



On the use of hemodynamics biomarkers to assess the benefit of high doses of sildenafil in some patients with pulmonary arterial hypertension (PAH)

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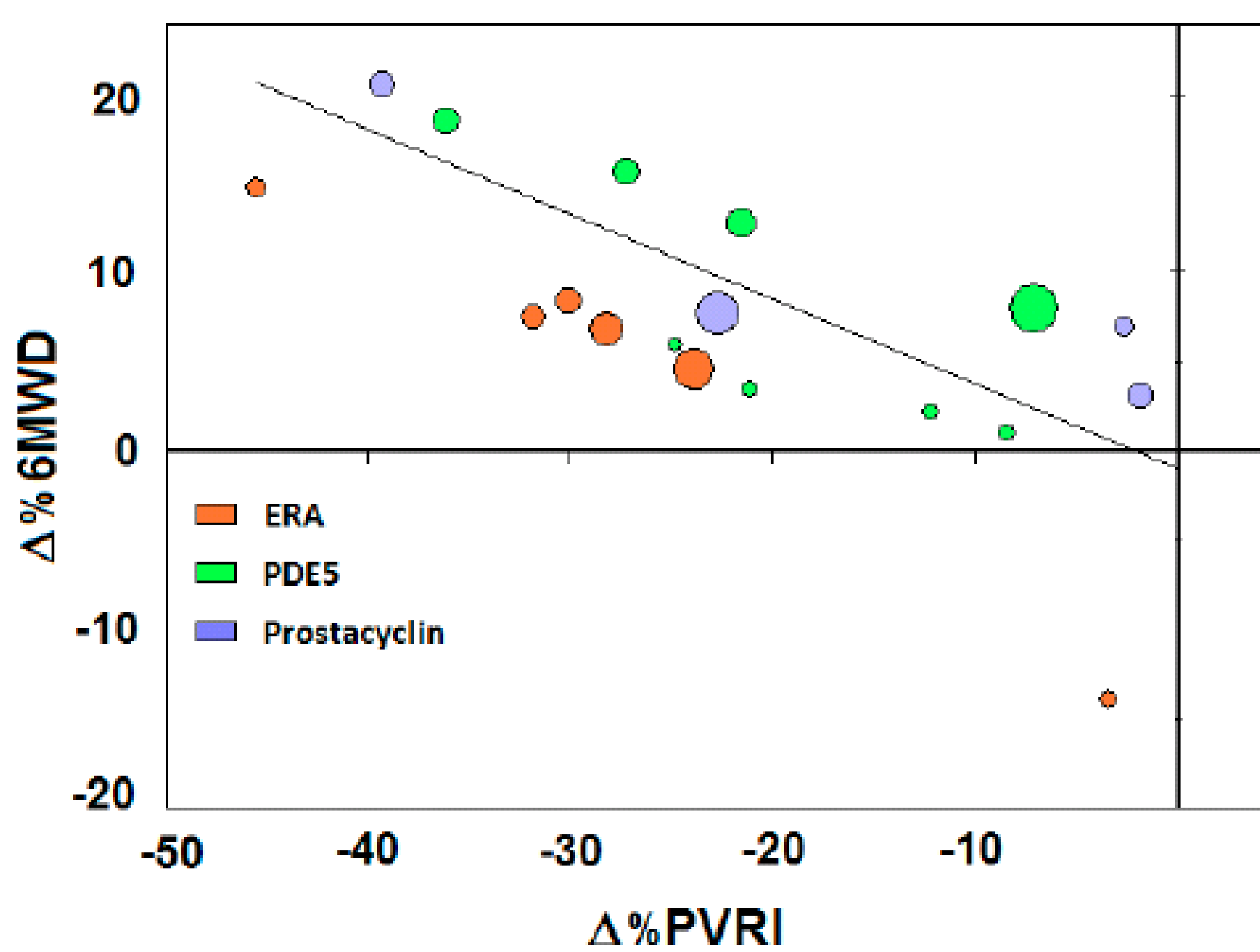


Background

• The assessment of efficacy of pulmonary arterial hypertension treatments is mainly based on improvements in exercise capacity as measured by six-minute walk distance (6MWD).

• Sildenafil (REVATIO®), 20 mg TID, received approval for the treatment of adult PAH in the US based on 6MWD data.

• A recent FDA analysis showed a relationship between changes from baseline in 6MWD and pulmonary vascular resistance index (PVRI), an hemodynamic (HD) endpoint in the adult PAH population.¹



FDA meta-analysis describing the difference from placebo in the % change in PVRI and 6MWD in adults. Each study is represented by a circle which size is proportional to the number of subjects.

From page 47 of FDA Core Presentation, Revatio (sildenafil), for the July 29, 2010 Meeting of the Cardiovascular and Renal Drugs Advisory Committee [http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM221824.pdf]

Objectives

The objective of this analysis was to assess whether some patients could have reached a reduction target in PVRI with a higher sildenafil dose than the one currently labeled according to their baseline and patho-physiological characteristics.

Methods

• A previous population PK/PD analysis of PVR data from two pivotal sildenafil trials in adult² (n=218) and pediatric patients (n=219, 1-17 y) was performed in NONMEM 7 to characterize the relationships between PVR (=PVRI/BSA), baseline patho-physiological covariates and sildenafil exposure³.

• Simulations, based on pre-defined success criteria to achieve expected HD responses as a function of age, functional class and baseline PVR were conducted to assess the potential PVRI reduction associated with higher doses (40 and 80 mg TID) of sildenafil in some PAH patients compared to the labeled dose.

• Simulations were performed based on PK and PVR models accounting for inter-individual variability, residual variability and parameter uncertainty.

• Efficacy criteria 1 was defined as the percentage of patients achieving a 200 dyne.s.cm⁻⁵ PVR improvement from baseline.

• Efficacy criteria 2 was defined as the percentage of patients achieving a PVR of 350 dyne.s.cm⁻⁵ at the end of the treatment.

• 10000 virtual subjects were simulated for each combination of dose, baseline characteristics (age, functional class), and target value.

• Simulations assumptions:

Adult patients having either primary PAH or PAH subsequent to a surgical repair,

Median adult body weight of 70 kg corresponding to a BSA of 1.77 m²

Modeling results

Model structure

At baseline

$$PRV_{i,base} = exp(Baseline)$$

$$Baseline_{adults} = BASE \cdot (1 + (BASE_{Age} \cdot (AGE - 18) + BASE_{BSA} \cdot (BSA - 1.5) + BASE_{FC} \cdot FCL))$$

$$Baseline_{pediatrics} = BASE \cdot (1 + (BASE_{BSA} \cdot (BSA - 1.5) + BASE_{FC} \cdot FCL))$$

-FCL taking the values -1,0,1 for subjects of functional class (FC) 1, 2, 3&4, respectively

-For adults with Connective Tissue Disease (CTD) as etiology, BASE substituted with BASE_{CTD}

At end of treatment

For $C_{av,ss} \leq$

$$PRV_{i,end} = exp(Baseline + E_0 + Slope_1 \cdot C_{av,ss})$$

For $C_{av,ss} > Thrs$ $PRV_{i,end} = exp(Baseline + E_0 + Slope_1 \cdot Thrs + Slope_2 \cdot (C_{av,ss} - Thrs))$

-E₀ placebo effect (disease worsening)

-C_{av,ss} average concentration at steady state derived from the population PK model using the individual empirical Bayesian estimates of clearance based on dose and covariates

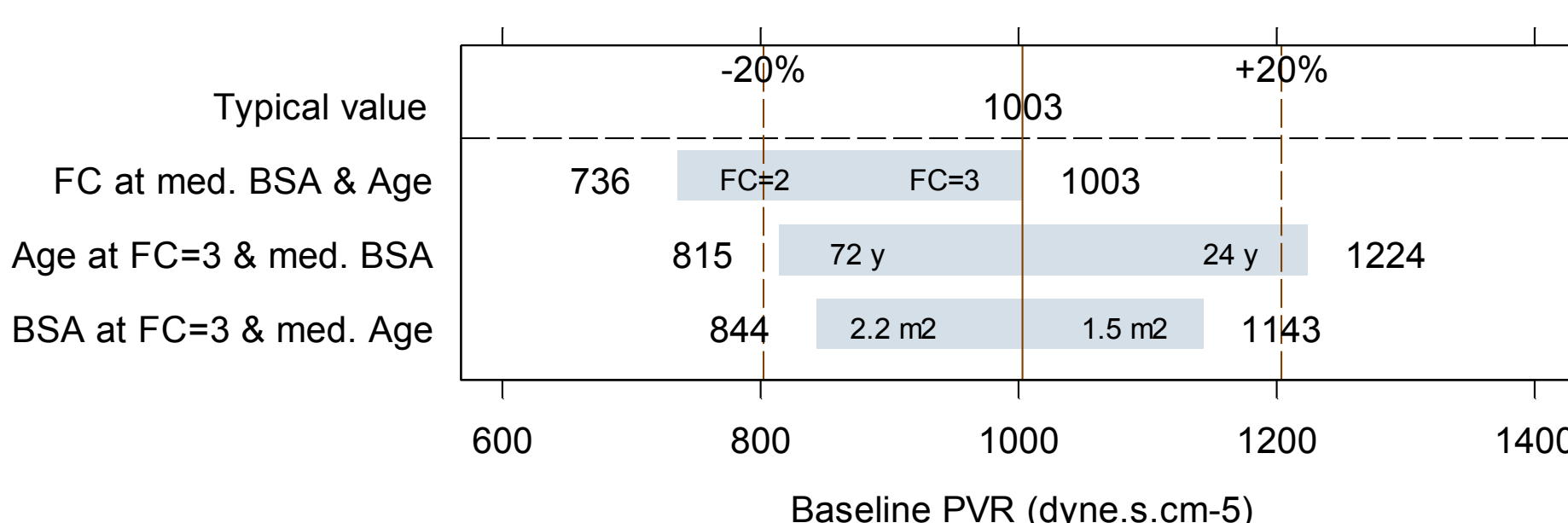
-For developmentally able children, not having a shunt as their etiology,

Slope₁ substituted with Slope_{1,deivable}

Model parameters (adult related ones in blue boxes)

Parameter	Estimate	RSE (%)	Value and unit on			95% CI
			transformed parameter			
BASE	6.97	0.613	1064	dyne.s/cm ⁵	978.8	1157
BASE _{CTD}	6.71	1.26	820.6	dyne.s/cm ⁵	694.9	968.9
BASE _{BSA}	-0.0627	17.5	0.804	/0.5m ²	0.7433	0.8641
BASE _{Age}	-0.00122	22.3	0.919	/10y	0.8843	0.9526
BASE _{FC}	0.0444	14	1.363	/1 FC	1.247	1.479
E ₀	0.0606	57.8	6.247	%	-0.7968	13.79
Slope ₁	-0.00506	19.4	-22.35	%/50ng/mL	-29.47	-14.52
Slope _{1,deivable}	-0.00829	24.4	-33.93	%/50ng/mL	-45.8	-19.47
Slope ₂	-0.000525	42.1	-2.591	%/50ng/mL	-4.678	-0.4581
Thrs	48.9	0.00301	48.9	ng/mL	48.9	48.9
IIV _{ADULT}	0.47	5.21	47	%	42.2	51.8
IIV _{PED}	0.57	5.67	57	%	50.67	63.33
RV _{ADULT}	0.22	9.64	22	%	17.84	26.16
RV _{PED}	0.336	4.91	33.6	%	30.37	36.83

Covariates influence on baseline PVR in adults



Simulation results

• The model based simulations of HD outcomes showed that while 20 mg TID provides a clear improvement over placebo, the 80 mg TID regimen provides a substantial additional improvement over the labeled dose, whereas a 40 mg TID regimen provides only a marginal additional improvement.

• Simulations focusing on a target PVR improvement (reduction) from baseline of 200 dyne.s.cm⁻⁵ showed that elderly patients (60 to 80 y) may expect a lower response rate with the labeled dose but a similar response rate with 80 mg TID compared to that obtained in younger patients at the labeled dose (Figure 1).

• More severe patients i.e. with functional class 3 or 4 and/or high baseline PVR are more likely to show a 200 dyne.s.cm⁻⁵ reduction from baseline, there is a greater improvement rate expected in those patients when they receive 80 mg TID than with the labeled dose (Figure 2).

Figure 1

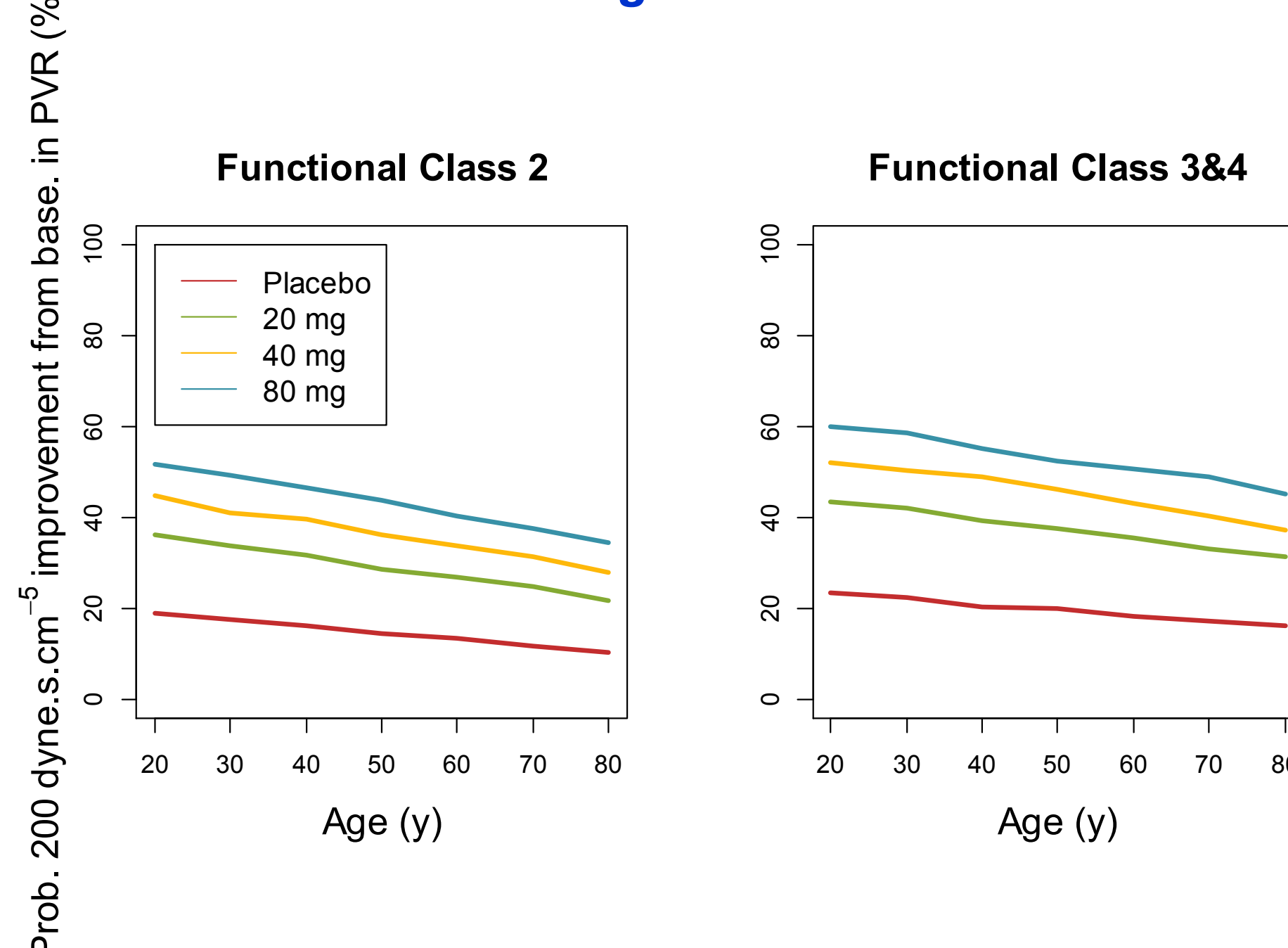
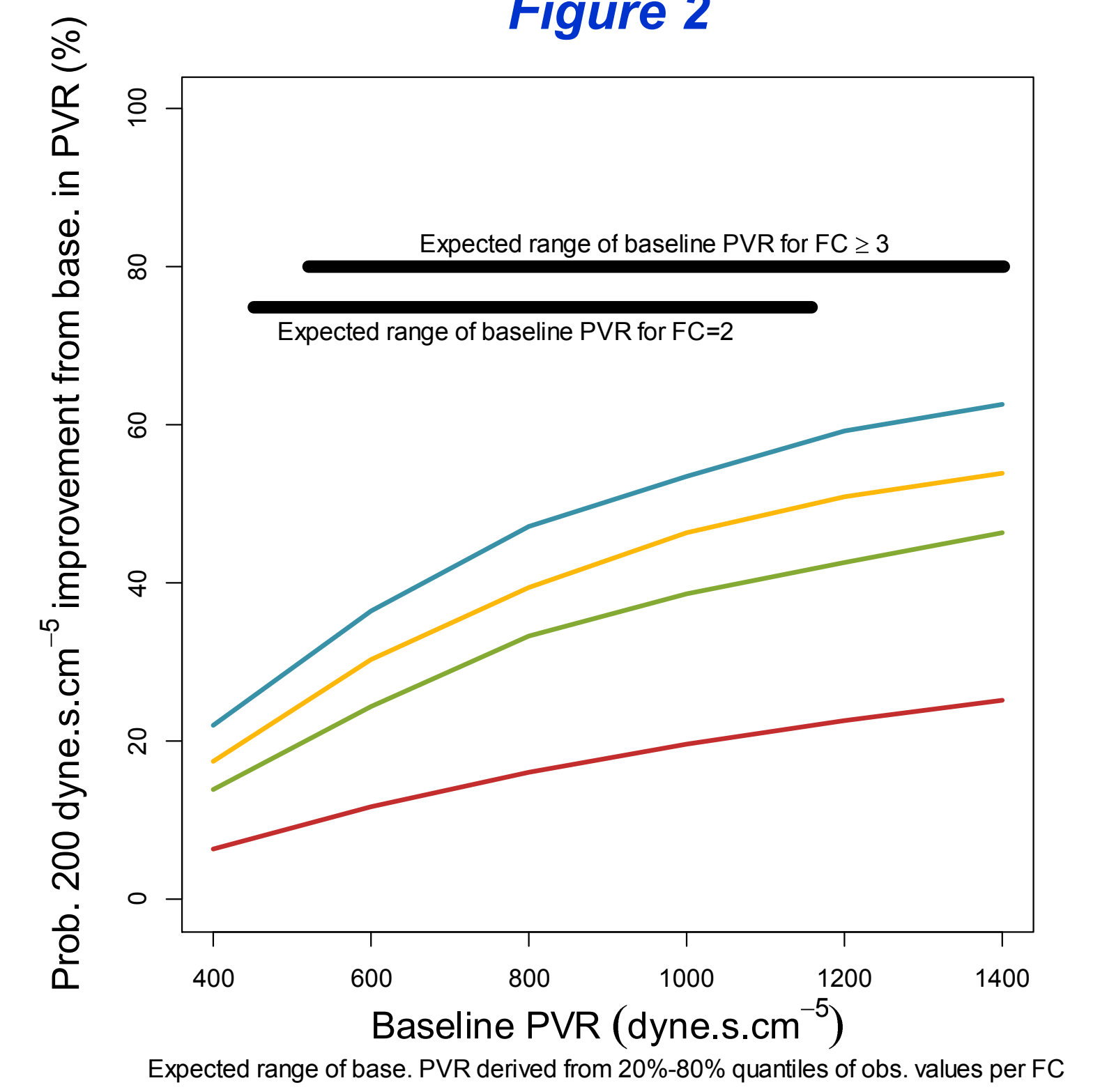


Figure 2



• Simulations focusing on the achievement of a target absolute PVR value of less than 350 dyne.s.cm⁻⁵ showed that more severe patients with functional class 3 or 4 and/or high baseline PVR may also reach this target with a 80 mg TID regimen similarly to less severe patients treated at the labeled dose (Figures 3 and 4). As baseline PVR is decreasing with age, elderly patients are more likely to reach an a PVR value lower than 350 dyne.s.cm⁻⁵ especially if they receive 80 mg TID (Figure 3).

• A very small fraction (<10% of subjects) at the typical baseline PVR i.e. around 1000 dyne.s.cm⁻⁵ is expected to reach a PVR value ≤ 350 dyne.s.cm⁻⁵ even treated with 80 mg TID (Figure 4).

Figure 3

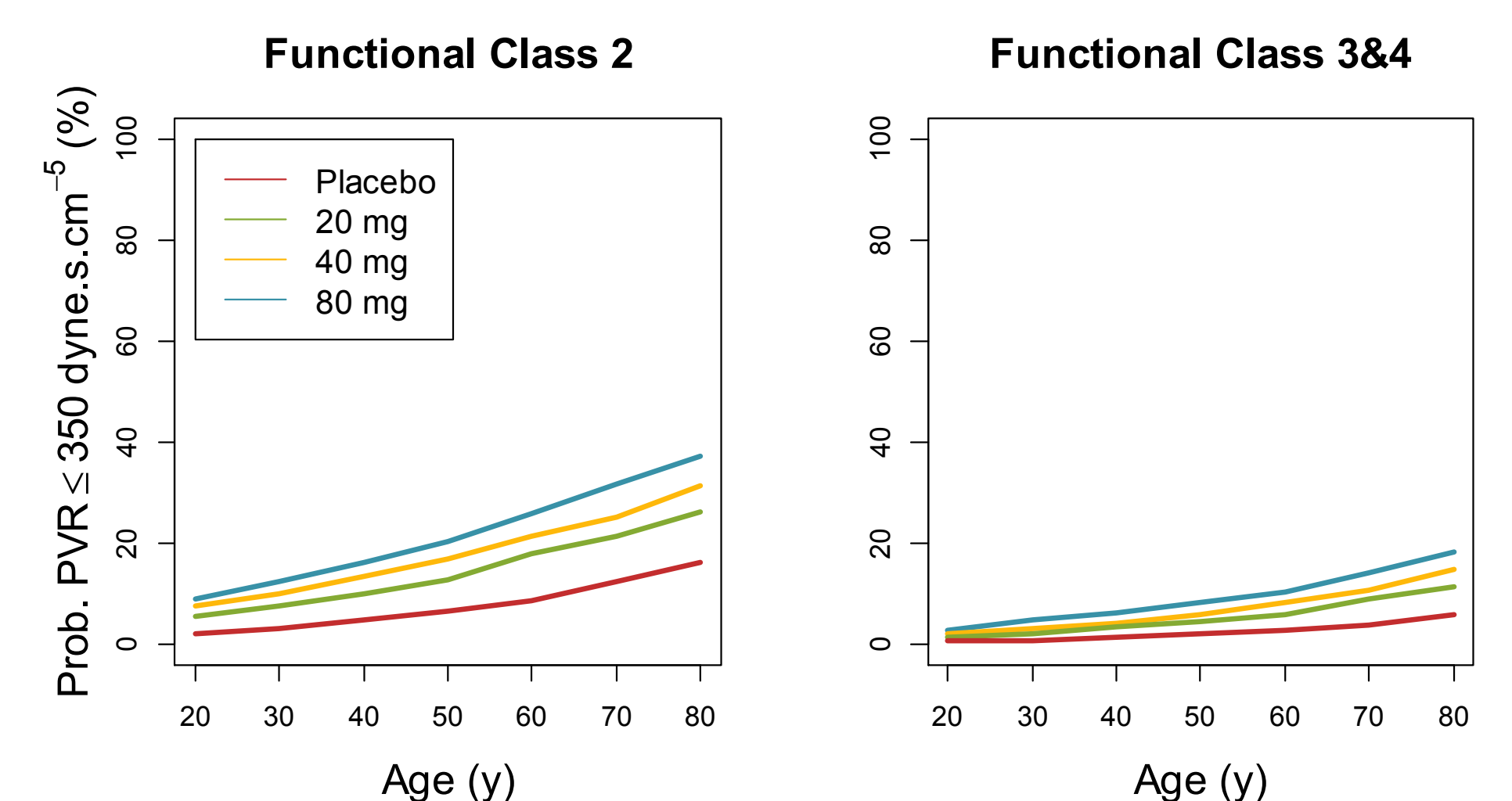
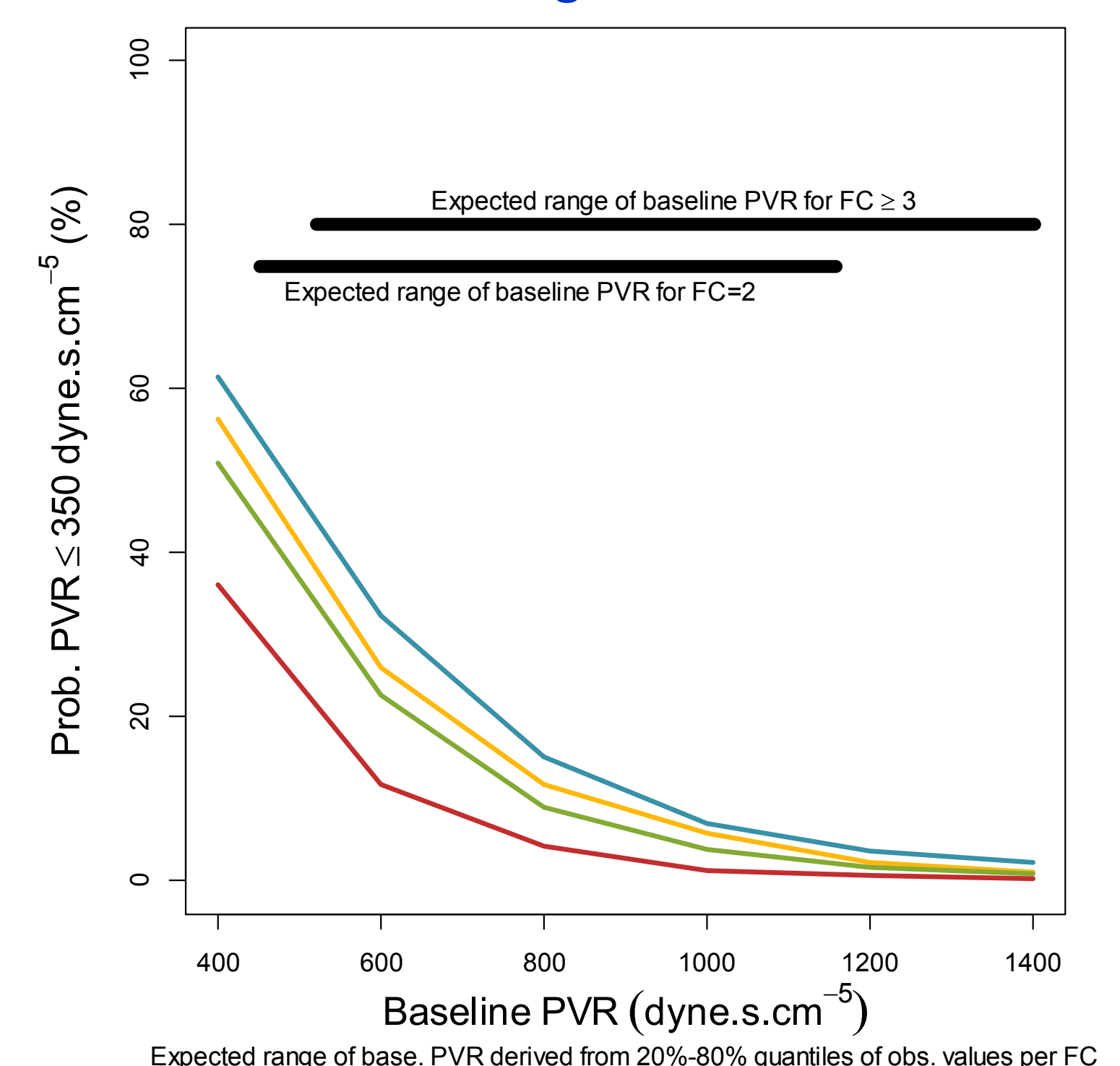


Figure 4



Discussion and conclusions

• Model based simulations of PVR outcome showed that a dose of 80 mg TID might provide additional PVR improvement in specific PAH populations i.e. elderly, severe patients.

• The implication of these simulation results to 6MWD improvement remains to be further investigated.

References

1. FDA Cardiovascular and Renal Drugs Advisory Committee Meeting, July 29, 2010. [http://www.fda.gov/AdvisoryCommittees/Calendar/ucm217266.htm].
2. Galie et al, Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension N Engl J Med, 353:2148-57, 2005.
3. P Chanu, X Gao, M Smith, R Bruno, L Harnisch, A dose selection rationale based on hemodynamics for sildenafil in pediatric patients with pulmonary arterial hypertension (PAH), PAGE, Athens, 2011, PAGE 20 (2011) Abstr 2104 [www.page-meeting.org/?abstract=2104].

