Challenges for comparative designs in rare diseases

Johnson&Johnson
Innovative Medicine

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13 June 2024
Basel Epidemiology Seminar

Conflicts of interest

Audrey Muller is an employee of Johnson & Johnson and has Johnson & Johnson shares.

The study was funded by Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson

Background

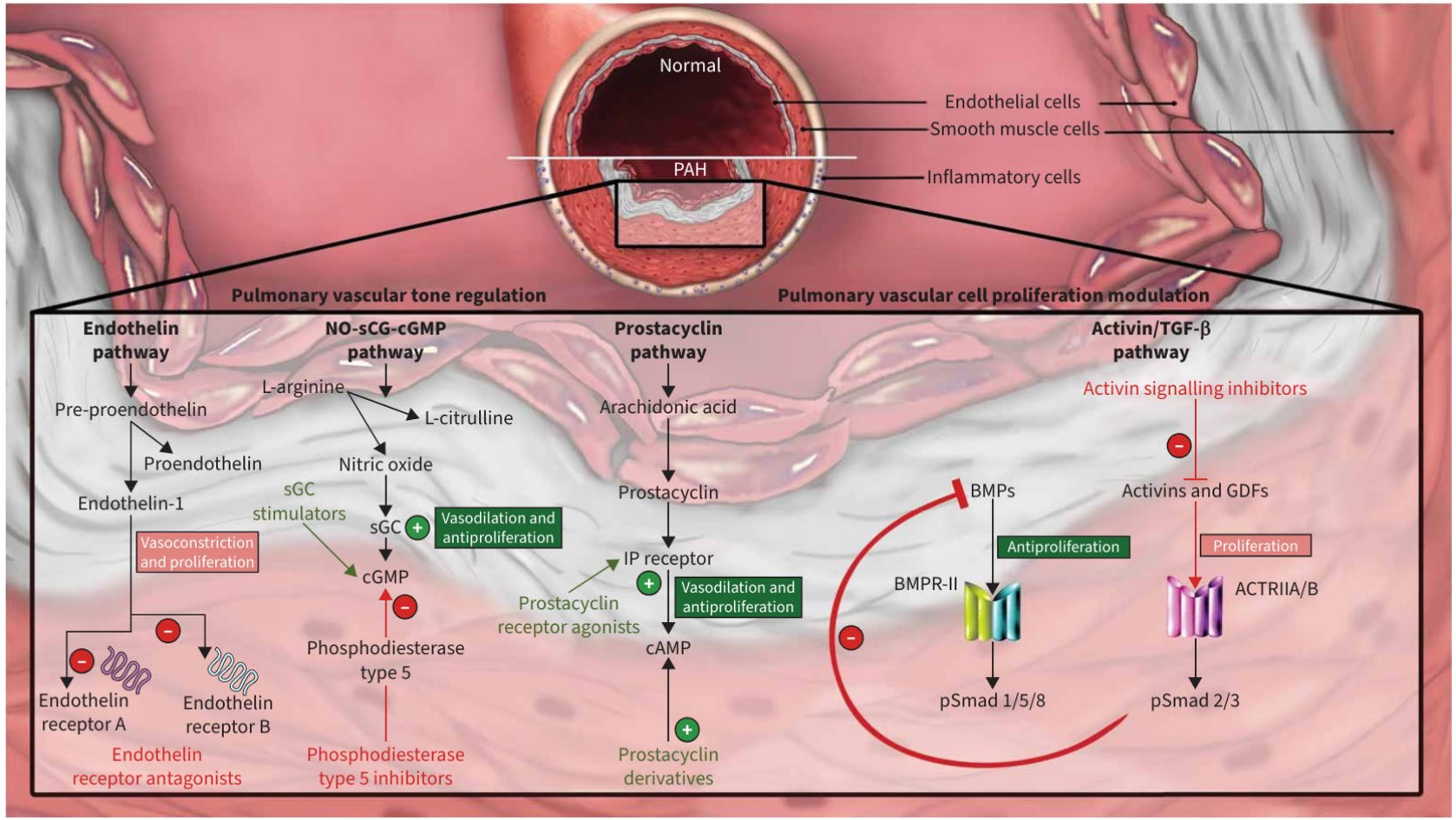
Disease and treatment patterns

Pulmonary Arterial Hypertension (PAH) is

- a progressive disease characterisedby increased pulmonary vascular resistance, leading to right heart failure and death
- a rare disease ≈50ppm adult

Complex treatment pattern

- 4 drug classes
- Add-on treatment strategy as disease worsened
- selexipag prescribed as 3rd line therapy, usually in triple combination



Background

Regulatory context

- Selexipag is approved for the treatment of adult PAH patients
- Benefits and tolerability of selexipag were demonstrated in the GRIPHON clinical trial
- No equivalent in EU (unique oral in class)

EU Health Authority requirement:

- Evaluating effects of selexipag treatment on survival in PAH
- Contemporaneous comparator

Limitation in the use administrative databases

- Disease identification not straight forward
- Limited clinical/safety information
- Sparse availability in the EU

Methods

EXPOSURE: study design

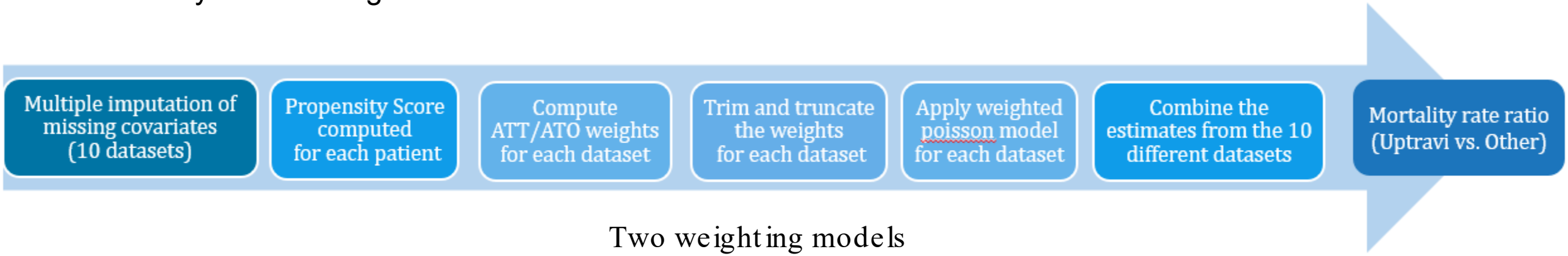
EXPOSURE (EUPAS19085) is an EU PASS designed to prospectively assess the impact and safety profile of selexipag in a real-world setting.

- Ongoing, multicentre, prospective, real-world cohort study conducted in Europe and Canada, on adult PAH patients, new users of:
  - selexipag (n=1184)
  - any other PAH-specific therapy (comparator cohort; n=1850)
- To compare rates of all-cause death between selexipag exposed patients and patients initiating another PAH-specific therapy

Methods

EXPOSURE: statistical methodology

Propensity score analysis performed to make the treatment cohorts more comparable and reduce the potential bias caused by confounding factors.



Two weighting models

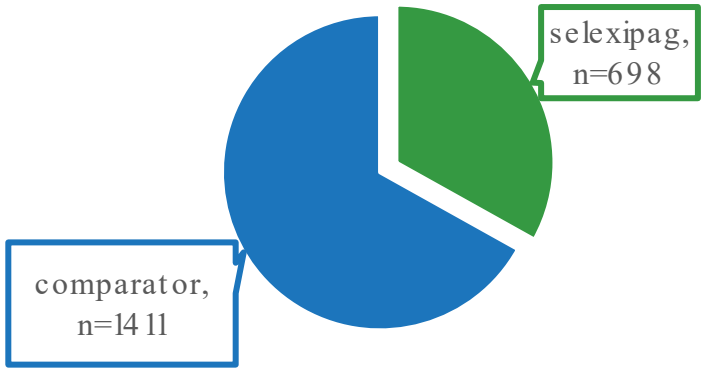
ATO
(average treatment effect in the overlap)
Patients from the two cohorts with overlapping characteristics

ATT
(average treatment effect in the treated)
All selexipag patients + selexipag-like patients from the Other PAH therapy cohort

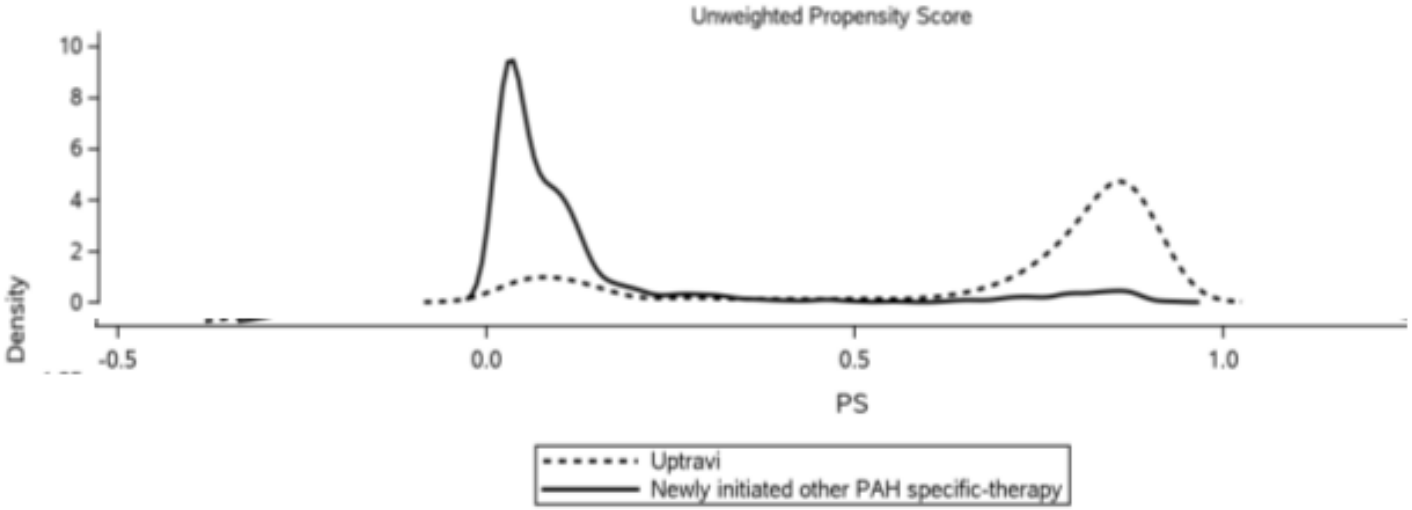
Results (Nov 2022)

Characteristics of the two study cohorts

Sample size as of Nov 2022



Substantial differences between cohorts



In the selexipag cohort:

- Longer time since PAH diagnosis
- selexipag initiation in the context of disease progression as triple combination therapy

Patients in the selexipag cohort appear to be enrolled in the study at a more severe and more advanced stage of PAH compared to patients initiating another PAH-specific therapy.

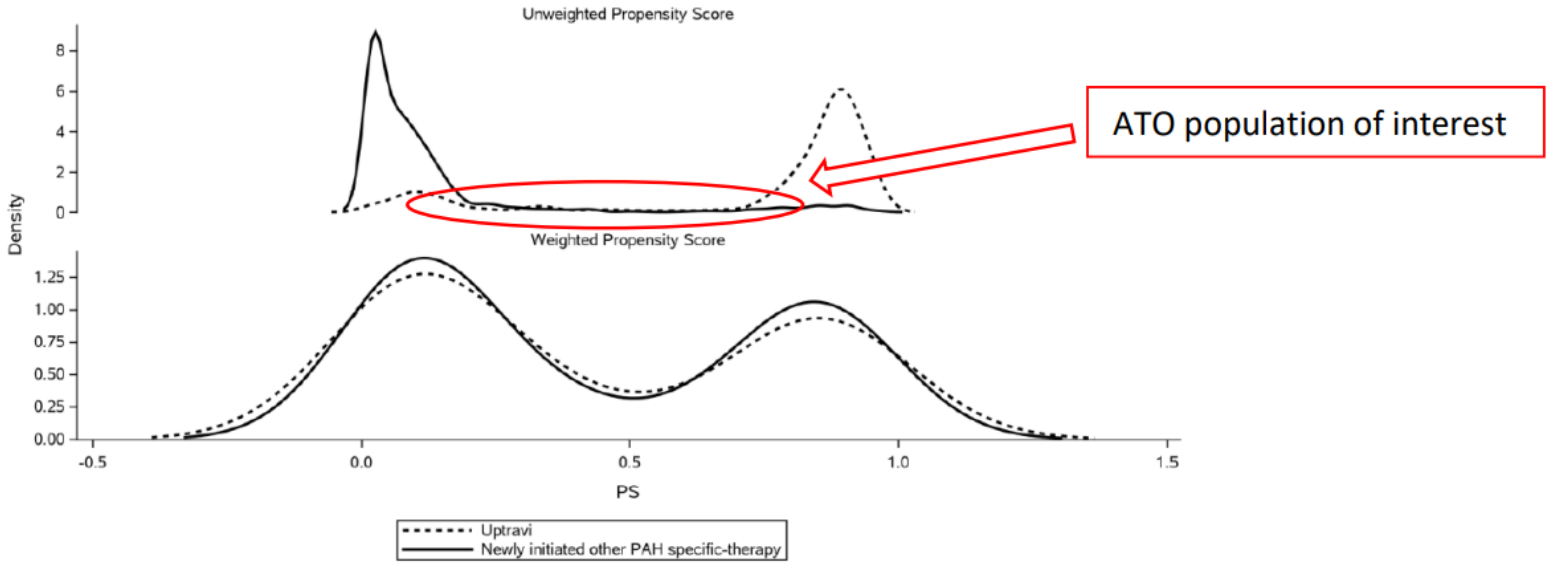
Results (Nov 2022)

ATO population

Standardized Mean Differences before and after ATO weighting

Variable	Before weighting	After weighting with ATO
Age	0.294	0.002
Country	0.322	0.007
CV risk factors	0.297	0.002
WHO FC	0.424	0.027
Time since diagnosis	0.495	0.010
PAH bsl regimen	3.380	0.019
6MWD	0.283	0.006
Comorbidities	0.214	0.002
Other 8 covariates	✓	✓

SMD < 0.1 is considered optimal
SMD < 0.2 is considered acceptable
SMD ≥ 0.2 is considered not balanced



ATO Sample Size after weighting

	Selexipag	Other PAH therapy
n patients after trimming	669	1345
Weighted Sample Size	169 (25%)	168 (12%)

Results (Nov 2022)

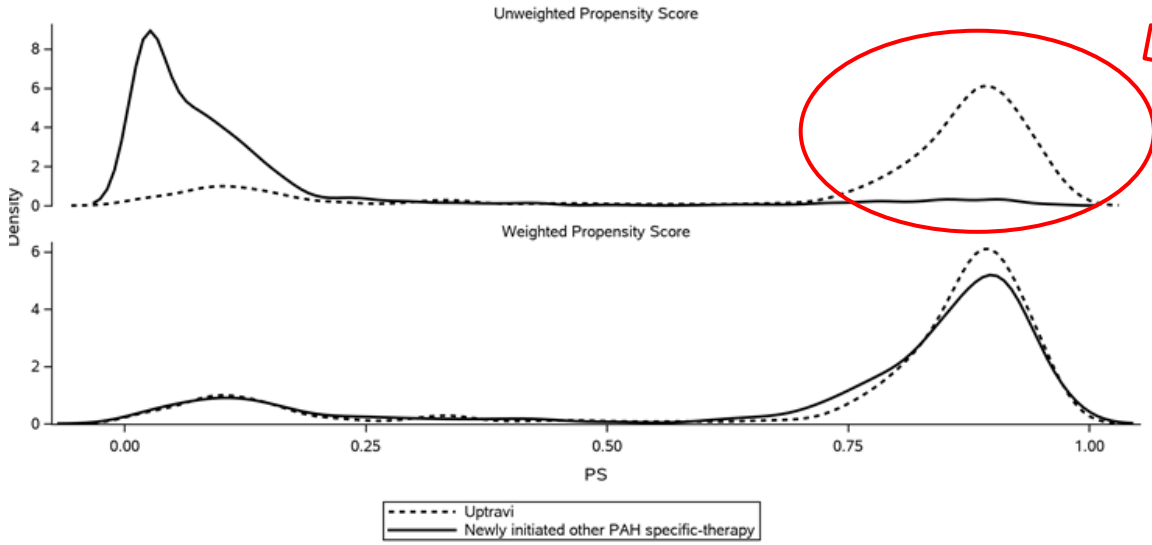
ATT population

ATT population of interest

Standardized Mean Differences before and after ATT weighting

Variable	Before weighting	After weighting with ATT
Age	0.294	0.255
Country	0.322	0.265
SVo2	0.132	0.211
WHO FC	0.424	0.165
Time since diagnosis	0.495	0.199
PAH bsl regimen	3.380	0.192
6MWD	0.283	0.039
Comorbidities	0.214	0.010
Other 8 covariates	✓	✓

SMD < 0.1 is considered optimal
SMD < 0.2 is considered acceptable
SMD ≥ 0.2 is considered not balanced



ATT Sample Size after weighting

	Selexipag	Other PAH therapy
n patients after trimming	669	1345
Weighted Sample Size	669 (100%)	614 (46%)

Outcome model results (Nov 2022)

Unweighted (before PSW)	selexipag	Other PAH
n patients after triming	669	1345
n patients with event	70	177
Exposure time, person-year	827.93	1753.05
Mortality rate ratio (selexipag vs Other PAH therapy)	1.02 (0.62, 1.70)	

The unweighted mortality rate ratio suggests no harm in the use of selexipag

Weighted	ATO		ATT	
	selexipag	Other PAH	selexipag	Other PAH
n Weighted patients	169	168	669	614
n Weighted patients with event	20	23	70	108
Weighted Exposure, person-year	192.24	224.44	827.93	840.51
Weighted Mortality rate ratio (selexipag vs Other PAH therapy)	**1.01 (0.61, 1.68)**		**0.55 (0.31, 0.99)**	

After adjustment through the PS analysis, the results remain consistent:

- ATO weighting suggests no harm in the use of selexipag
- ATT weighted mortality rate ratio indicates an observed 45% lower mortality in the selexipag cohort

Note the decreased number of patients, patients with events and patient-year of exposure due to weighting

Discussion

We are no longer observing the whole study population, but a**subgroup of it**

- ATO provides a poor overlap between the two cohorts
  - High loss of information (fewer patients, events and exposure time)
  - results not generalizable to the overall PAH population, nor the selexipag treated population

ATO answers the question “for the exact same patients within the 2 cohorts, is there a difference in mortality rate?”

Discussion

- ATT result is restricted to a specific subset of the PAH population but is clinically interpretable for selexipag patients
  - number of events and exposure time allow a comparative analysis with good precision estimate
  - lower mortality observed in selexipag patients
    compared to patients that could have been treated with selexipag but are not

ATT answers the question “Are patients treated with selexipag having a lower mortality rate compared to ramdomized-like control patients?”

Conclusion

Choice of the weighting model is key to address study objectives

Attrition of patients, events and exposure time when weighting is to be taken into consideration when assessing feasibility of comparative analyses in small populations

Interpretation and generalizability of the results can only be done if the weighted cohorts are well described

Thank you

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If you have more questions, please contact:
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