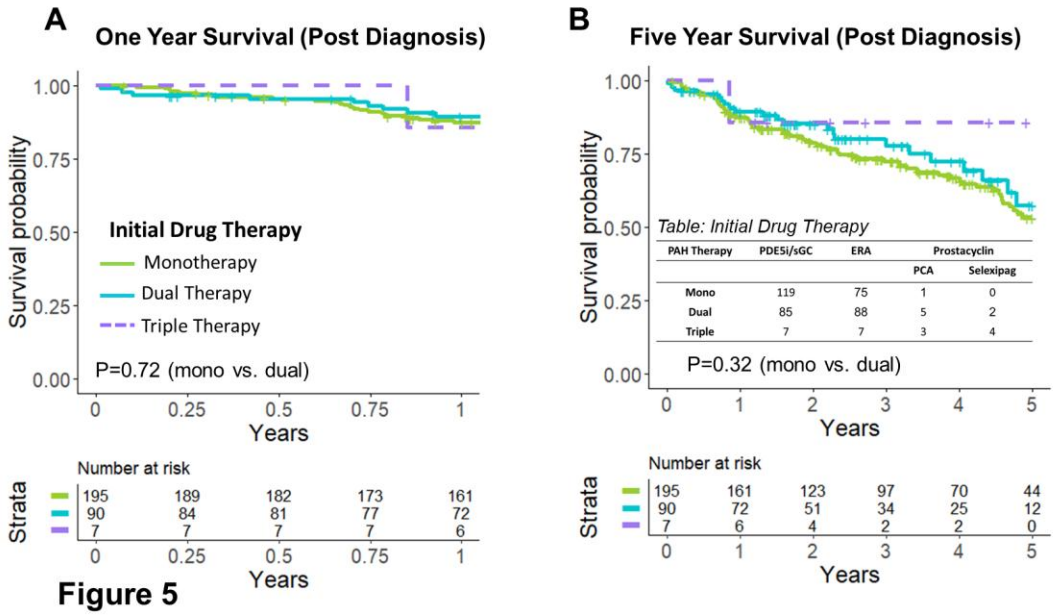
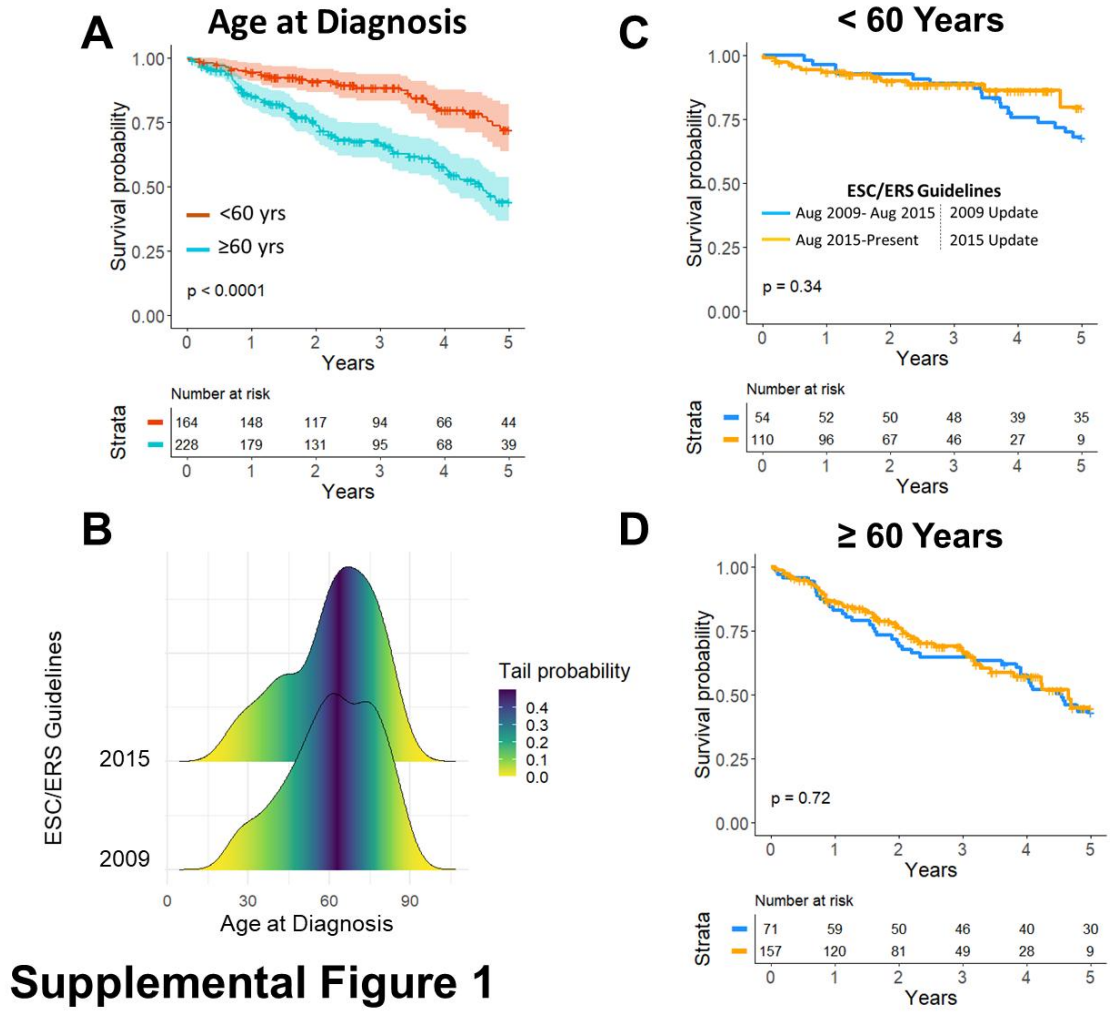
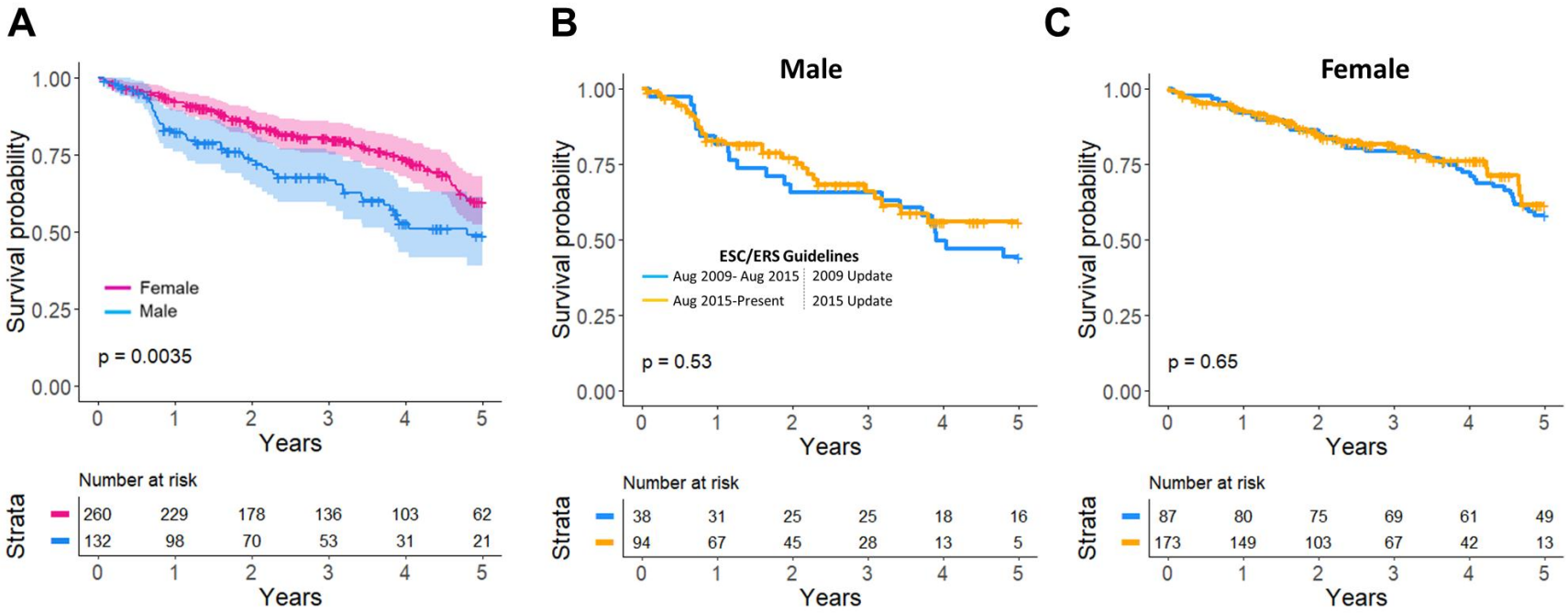

A
One Year Survival (Post Diagnosis)
Survival probability
1.00
0.75
0.50
0.25
0.00
Initial Drug Therapy
Monotherapy
Dual Therapy
Triple Therapy
P=0.72 (mono vs. dual)
0
0.25
0.5
0.75
1
Years
Number at risk
Strata
195 189 182 173 161
90 84 81 77 72
7 7 7 7 6
0 0.25 0.5 0.75 1
Years
B
Five Year Survival (Post Diagnosis)
Survival probability
1.00
0.75
0.50
0.25
0.00
Table: Initial Drug Therapy
PAH Therapy | PDE5i/sGC | ERA | Prostacyclin | |
PCA | Selexipag
Mono 119 75 1 0
Dual 85 88 5 2
Triple 7 7 3 4
P=0.32 (mono vs. dual)
0 1 2 3 4 5
Years
Number at risk
Strata
195 161 123 97 70 44
90 72 51 34 25 12
7 6 4 2 2 0
0 1 2 3 4 5
Years

Figure 5



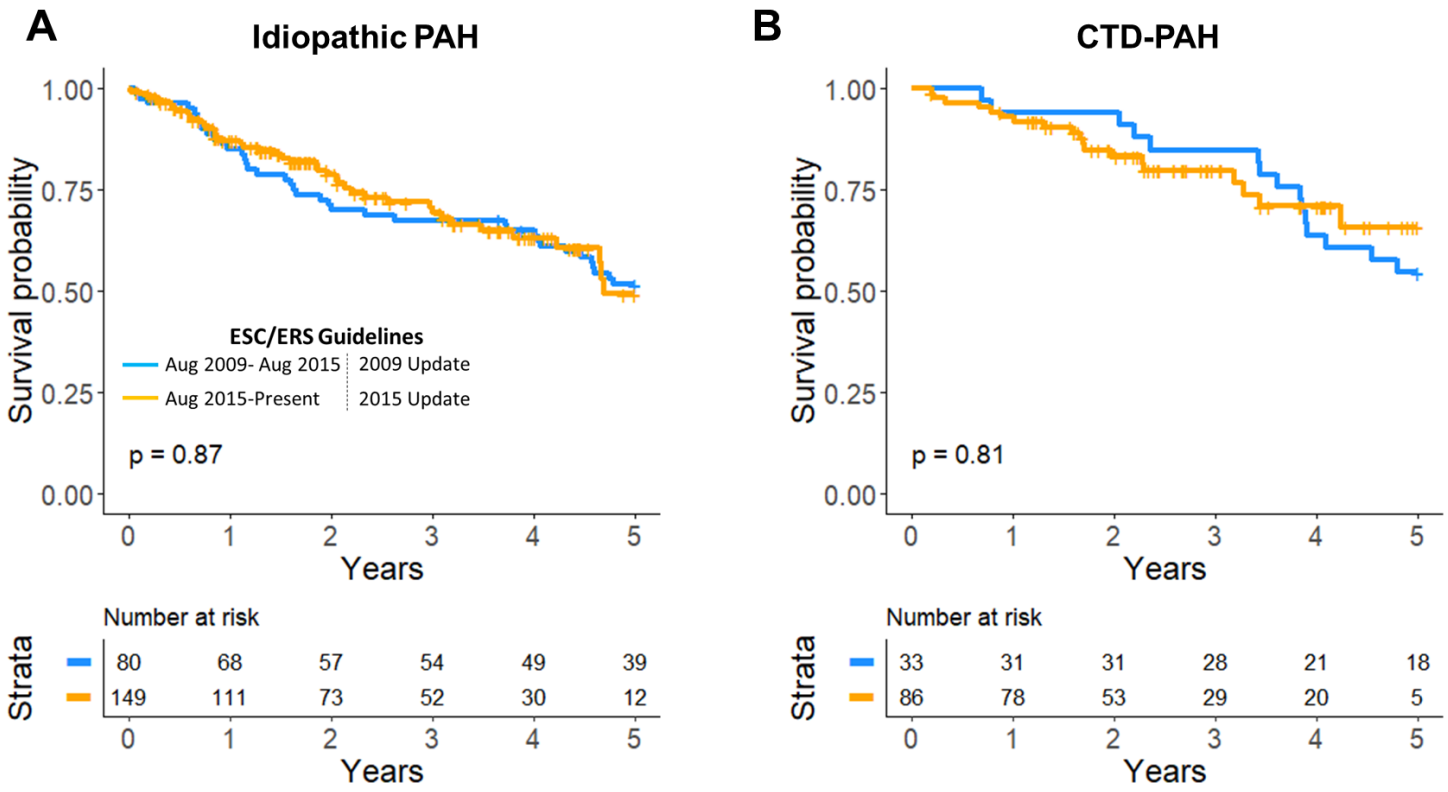
Supplemental Figure 1

Supplemental Figure 1. Patient age and survival per treatment era. In the overall cohort, older age portends a worse prognosis (A). The mean age was not different between the treatment era with similar distributions (B). In PAH patients <60 (C) and >60 (D), there was no difference in survival before and after publication of the 2015 guidelines.



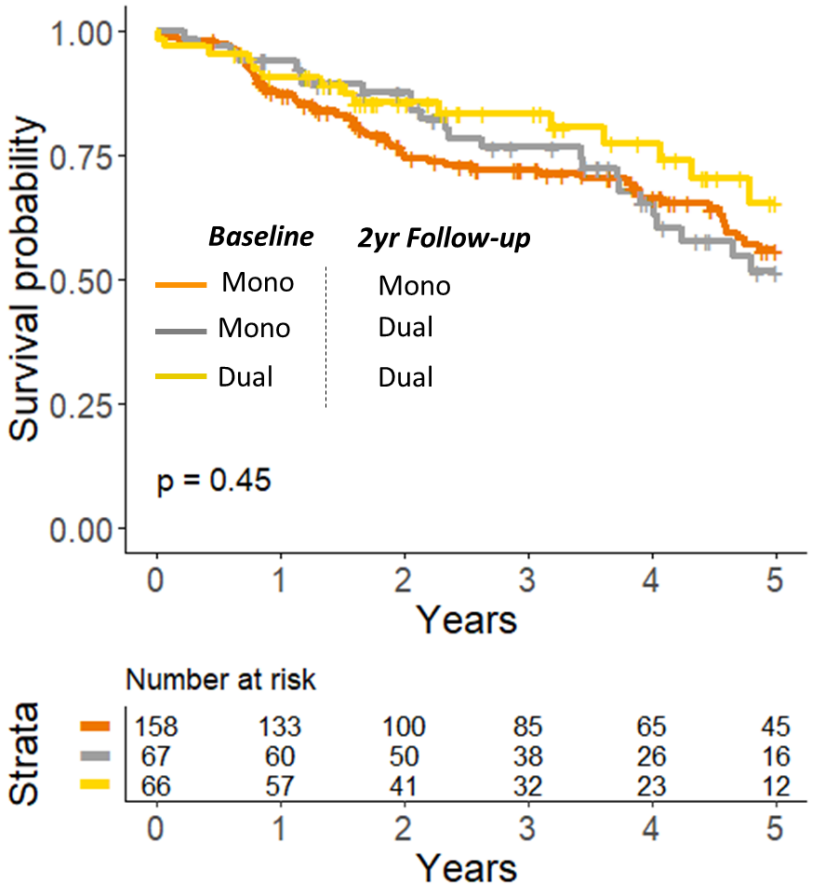
Supplemental Figure 2

Supplemental Figure 2. Patient sex and survival per treatment era. In the overall cohort, males had a worse prognosis (A). In both males (B) and females (C), there was no difference in survival before and after publication of the 2015 guidelines.



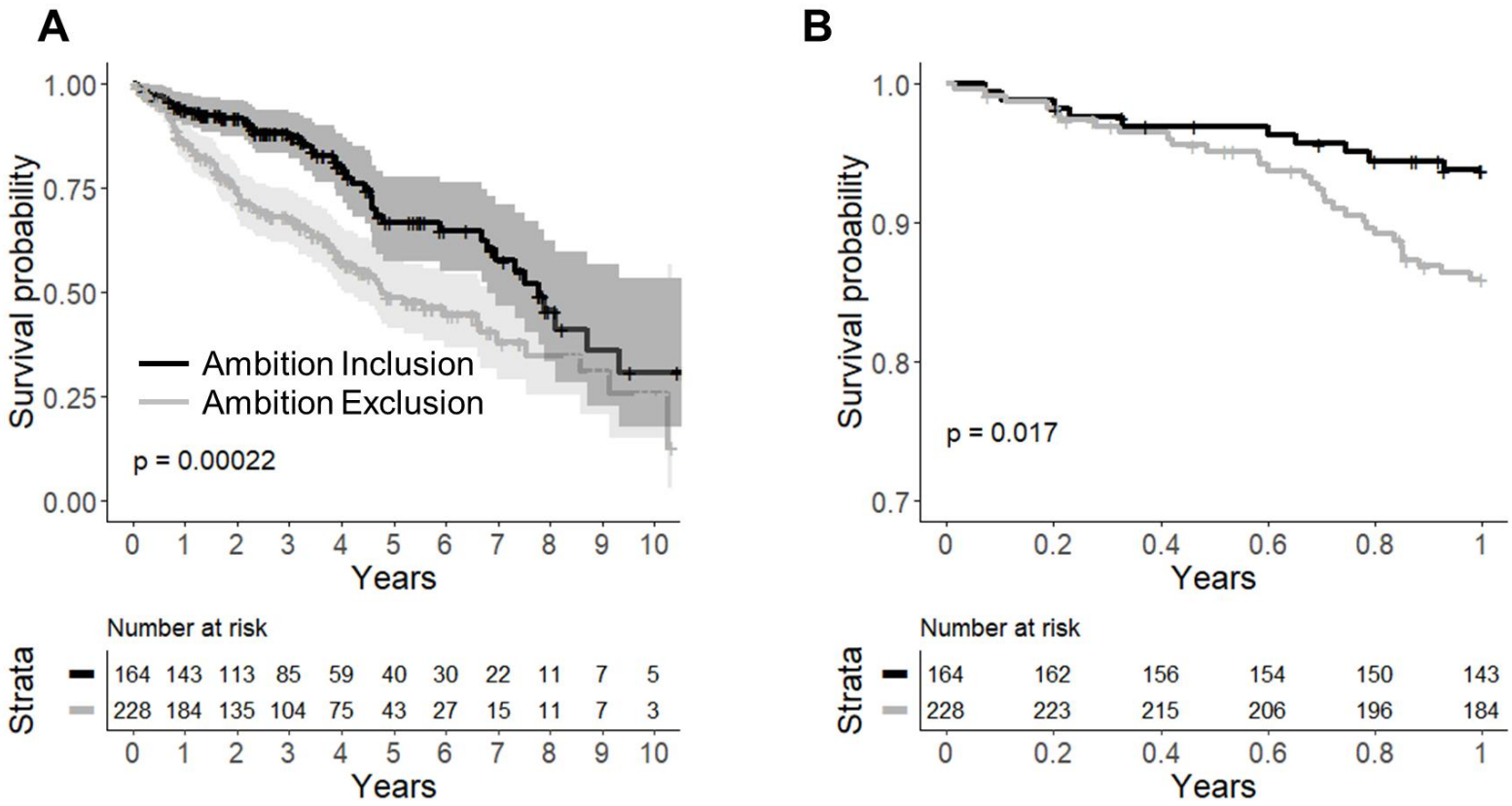
Supplemental Figure 3

Supplemental Figure 3. PAH subtype and survival. In iPAH (A) and CTD-aPAH (B), there was no difference in survival before and after publication of the 2015 guidelines.



Supplemental Figure 4

Supplemental Figure 4. Survival and initial combination versus sequential combination therapy. There was no difference in survival in PAH patients initiated on dual therapy as compared to sequential combination therapy.



Supplemental Figure 5

Supplemental Figure 5. The Ambition trial inclusion/exclusion criteria was applied to our Canadian Cohort. Canadian PAH patients who satisfied the Ambition inclusion/exclusion criteria had a more favorable prognosis (A/B).

Supplemental Table 1. Patient demographic and disease characteristics by therapy in patients diagnosed after 2015 ESC/ERS guideline.

Variables	Total		Mono Therapy	Combination Therapy	P Value
	(N=244)	% Missing	(N=148)	(N=96)	
Age (Years)	61.0±16.4	0%	63.1±15.9	57.8±16.6	0.013
BMI (kg/m^2)	29.2±8.5	0.8%	29.6±8.2	28.8±9.0	0.50
Sex (Female)	156 (63.9)	0%	90 (60.8)	66 (68.8)	0.21
Diabetes	61 (29.8)	16%	45 (35.2)	16 (20.8)	0.029
Hypertension	100 (47.6)	13.9%	65 (50.0)	35 (43.8)	0.38
Coronary Artery Disease	36 (17.8)	17.2%	25 (20.2)	11 (14.1)	0.30
Atrial Fibrillation	36 (17.6)	16.4%	27 (21.4)	9 (11.5)	0.08
COPD	26 (13.0)	18.0%	21 (16.9)	5 (6.6)	0.034
Obstructive Sleep Apnea	45 (24.5)	24.6%	35 (29.7)	10 (15.2)	0.028
eGFR (mL/min/1.73m^2)	70.1±24.9	8.6%	70.1±25.2	70.0±24.8	0.97
NYHA Class		0%			0.024
1	10 (4.1)		7 (4.7)	3 (3.1)	
2	54 (22.1)		41 (27.7)	13 (13.5)	
3	159 (65.2)		91 (61.5)	68 (70.8)	
4	21 (8.6)		9 (6.1)	12 (12.5)	
6MWD (m)	299.6±149.7	22.5%	299.4.0±144.4	299.8±157.7	0.98
mRAP (mmHg)	8.8±5.7	2.5%	8.2±5.3	9.6±6.1	0.06
mPAP (mmHg)	45.5±12.3	1.2%	43.8±11.6	48.1±12.9	0.008
PVR (Woods Units)	9.8±5.3	7.4%	8.4±4.4	11.9±5.8	<0.0001
Cardiac Index (L· min^{-1} ·m^{-2})	2.2±0.6	6.1%	2.3±0.6	2.0±0.6	0.0027

Data mean ±SD or count (%)

BMI= body mass index; 6MWD= 6-minute walk distance; WHO= World Health Organization; Association; eGFR= estimated glomerular filtration rate; mRAP= mean right atrial pressure; mPAP= mean pulmonary artery pressure; PVR= pulmonary vascular resistance; COPD = Chronic Obstructive Pulmonary Disease; NT-proBNP = N-Terminal pro-Brain Natriuretic Peptide