Regulatory Perspective: Biomarkers for Pediatric Extrapolation

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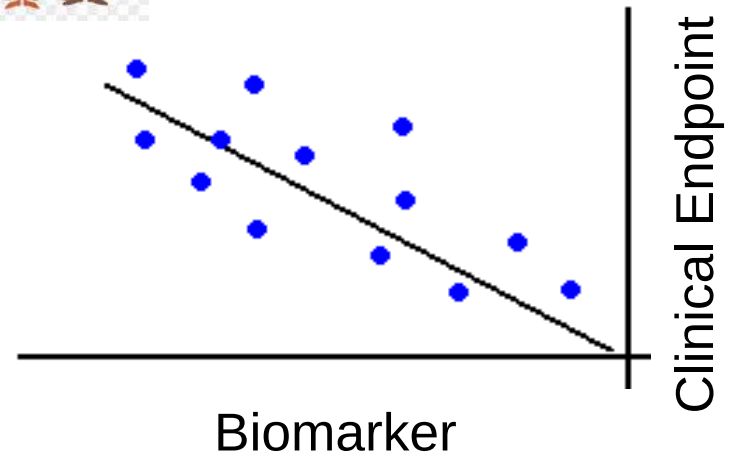
ADEPT 7 Complex Innovative Trial Design

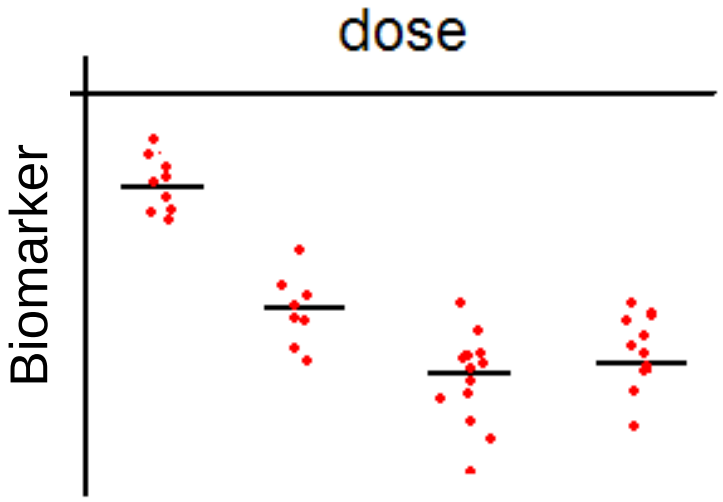
Disclaimer

My presentation reflects the evolving thinking of the Division Cardiology and Nephrology and should not be considered official FDA guidance.

Pediatric extrapolation: leveraging adult efficacy data for pediatric development



Establish relationship between biomarker and clinical endpoint in adults



Dose-ranging study performed to achieve biomarker response in pediatrics

Criteria for an extrapolating biomarker

1. Disease is similar between adults and pediatrics

2. Biomarker is prognostic in pediatrics— identifies the likelihood of a clinical event, disease recurrence or progression in patients who have the disease of interest

3. Biomarker is **reasonably likely** to predict the treatment effect of a clinical endpoint
   - ✓There is biologic plausibility of the relationship between the biomarker and clinical endpoint

FDA Uses Bridging Analyses of Pediatric Hemodynamic Data to Adult Exercise Capacity in the Approval of Tracleer® (Bosentan) for Pediatric Pulmonary Arterial Hypertension Patients 3 Years of Age and Older

On September 5, 2017, the US Food & Drug Administration (FDA) approved Tracleer (bosentan) for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in pediatric patients aged 3 years and older. This is the first approval of a drug for the treatment of pediatric PAH with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability. FDA's efficacy evaluation relied on the findings from one of the trials − BREATHE-3, an open-label, uncontrolled study in 19 pediatric patients with PAH aged 3 to 15 years which measured PVR, a cardio-pulmonary hemodynamic variable. FDA conducted analyses using data from previously approved programs in adults that established the relationship between improvements in the 6-minute walk distance (6MWD) and PVR in adults and showed that the relationship was consistent across different approved drug classes (e.g., endothelin receptor antagonist, prostanoids, PDE5 inhibitor, and soluble guanylate cyclase stimulator). The observed reduction in PVR in pediatrics from the BREATHE-3 study was used to bridge the bosentan efficacy findings in adults.

–American College of Clinical Pharmacology, 2017

Bosentan approach for pediatric extrapolation

Adult PVR-6MWD relationship

↓

Pool patient-level data from placebo-controlled trials of approved PAH treatments.

↓

Determine the proportion of the bosentan treatment effect explained by PVR

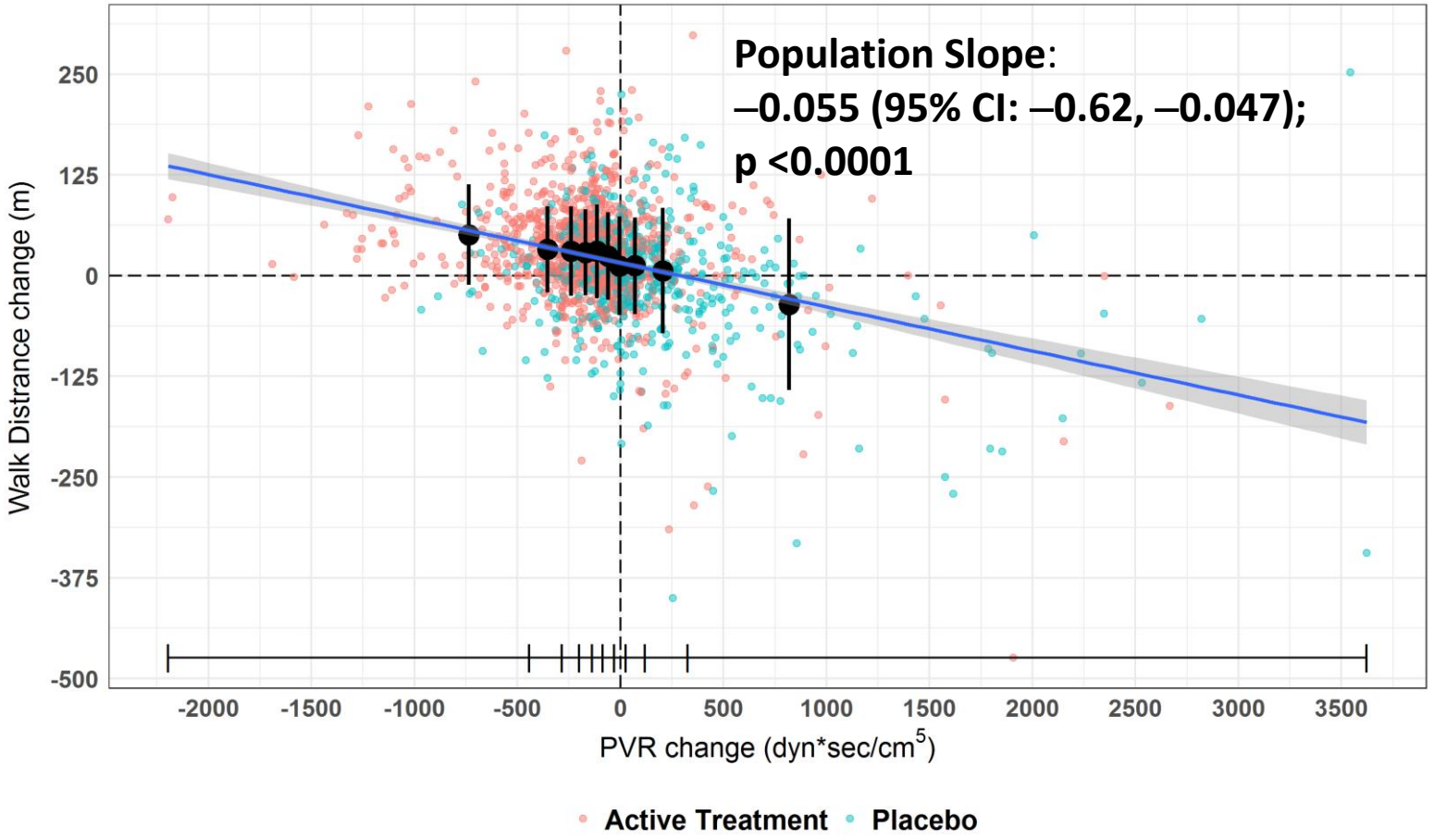
Pediatric dose-PVR relationship*

↓

Assess the PVR response in children to determine if it meets the targeted response from the adult relationship.

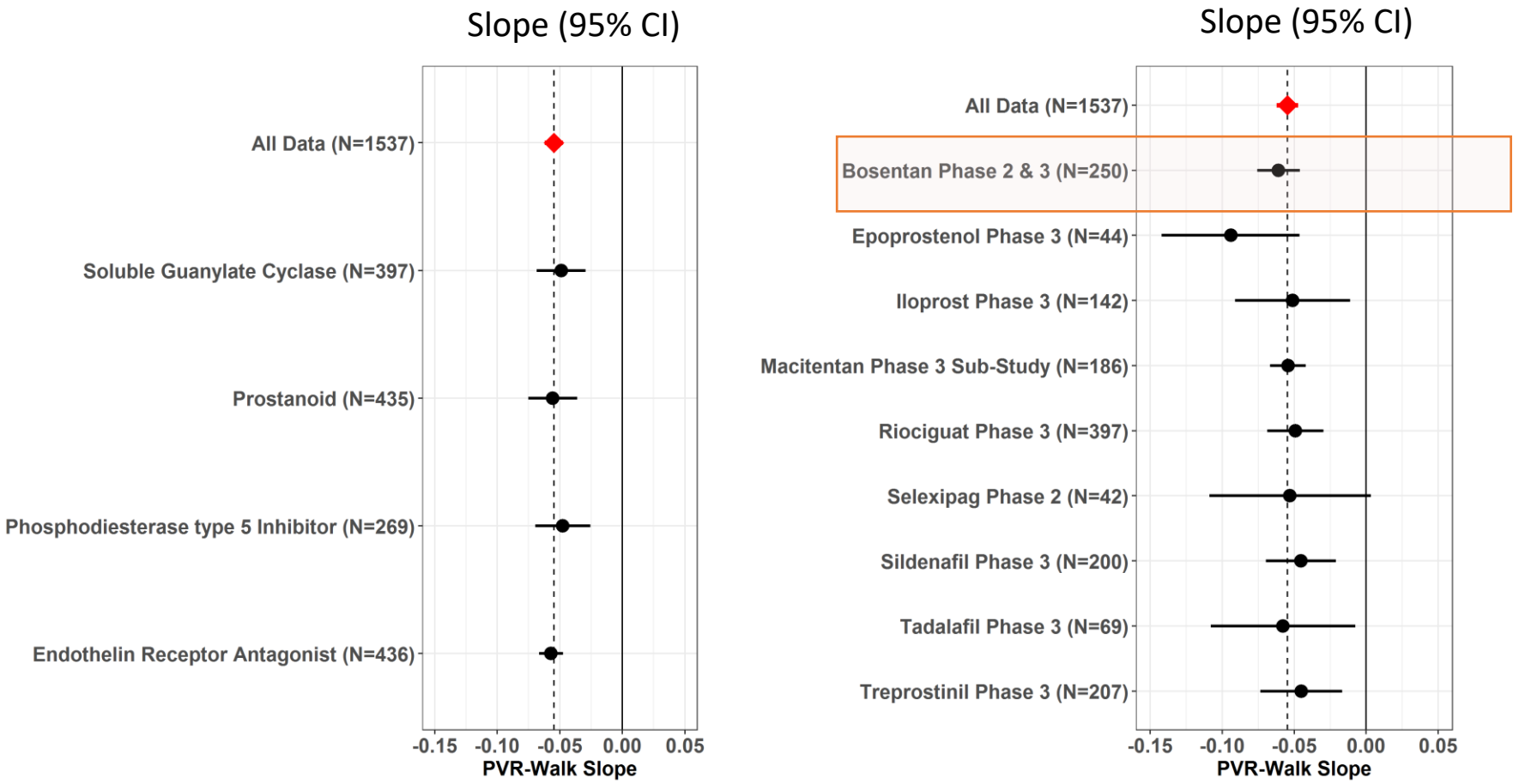
*Bosentan pediatric program did not have placebo-controlled trials. Therefore, the placebo arm from the sildenafil STARTS-1 trial was used for control.

Improvement in Δ6MWD corresponds to decrease in ΔPVR in adults



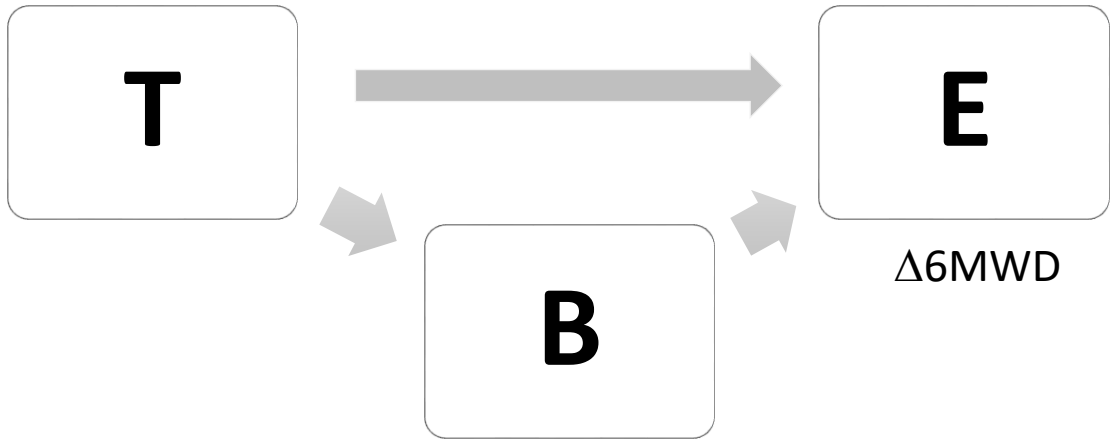
Shown are the observed data by treatment assignment overlaid with regression slope and 95% confidence interval. Black error bars represent mean and standard deviation Δ6MWD within each decile of ΔPVR.

Consistent relationship across drug classes and drugs in adults



Forest plot of mean (95% CI) regression slopes shown by drug class (left) and individual drugs (right). The dashed line is the mean slope of pooled data.

PVR is reasonably likely to explain the treatment effect on 6 min walk distance

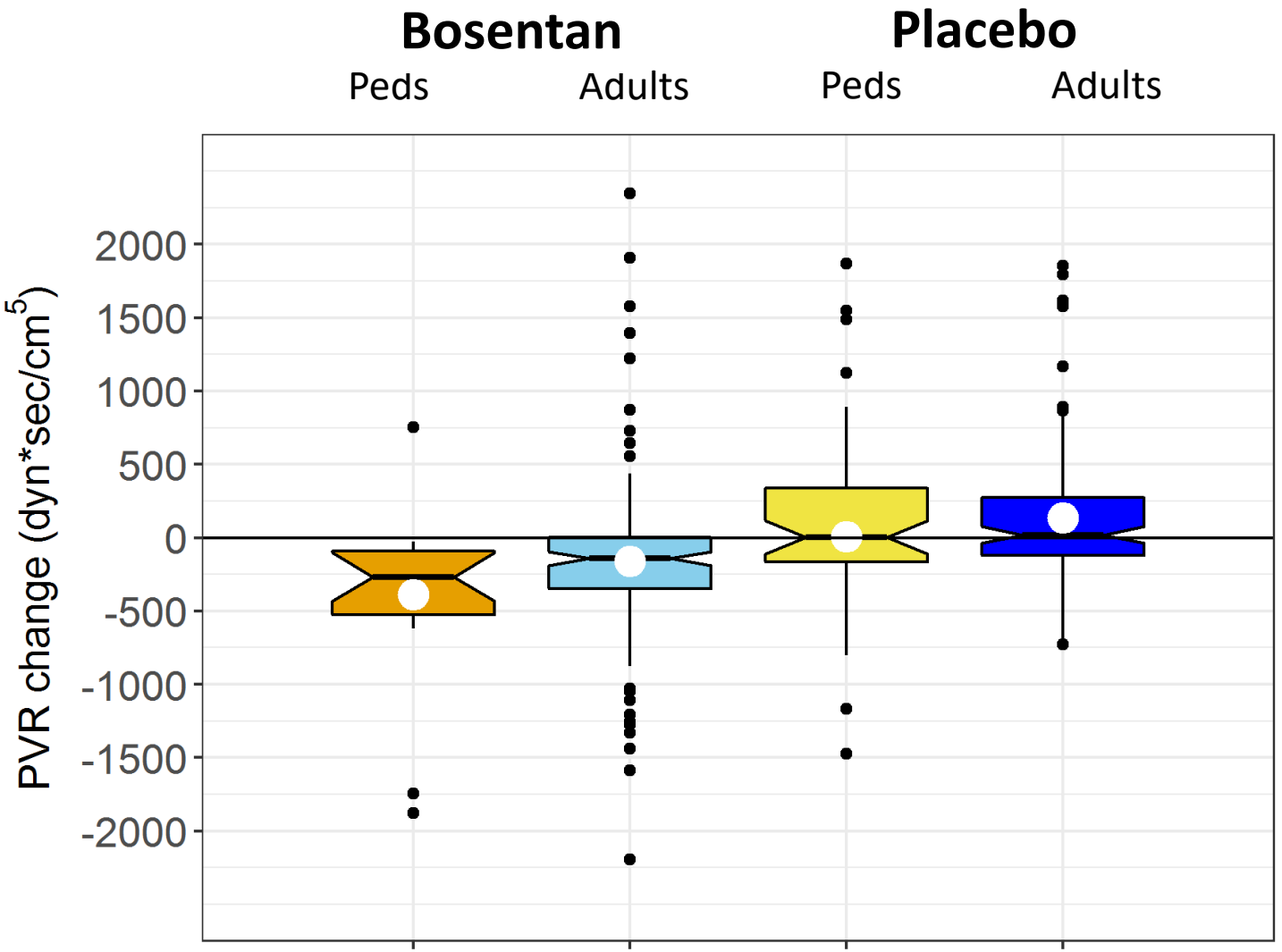


Where T is treatment, B is the biomarker and E is the clinical endpoint or outcome.

- Bosentan treatment had significant effects on Δ6MWD and ΔPVR:
  - Δ6MWD : +35 m
  - ΔPVR : -250 dyne*sec/cm^5
- 50% treatment effect on Δ6MWD explained by ΔPVR

De Gruttola et al. Considerations in the Evaluation of Surrogate Endpoints in Clinical Trials: Summary of a NIH Workshop. Controlled Clinical Trials 22:485–502 (2001)

Observed ΔPVR response in children is similar to adults



Box plots show the mean (white circles), median (notch); 95% CI of median (width of notch); 25th and 75th percentile (width of box); 1.5* interquartile range (whiskers); and outliers (filled circles).

Bosentan Indication

- Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):
  - in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).
  - **in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.**

Few drug approvals for pediatric PAH population

Drug Class	Drug	Approved in Children?
Prostacyclin Analogue	Treprostinil	No
	Selexipag	No
	Treprostinil diethanolamine	No
	Iloprost	No
Endothelin Receptor Antagonist	Bosentan	Yes (US) PK only (EU, Canada)
	Ambrisentan	No
	Macitentan	No
Phosphodiesterase type 5 inhibitor	Sildenafil	Yes (EU)
	Tadalafil	No
Guanylate cyclase stimulator	Riociguat	No
Vasodilator	Epoprostenol	No

Regulatory response to challenges in pediatric PAH

- Offer parallel scientific advice for companies who request this program
- Provide a common commentary on regulatory expectations across regions
- Discuss pediatric plans with companies during the adult development program
- Utilize pediatric extrapolation and other novel study designs and endpoints, where appropriate.
- Partner with external stakeholders on developing/testing of age-appropriate endpoints

New Strategies for the Conduct of Clinical Trials in Pediatric Pulmonary Arterial Hypertension: Outcome of a Multistakeholder Meeting With Patients, Academia, Industry, and Regulators, Held at the European Medicines Agency on Monday, June 12, 2017. J Am Heart Assoc. 2019 May 21;8(10)

Summary

- An extrapolating biomarker is one that is prognostic in pediatrics for the disease of interest and is reasonably likely to predict the treatment effect of a clinical endpoint.

- Pediatric extrapolation using an extrapolating biomarker has been used to approve medicines in pediatrics
  - Pediatric PAH
  - Pediatric heart failure

References

- Bosentan pediatric extrapolation: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209279Orig1s000SumR.pdf

- Ollivier C et al. New Strategies for the Conduct of Clinical Trials in Pediatric Pulmonary Arterial Hypertension: Outcome of a Multistakeholder Meeting With Patients, Academia, Industry, and Regulators, Held at the European Medicines Agency on Monday, June 12, 2017. J Am Heart Assoc. 2019 May 21;8(10):e011306. doi: 10.1161/JAHA.118.011306. PMID: 31088189; PMCID: PMC6585335.