Hemodynamic Endpoints

Christine Garnett, PharmD

Clinical Analyst, Division of Cardiovascular and Renal Products, FDA

Discussion Topic

- *Presentation*: Hemodynamic measure as a surrogate for translation of exercise benefits for adults to children with the same PAH disease spectrum and the same specific intervention.

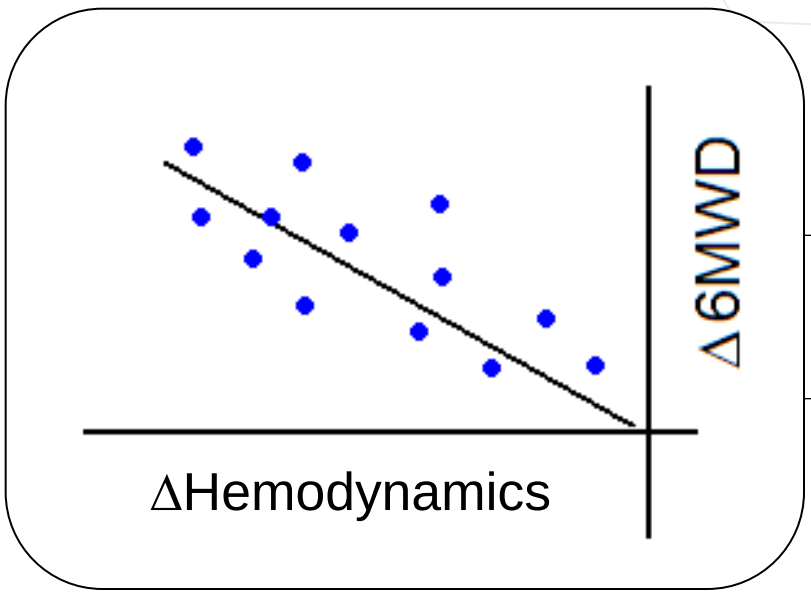
- Is there a place for noninvasive methods to evaluate the hemodynamics for pediatric PAH patients in clinical trials?

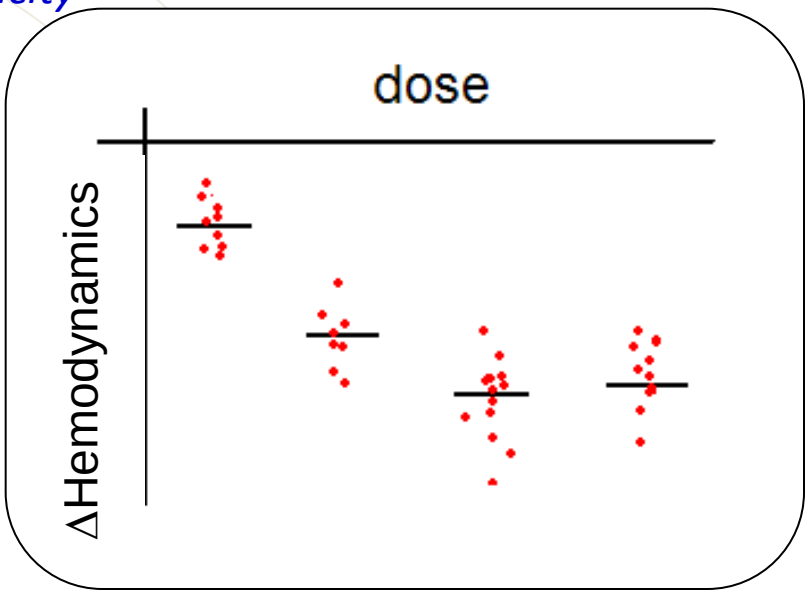
Exercise Test is Efficacy Endpoint for Most Drugs Approved in Adults

Treatment	Primary Efficacy Endpoint
Epoprostenol (FLOLAN, 1995)	6MWD at 12 weeks
Bosentan (TRACLEER, 2001)	6MWD at 16 weeks
Treprostinil (TYVASO, 2002)	6MWD at 12 weeks
Treprostinil (REMODULIN, 2002)	6MWD at 12 weeks
Tadalafil (ADCIRCA, 2003)	6MWD at 16 weeks
Iloprost (VENTAVIS, 2004)	Clinical response at 12 weeks (composite of 6MWD, NYHA functional class, death or disease progression)
Sildenafil (REVATIO, 2005)	6MWD at 12 weeks
Ambrisentan (LETAIRIS, 2007)	6MWD at 12 weeks
Riociguat (ADEMPAS, 2013)	6MWD at 12 weeks
Macitentan (OPSUMIT, 2013)	Composite endpoint (time to death, significant morbidity event, or other worsening of PAH)
Selexipag (UPTRAVI, 2015)	Composite endpoint (time to death, hospitalization for PAH, PAH worsening, initiation of parenteral prostanoid therapy or chronic oxygen therapy, or other disease progression)

Hemodynamic Marker-Δ6MWD Relationship Can Guide Pediatric Drug Development

Derive dosing based on desired benefit in exercise capacity





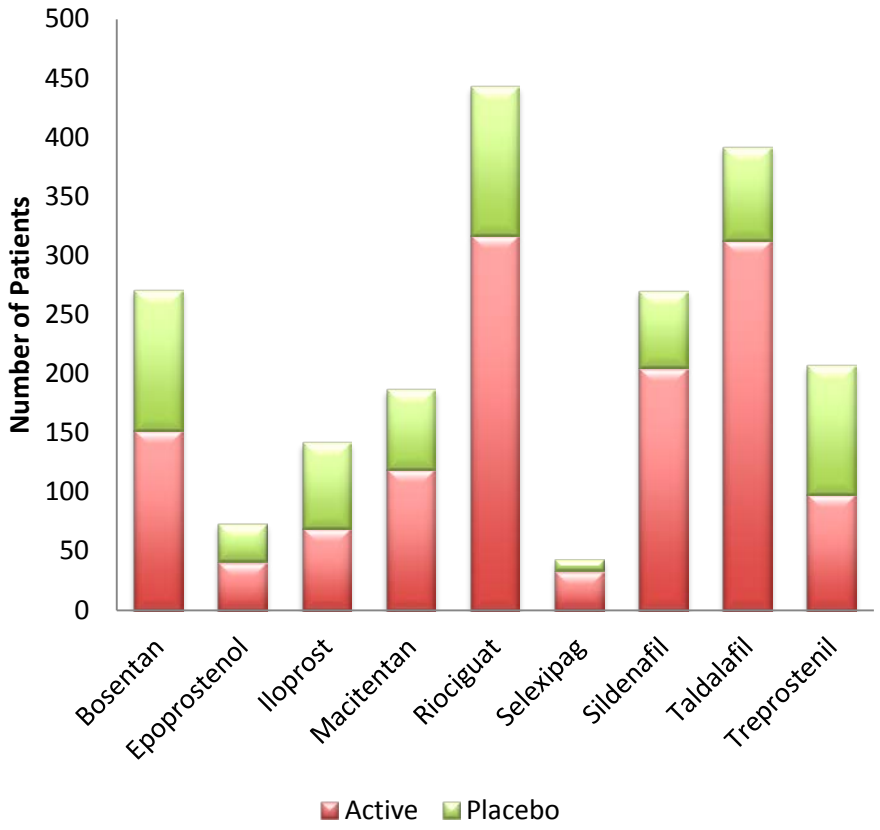
Adults: Establish relationship between Δhemodynamic marker and Δ6MWD to specify target for pediatrics

Pediatrics: Dose-ranging studies to be performed to achieve different degrees of hemodynamic benefit

Questions for Pediatric Efficacy

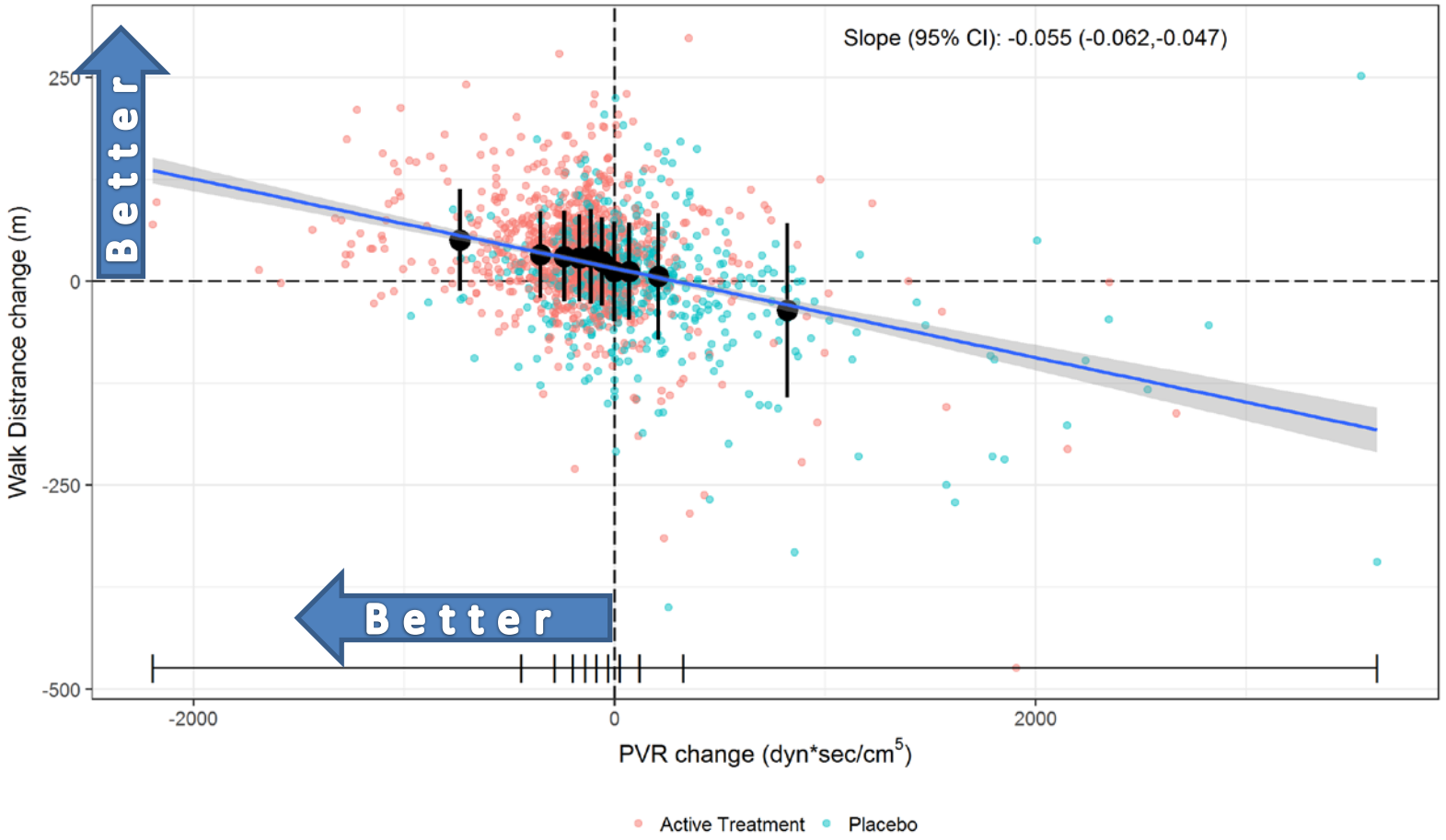
- Can relationship between ΔPVRI and Δ6MWD developed using data from intervention trials in adult patients with PAH be used to extrapolate efficacy to pediatric patients?
- Do pediatric PAH patients achieve sufficient decrease in ΔPVRI with treatment to establish clinical efficacy?

Pooled Patient-Level Data from 2028 Adults in 12 Randomized, Placebo-Controlled Trials



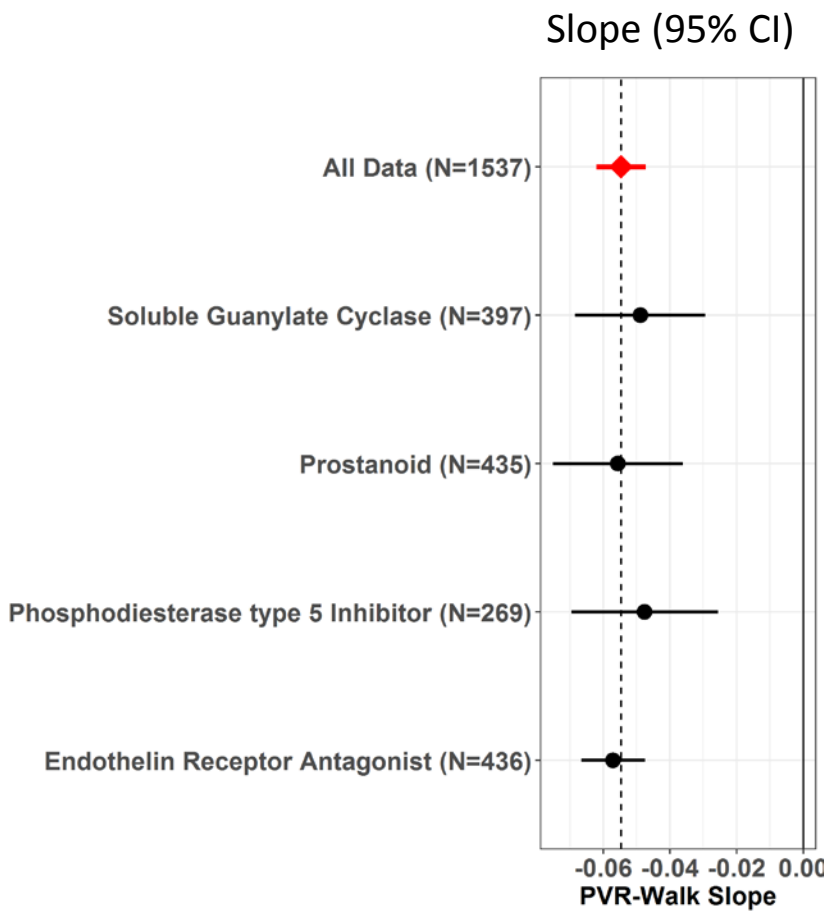
	Active Treatment (N=1343)	**Placebo (N=685)**
Age	49.3±16.0	48.5±15.4
Sex		
Males	312 (23%)	175 (26%)
Females	1031 (77%)	510 (74%)
NYHA		
1	56 (4%)	53 (8%)
2	497 (37%)	282 (41%)
3	760 (57%)	332 (48%)
4	30 (2%)	21 (2%)
Baseline 6MWD, m	355±84	360±93
Baseline PVR, dyne*sec/cm5	1006±734	1008±619

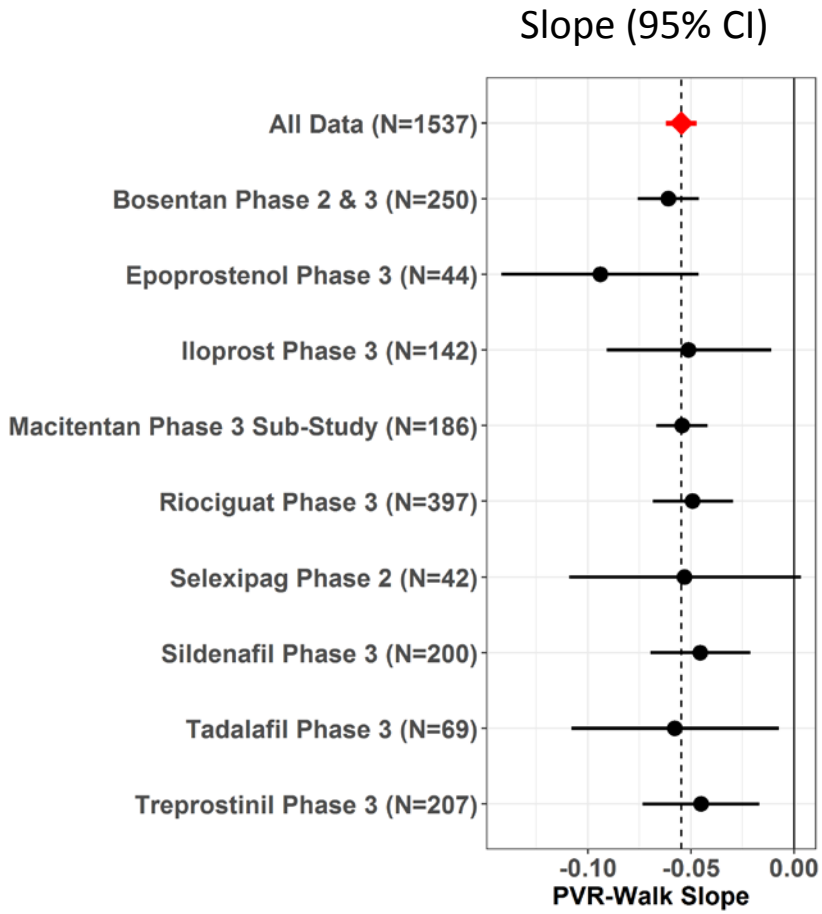
Relationship between Improvement in Δ6MWD and Decrease in ΔPVR in Adults



Shown are the observed data by treatment assignment overlaid with regression slope and 95% confidence interval. Black error bars represent mean and standard deviation Δ6MWD within each decile of ΔPVR.

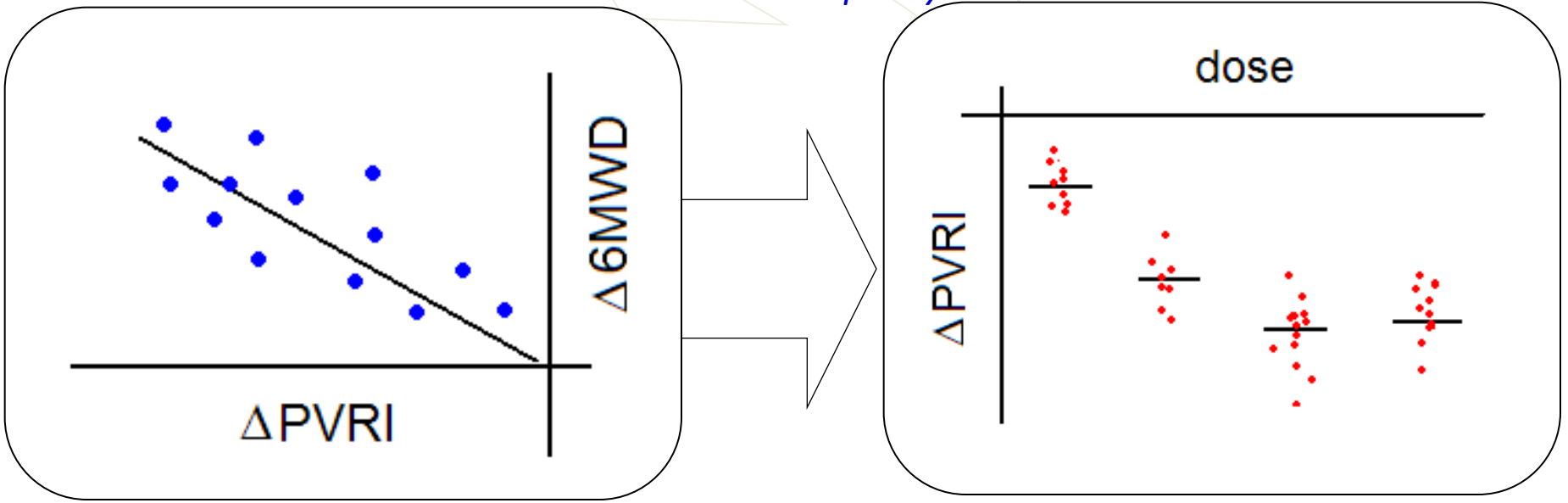
Consistent Relationship Across Drug Classes and Drugs in Adults





ΔPVRI-Δ6MWD Relationship Can Guide Pediatric Drug Development

Derive dosing based on desired benefit in exercise capacity

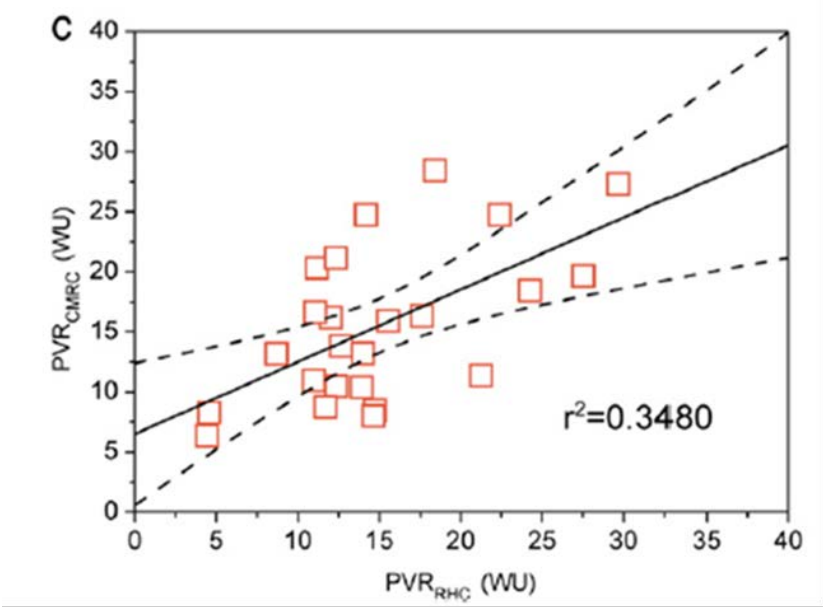


Adults: Establish relationship between ΔPVRI and Δ6MWD to specify target for pediatrics

Pediatrics: Dose-ranging studies to be performed to achieve different degrees of hemodynamic benefit

Noninvasive Assessments

- Echocardiography
  - Tricuspid annular plane systolic excursion
  - Left ventricular eccentricity index
  - CW Doppler measurements of RV systolic pressure
  - PW Doppler measurements of PA acceleration times
- Cardiac MRI
  - RV ejection fraction
  - LV end diastolic volume
  - $mPAP_{CMR}$, PVR_{CMR} computed from RV and LV functional indices



Zhang et al. International Journal of Cardiology 227 (2017) 915–922

Summary

- FDA developed quantitative relationship between ΔPVR (based on RHC) and Δ6MWD in adults using pooled data from 12 randomized, placebo-controlled trials.
  - Relationship is consistent across 4 drug classes and 9 individual drugs

- ΔPVR-Δ6MWD relationship can guide pediatric drug development for drugs already approved in adults.

- Is there a place for noninvasive methods to evaluate the hemodynamics of pediatric PAH patients in clinical trials?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