SYSTEMATIC REVIEW OF TRIALS IN PAH
WHY A NEW APPROACH IS NEEDED

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Rencontres Genevoises de Pneumologie

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NO CONFLICT OF INTERESTS

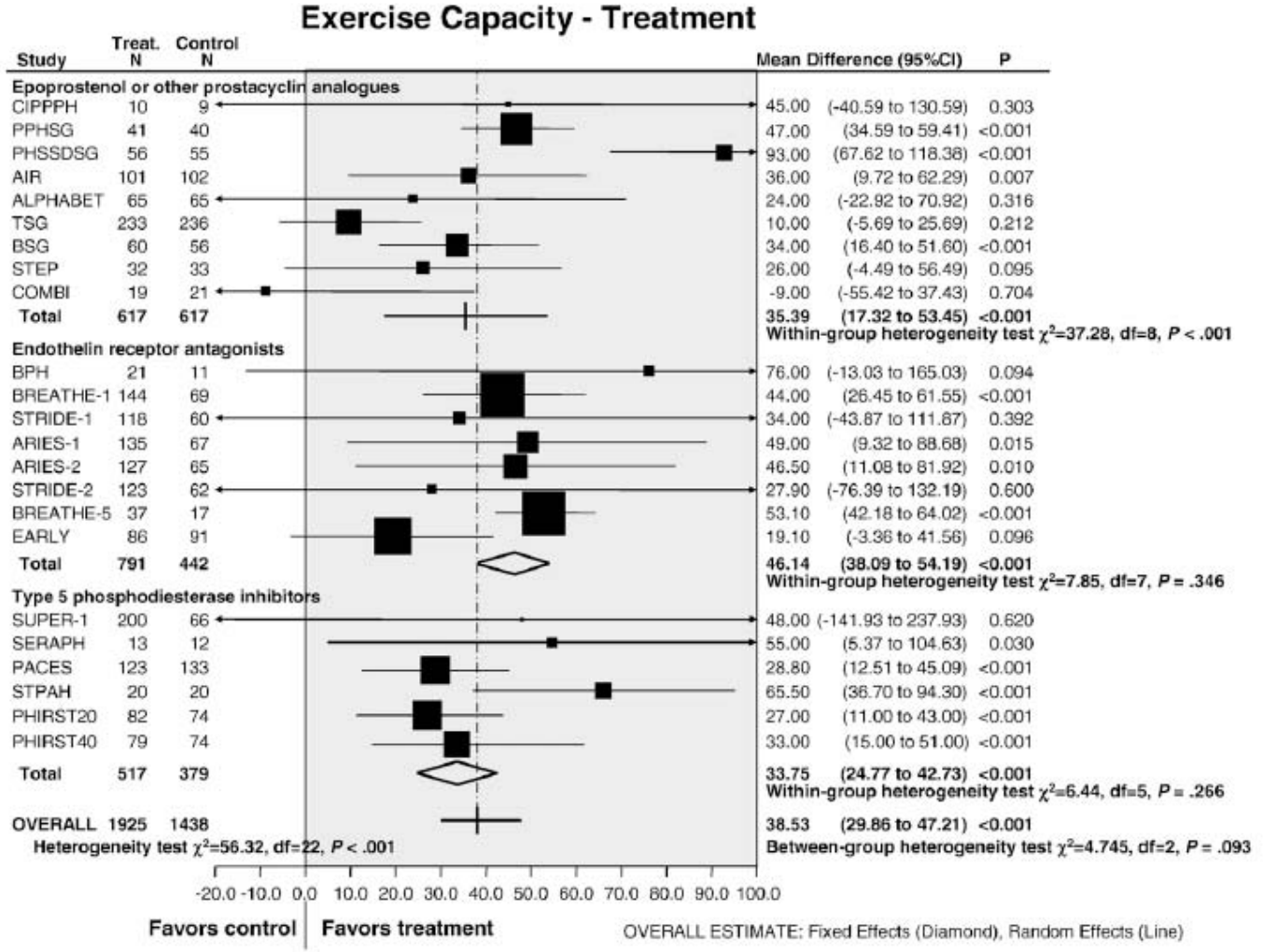
1. **The state of the art**

2. **The historical/pharmacological framework**

3. **Key words for PAH**

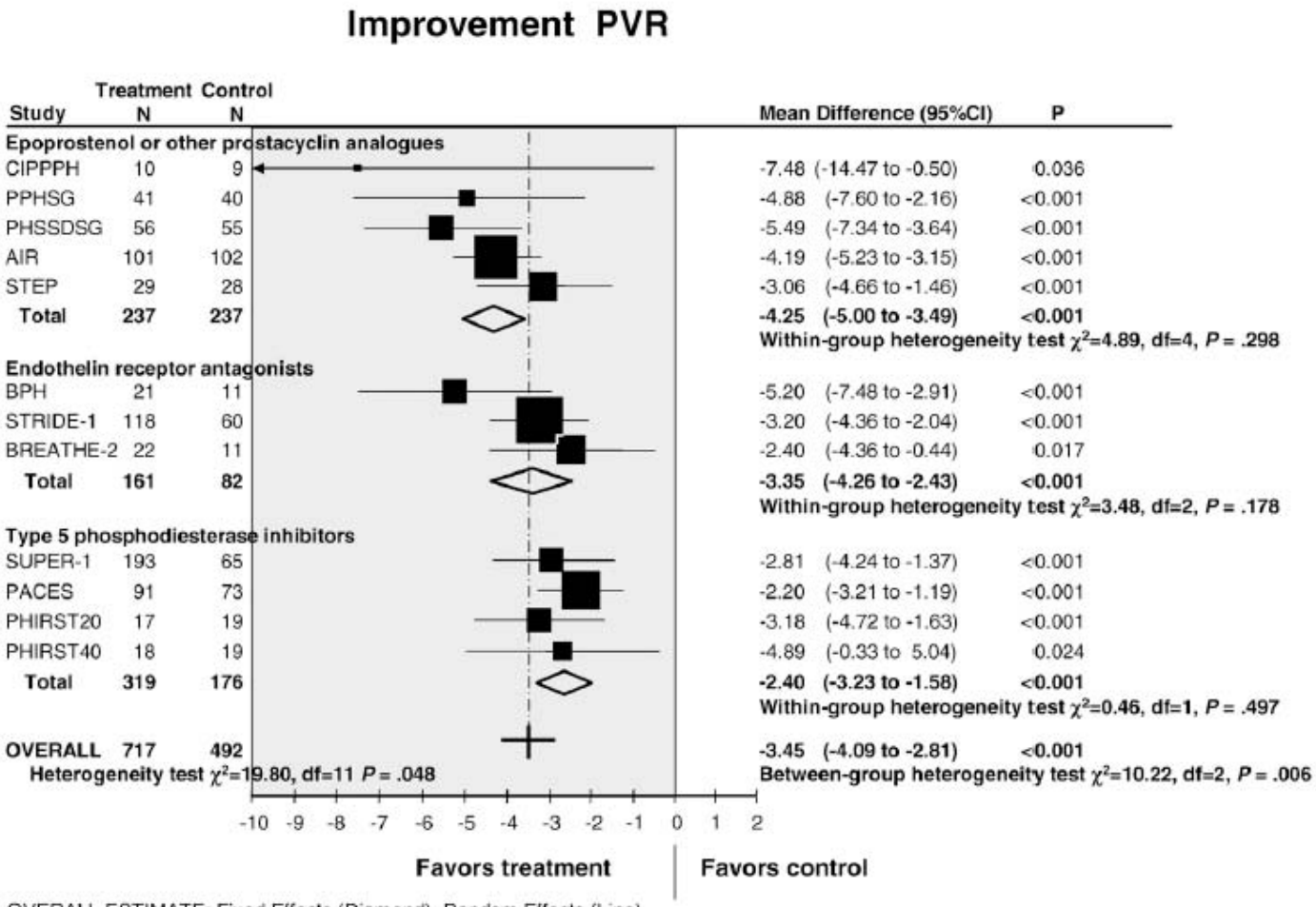
   - behind/beyond
   - to look forwards

Figure 1



Weighted mean improvement of exercise capacity in patients allocated to experimental treatments as compared with control groups. There was significant heterogeneity only within the group of EPO reflecting the dispersion of results within this category.

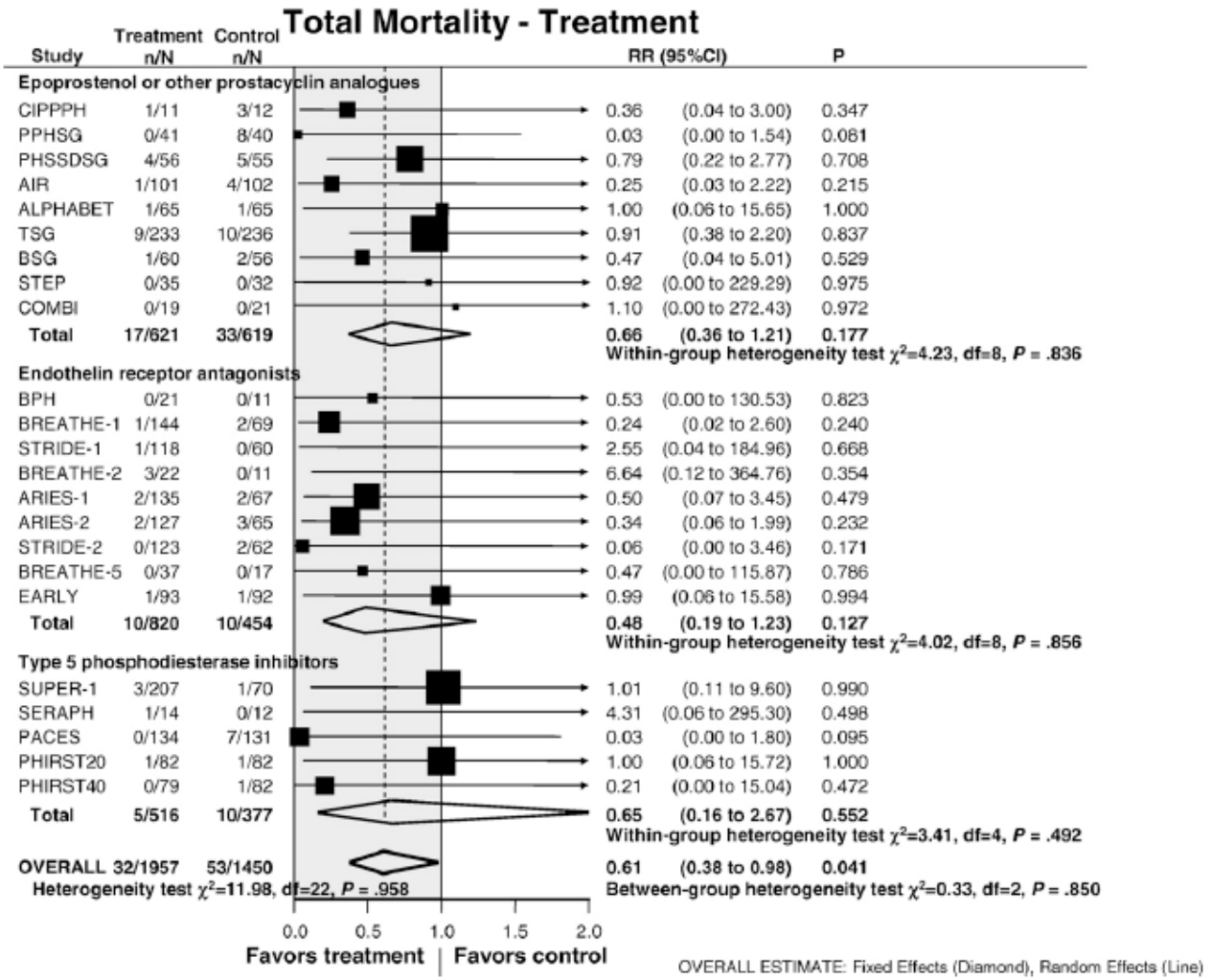
Figure 2



OVERALL ESTIMATE: Fixed Effects (Diamond), Random Effects (Line)

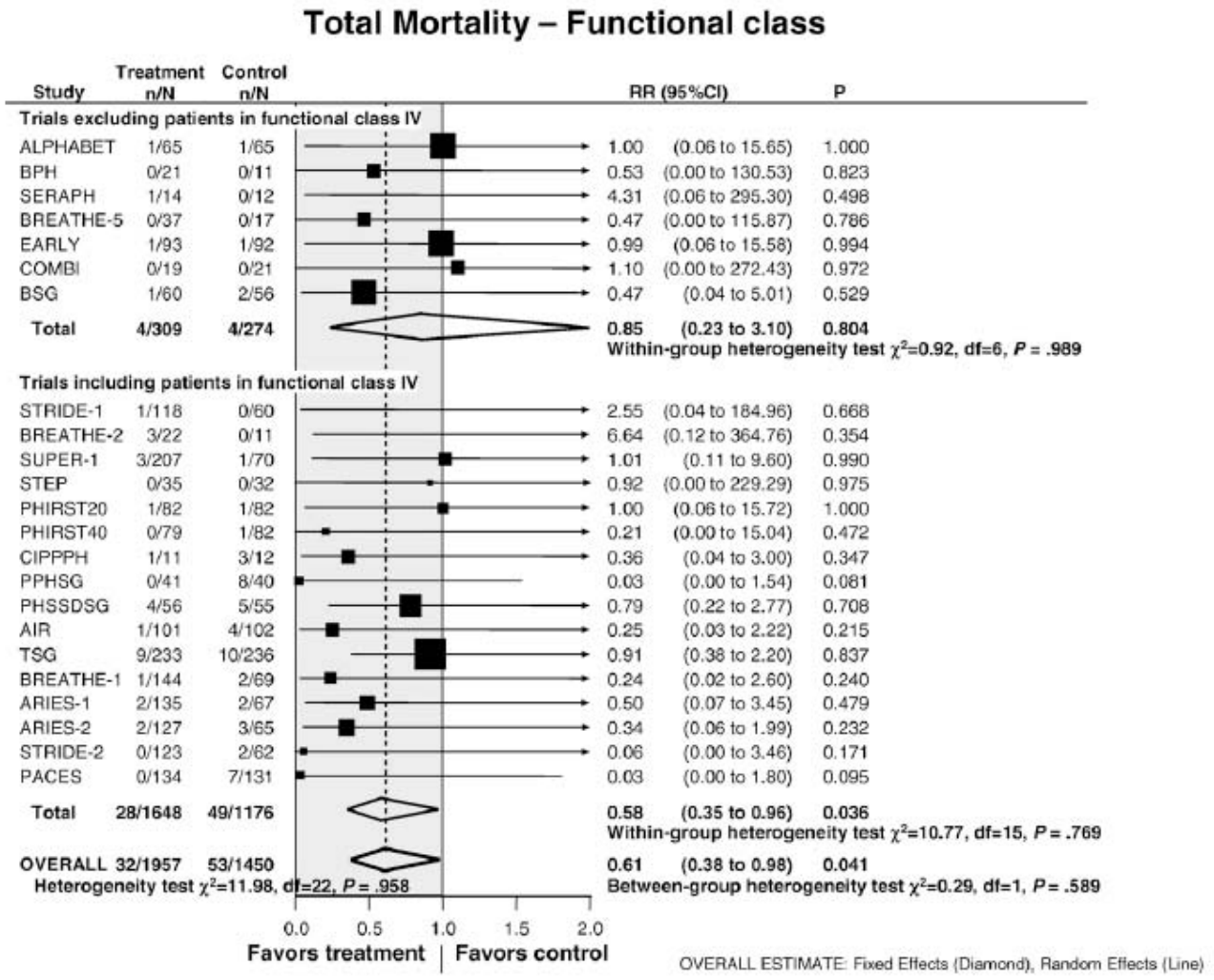
Improvement in PVR in patients allocated to experimental treatments as compared with control groups. Although the effect was statistically significant, it represents only a 6% fall from baseline in the treated patients.

Figure 3



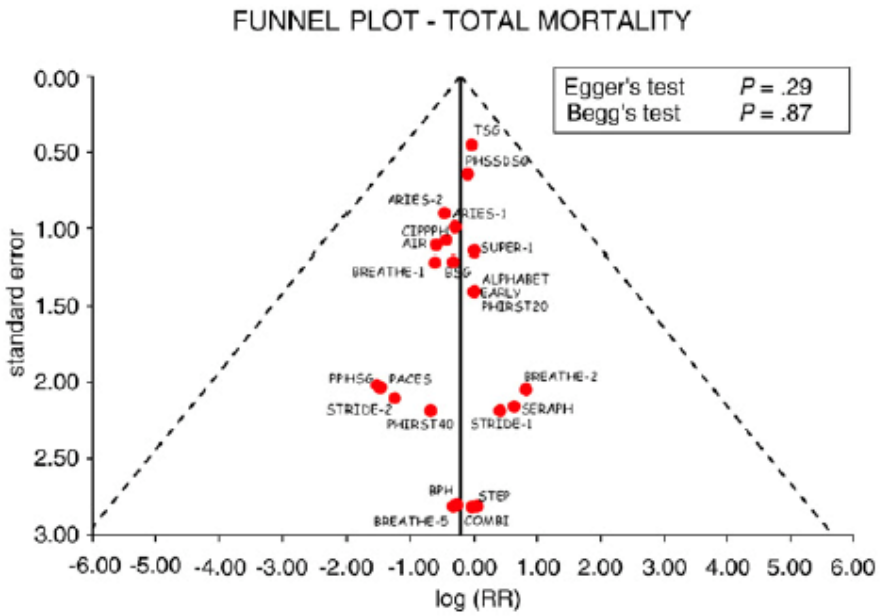
Cumulative estimate of death in active treatment groups as compared with control groups. The pooled effect of all treatments was a reduction of 39% (2% to 62%) in all-cause mortality. When considering the cumulative effects within each drug family, no class of drug produced a statistically significant reduction in all-cause mortality.

Figure 5



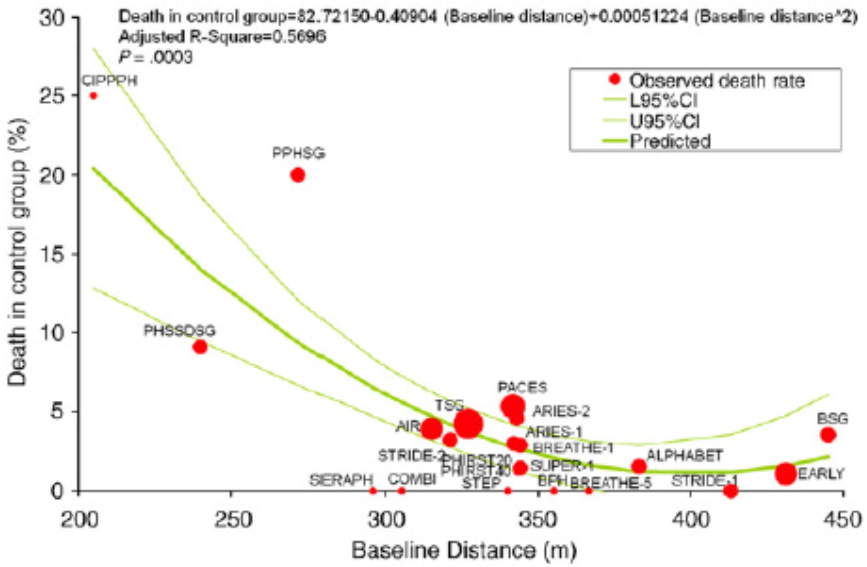
Benefit of tested treatments on mortality in trials including and excluding patients in functional class IV.

Figure 6



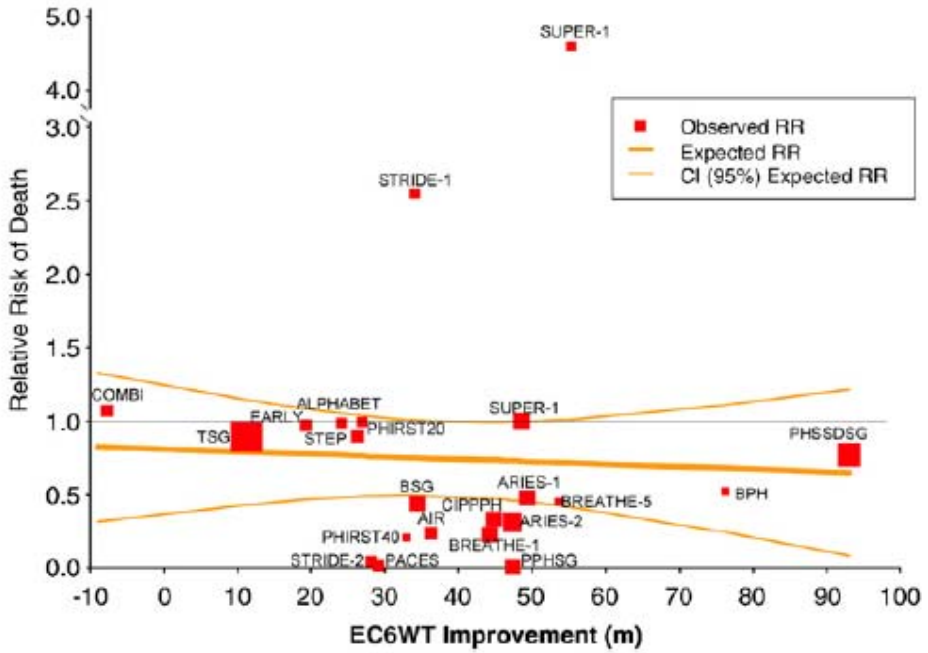
Funnel plot. There was no evidence of publication bias.

Figure 7



Relation between baseline walking distance and mortality during follow-up. The relationship was linear for those who exercised less than 340 m.

Figure 8



Relation between the degree of improvement in exercise capacity and the reduction of death. There was no difference in the change in 6MW between the classes of agents or among patients with advanced disease.

SYSTEMATIC REVIEW OF TRIALS IN PAH

EPO & PCA TRIALS (9; n=1,241)

Trial	N	ACRONYSM	
Rubin (1990)	23	-	Epoprostenol
Barst (1996)	81	PPHSG	Epoprostenol
Badesch (2000)	111	-	Epoprostenol
Olschewski (2002)	203	AIR	Iloprost
Galiè (2002)	130	ALPHABET	Beraprost
Simmoneau (2002)	470	TSG	Treprostinil
Barst (2003)	116	BSG	Beraprost
McLaughlin	67	STEP	Iloprost
Hoeper	40	COMBI	Iloprost

SYSTEMATIC REVIEW OF TRIALS IN PAH

ETRA TRIALS (9; n=1,274)

Trial	N	ACRONYSM	
Channick (2001)	32	BPH	Bosentan
Rubin (2002)	213	BREATHE -1	Bosentan
Barst (2003)	178	STRIDE-1	Sitaxentan
Humbert (2004)	33	BREATHE-2	EPO + Bosentan EPO
Galiè (2008)	202	ARIES 1	Ambrisentan
Galiè (2008)	192	ARIES 2	Ambrisentan
Barst (2006)	185	STRIDE 2	Sitaxentan
Galiè (2006)	54	BREATHE 5	Bosentan
Galiè (2008)	185	EARLY	Bosentan

SYSTEMATIC REVIEW OF TRIALS IN PAH
PDT5I TRIALS (8; n=1,004)

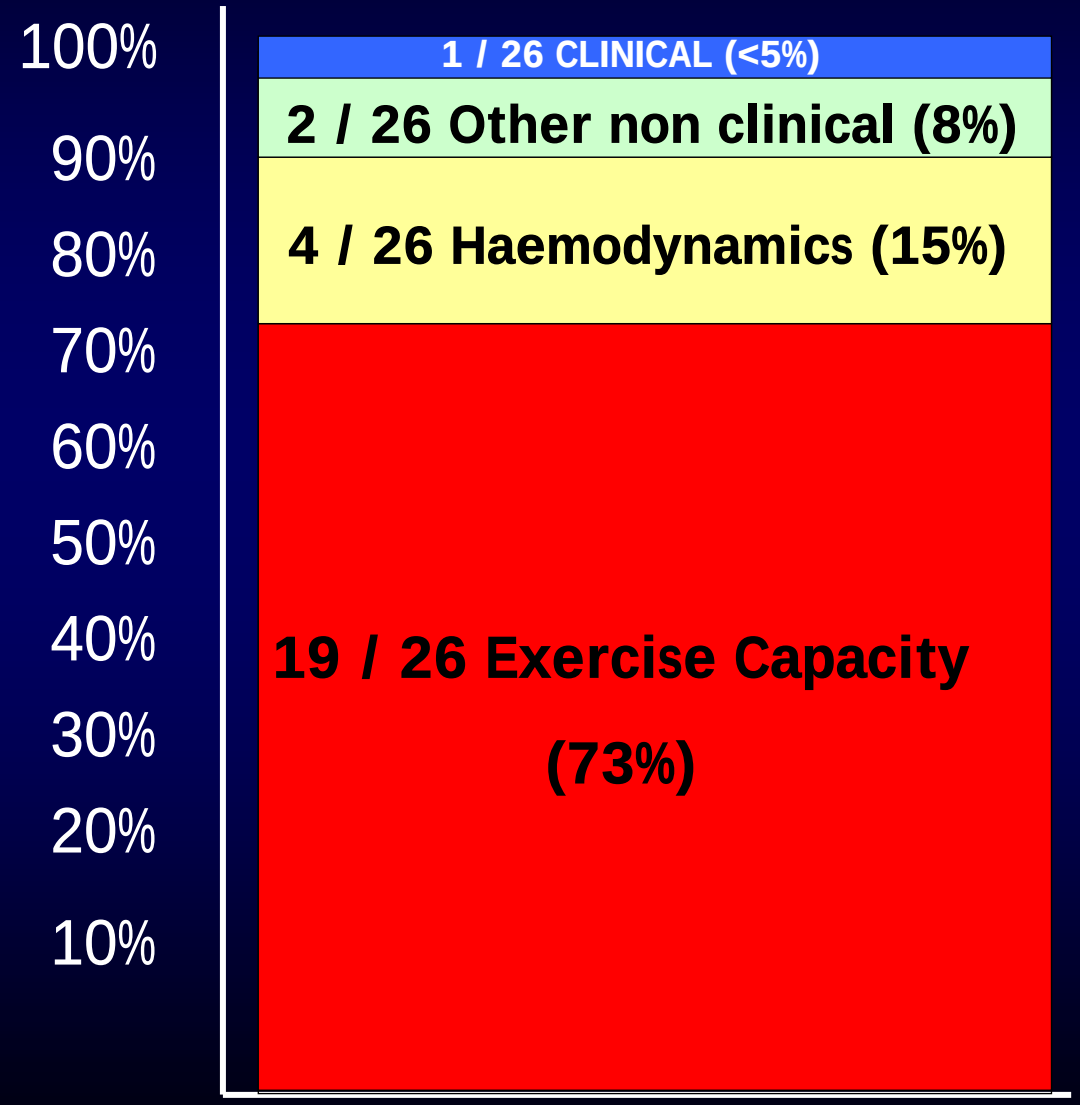
Trial	N	ACRONYSM	
Ghofrani	30	S and ISPH	Sildenafil Sildenafil + Iloprost
Ghofrani	16	SLFPH	Sildenafil EPO
Sastry	22	SPPH	Sildenafil
Galié	278	SUPER-1	Sildenafil
Wilkins	26	SERAPH	Sildenafil Bosentan
Simmonneau	267	PACES	EPO + Sildenafil EPO
Singh	40	STPAH	Sildenafil
Galié	164	PHIRST20	Tadalafil
Galié	161	PHIRST40	Tadalafil

Trial	N	ACRONYSM	
Rubin (1990)	23	-	NO
Barst (1996)	81	PPHSG	NO
Badesch (2000)	111	-	NO
Olschewski (2002)	203	AIR	NO
Galiè (2002)	130	ALPHABET	NO
Simmoneau (2002)	470	TSG	NO
Barst (2003)	116	BSG	YES
McLaughlin	67	STEP	NO
Hoeper	40	COMBI	NO

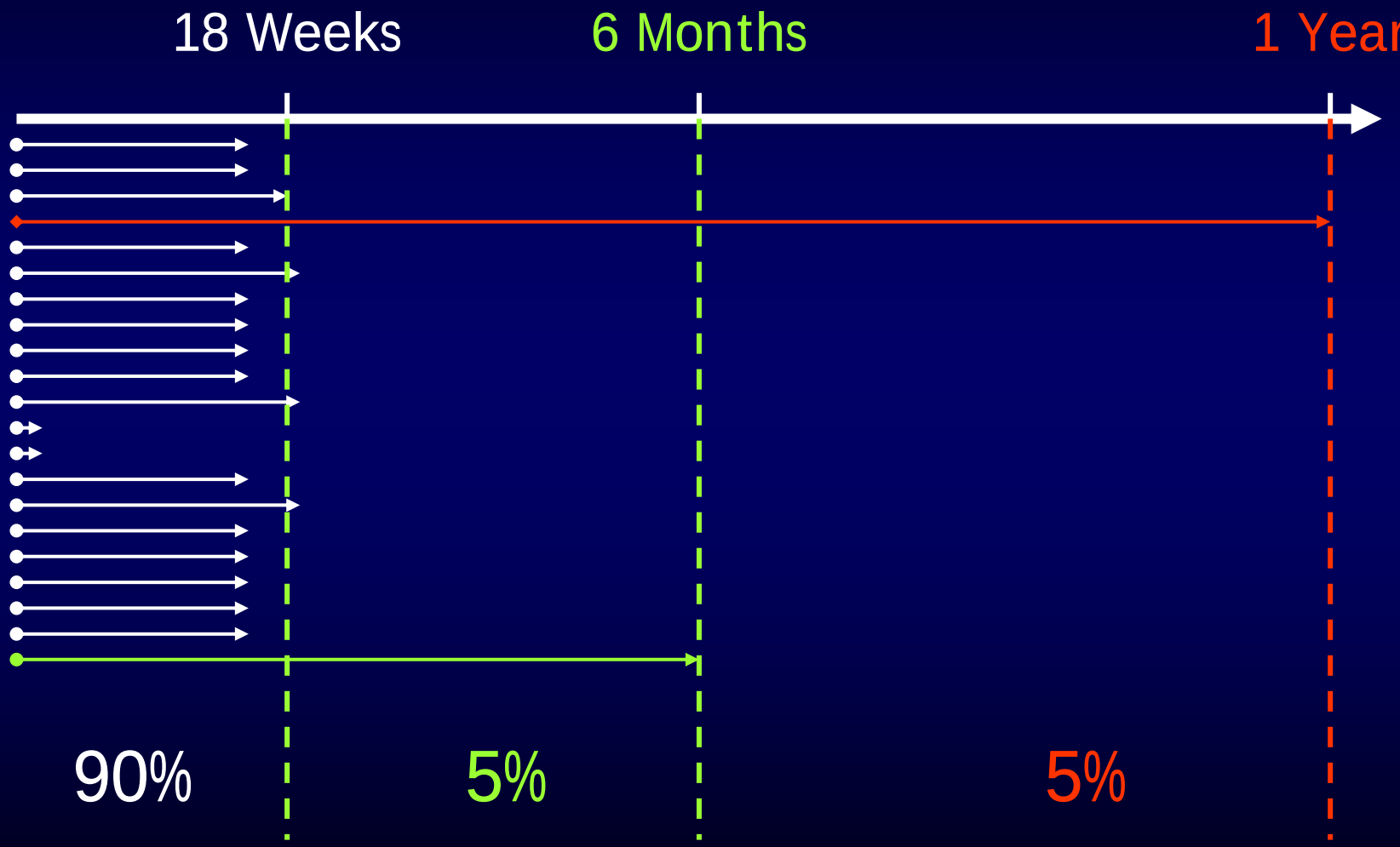
Channick (2001)	32	BPH	NO
Rubin (2002)	213	BREATHE -1	NO
Barst (2003)	178	STRIDE-1	NO
Humbert (2004)	33	BREATHE-2	NO
Galiè (2008)	202	ARIES 1	NO
Galiè (2008)	192	ARIES 2	NO
Barst (2006)	185	STRIDE 2	NO
Galiè (2006)	54	BREATHE 5	NO
Galiè (2008)	185	EARLY	NO

Ghofrani	30	S and ISPH	NO
Ghofrani	16	SLFPH	NO
Sastry	22	SPPH	NO
Galié	278	SUPER-1	NO
Wilkins	26	SERAPH	NO
Simmonneau	267	PACES	NO
Singh	40	STPAH	NO
Galié	164	PHIRST20	NO
Galié	161	PHIRST40	NO

WHAT (OUTCOMES) RCT TESTED ?



WHAT WAS THE DURATION OF RCT ?

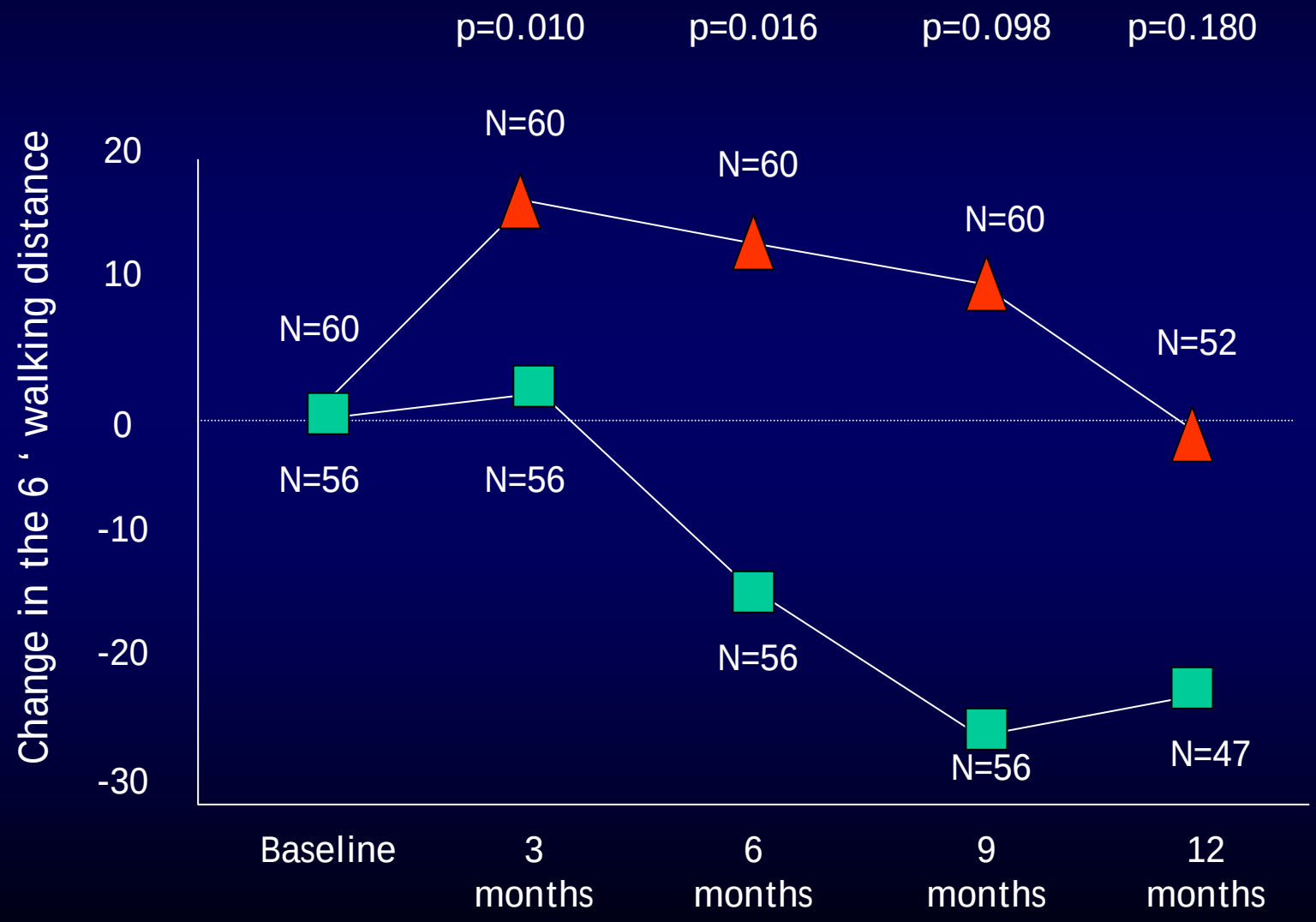


The only trial that address mortality as a primary point failed to demonstrate any benefit

	BERAPROST	PLACEBO	P
MONTH 3 Death Rescue Desaturation	0 / 60 0 0 0	3 / 56 0 2 1	0.109
MONTH 6 Death Rescue Desaturation	1 / 60 0 1 0	11 / 56 2 6 3	0.002
MONTH 9 Death Rescue Desaturation	8 / 60 1 4 3	15 / 56 2 7 6	0.102
MONTH 12 Death Rescue Desaturation	10 / 56 1 5 4	15 / 52 2 7 6	0.254

Barst RJ.JACC 2003;41:2119-25

If they would studied excercise capacity at 3-6 months, probably Beraprost would be approved it



Barst RJ.JACC 2003;41:2119-25

Key words

Behind/beyond

1. **Rare diseases: incidence, prevalence, clinically oriented epidemiology**
2. **Problem** *vs* **drug oriented trials**
3. **Registration requirements** *vs* **clinical relevance**
4. **Science** *vs* **ethics**

Key words

To look/forwards

1. Representative networks

2. RCTs as a component of prospective outcome oriented epidemiology (“effectiveness monitoring”)

3. Hard outcomes as a guide to understand surrogate/intermediate end-points