ACTION

Pneumologi in azione
nell'ipertensione arteriosa polmonare (PAH)

Dal test dei 6 minuti alla mortalità: il problema degli end-point

Roberto Cassandro

ACTION

Pneumologi in azione
nell'ipertensione arteriosa polmonare (PAH)

SINGLE CLINICAL ENDPOINT

COMPOSITE ENDPOINTS

PRIMARY ENDPOINT IN CLINICAL TRIAL

Clinical Endpoints

Must be:

- Consistently & readily measurable
- Sensitive
- Well defined & reliable
- Clinically meaningful

…a direct measure of how a patient functions, feels or survives …
(Robert Temple FDA)

Indirect Outcome Measures

Some indirect measures that are dependent on patient motivation or clinical judgment have been proposed or used as primary endpoints in registration trials.

These include the Six Minute Walk Distance (6MWD).

These measures are conducted in artificial settings and therefore provide only indirect assessments of the intervention's effect on how a patient feels, functions or survives.

6-MWT LIMITATIONS

BODY WEIGHT

LEG DISEASES

SEX

AGE

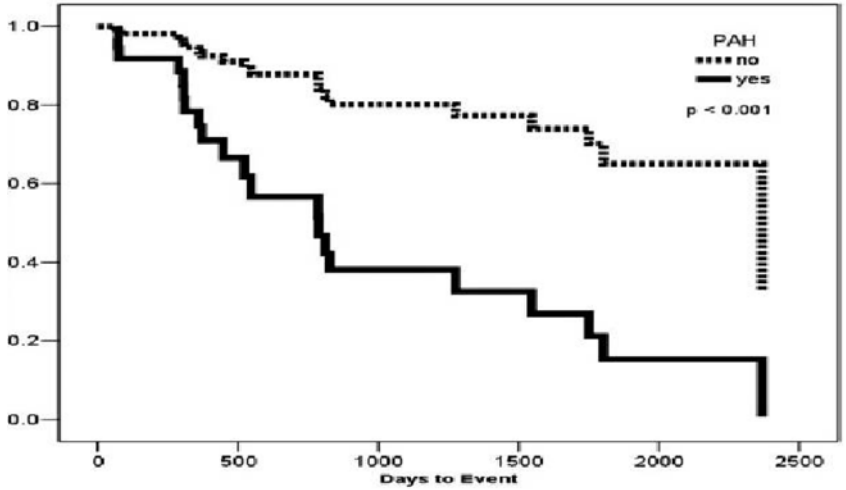
DAILY VARIATIONS

Indirect Outcome Measures

It still enough to prove that an intervention has just any effect on 6MWD in order to have reliable evidence that it provides a clinically meaningful improvement in a patient's ability to cross a street before a light changes to red, or to be able to carry out other usual daily activities.

As background therapies improve in PAH and incremental improvements in 6MWD become smaller in add-on trials evaluating new agents, the interpretability of the effects on 6MWD measure becomes more difficult.

Pulmonary hypertension in IPF



Variables	MAP ≤ 25 mmHg (n= 10)	MAP > 25 mmHg (n= 24)	P value
MPAP, mmHg	18.2 ± 3.6	29.8 ± 5.1	NA
6MWT distance, m	365.9 ± 81.8	143.5 ± 65.5	< 0.001
SpO2 nadir on 6MWT, %	88.0 ± 3.5	80.1 ± 3.7	< 0.001
Mortality rate, %	37.5	70.0	0.003

Lettieri CJ et al. Chest 2006, 129:746-52

RHC and 6MWD in IPF

Variables	MAP ≤ 25 mmHg (n= 17)	MAP > 25 mmHg (n= 13)	MAP > 35 mmHg (n= 4)	P value
MPAP, mmHg	19.4 ± 3.6	32.4 ± 6	40,5 ± 2,6	NA
6MWT distance, m	222.0 ± 118.5	222.3 ± 118.5	203.7 ± 128.3	>0.1
FVC, %	51.6 ± 13.8*	63.8 ± 16*	56.0 ± 6.7	<0.05
FEV1, %	58.3 ± 16.3	65.8 ± 18.8	55.2 ± 3.7	>0.05
DLCO, %	31.4 ± 9.6	24.2 ± 13.0	29.0 ± 7.4	>0.05
CI, l/min/m2	3.4 ± 0.55*	2.9 ± 0.7*	2.8 ± 0.6	<0.05
PVR, wood units	3.5 ± 1.1*	6.9 ± 1.4*	10.3 ± 2.0	<0.05

Harari S. et coll. Sarcoidosis 2015

Our data suggest that meters walked during 6MWT are not statistically different in IPF patients with or without PH.

6MWD should not be used as surrogate end point in clinical study in IPF-PH pts.

Harari S. et coll. Sarcoidosis 2015

End-point problems

- Major PAH treatments has been only approved by clinical trials of 12-16 weeks.
- They considered only the improvement of meters in 6MWT
- Only epoprostenol has been approved by a clinical mortality trial.

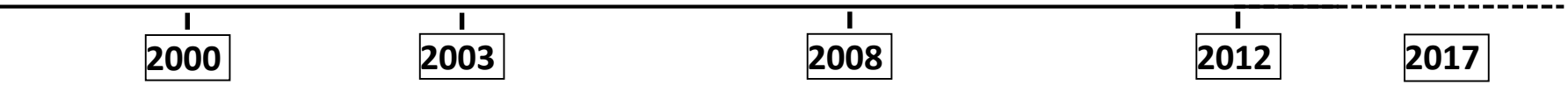
6-MWD

- **A simple,reproducible and valid tool to assess excercise capacity**
- **Initially thought Δ6-MWD was a reliable surrogate of outcome**
- **Accepted by regulatory authorities for registration of PAH drugs**

6-MWD

-Today, there is growing evidence that 6-MWD is not a reliable surrogate of outcome

- **In addition, short-term trials are not appropriate for evaluating new drugs in a chronic and severe disease**



Correlates

In PAH, biomarkers that are based on laboratory assessments, such as NT-proBNP, or hemodynamic measures, such as PVRI, mPAP or CO, have been considered as potential surrogate endpoints because of their strong correlation to valid clinical endpoints.

More research work should be done to validate e.g. PVR as a valid surrogate endpoint for PAH, unfortunately nobody seems to be interested.

SINGLE CLINICAL ENDPOINT

COMPOSITE ENDPOINTS

PRIMARY ENDPOINT IN CLINICAL TRIAL

Composite Endpoints

Composite endpoints may allow more efficient capture of clinically meaningful effects. This is especially appealing in disease settings of limited prevalence, such as PAH

For a composite endpoint to be interpretable, its components should be of similar clinical relevance or at least in a clear hierarchy.

When the endpoint's components have different relevance, it is implicit that the endpoint itself gets the weakest clinical relevance.

Composite Endpoints

In PAH, an important composite endpoint is Time to Clinical Worsening (TtCW). It has been defined at the 4th and 5th World Symposium in PH at Dana Point and Nice as time to the earliest occurrence of the following events: *death, lung transplantation, hospitalization for worsening PAH (including atrial septostomy), initiation of parenteral prostanoid therapy due to worsening PAH, worsening of function ((i.e., ↑NYHA & ↓6MWD),worsening of PAH Symptoms*

All events must be adjudicated by a blinded committee not involved in the conduct of the study.

Raccomandazione dell'EMA[2]

- L'EMA raccomanda simili componenti di morbilità/mortalità:
  - Decesso per tutte le cause
  - Tempo all'ospedalizzazione non previsto correlato alla PAH
  - Tempo al deterioramento correlato alla PAH identificato mediante:
    - Aumento della FC OMS
    - Deterioramento nel test sotto sforzo
    - Segni o sintomi di insufficienza cardiaca del lato destro
- L'EMA richiede inoltre che tutti i parametri scelti siano clinicamente rilevanti, definiti adeguatamente, ben validati e assegnati centralmente.

[2] EMA CHMP, 2009.

- Until 2013 the events described for TTCW were different for every study
- So, it's not possible to have the same definition of TTCW
- TTCW was never considered a primary end-point in PAH studies
- In studies that considered TTCW as a primary endopoint , all events were not adjudicated by a blinded independent committee
- All events of TTCW were only adjudicated by a single medical investigator

Evidenze cliniche per gli attuali trattamenti per la PAH [n. 1]: Bosentan (ERA)

	Studio 351 (Channick et al. 2001; Badesch et al. 2002)	BREATHE-1 (Rubin et al. 2002; Galiè et al. 2003)	BREATHE-5 (sindrome di Eisenmenger) (Galiè et al. 2006)	EARLY (Galiè et al. 2008)
N	32	213	54	185
Durata	12 settimane	16 settimane	16 settimane	6 mesi
Precedente terapia per la PHA*	Nessuna	Nessuna	Nessuna	16% dei pazienti trattati con SIL
FC NYHA/OMS basale	III	III/IV	III	II
Bracci di trattamento	• BOS 62,5 mg BID per 4 settimane, dopodiché 125 mg BID • PBO	• BOS 62,5 mg BID per 4 settimane, dopodiché 125 o 250 mg BID • PBO	• BOS 62,5 mg BID per 4 settimane, dopodiché 125 mg BID • PBO	• BOS 62,5 mg BID per 4 settimane, dopodiché 125 mg BID • PBO
Idoneità	• PPH o PH sintomatica grave a causa di scleroderma, FC OMS III–IV	• PAH sintomatica grave, primaria o associata a CTD (scleroderma o lupus eritematoso sistemico [SLE]), FC OMS III–IV	• Sindrome di Eisenmenger, FC OMS III, età >12 anni	• IPAH, FPAH, PAH associata ad anoressizzante, CHD, CTD, HIV, FC OMS II, età ≥12 anni
Significatività rispetto al placebo				
Miglioramento della FC NYHA/OMS	✓	(✓)	(✓)	NR
TTCW	✓	✓	NA	✓
Variazione nel test 6MWD	✓	✓	✓	×
PVR	✓	NR	✓	✓
CI	✓	✓	NA	✓
SF-36	NA	NA	NA	× eccetto indice di transizione sanitaria

■ = endpoint primario; 6MWD = distanza percorsa in 6 minuti; BID = due volte al giorno; BOS = bosentan; CI = indice cardiaco; EPO = epoprostenolo; FC = classe funzionale; NA = non valutato; NR = non riportato; NYHA = New York Heart Association; PBO = placebo; PVR = resistenza vascolare polmonare; SF-36 = questionario Short Form 36; SIL= sildenafil; * = agente mirato alla PAH (ERA, inibitore della PDE-5, prostanoide); ✓ = P < 0,05 rispetto a placebo; (✓) = significatività statistica borderline; × = P ≥ 0,05 vs. placebo

Evidenze cliniche per gli attuali trattamenti per la PAH [n. 2]: Ambrisentan (ERA)

	ARIES-1 (Galiè et al. 2008; Torres 2007)	ARIES-2 (Galiè et al. 2008 ; Torres 2007)
N	202	192
Durata	12 settimane	12 settimane
Precedente terapia per la PHA*	Nessuna	Nessuna
FC NYHA/OMS basale	I–IV (II: 32%, III: 58%)	I–IV (II: 45%, III: 52%)
Bracci di trattamento	• AMB 2,5 mg QD • AMB 5 mg QD • PBO	• AMB 5 mg QD • AMB 10 mg QD • PBO
Idoneità	• IPAH, PAH associata ad anoressizzante, CTD, HIV	• IPAH, PAH associata ad anoressizzante, CTD, HIV
Significatività rispetto al placebo		
Miglioramento della FC NYHA/OMS	✓	✗
TTCW	✗	✓
Variazione nel test 6MWD	✓	✓
PVR	NR	NR
CI	NR	NR
SF-36	✗	PF ✓, altre scale NR
	PF, RP, V, PCS (aggregate) ✓	

■ = *endpoint primario; 6MWD = distanza percorsa in 6 minuti; AMB = ambrisentan; CI = indice cardiaco; FC = classe funzionale; NA = non valutato; NR = non riportato; NYHA = New York Heart Association; PF = scala del funzionamento fisico; PBO = placebo; PCS = scala riassuntiva della componente fisica (Physical Component Summary); PVR = resistenza vascolare polmonare; RP = scala del ruolo fisico; SF-36 = questionario Short Form 36; V = scala della vitalità; * = agente mirato alla PAH (ERA, inibitore della PDE-5, prostanoide); ✓ = P < 0,05 rispetto a placebo; (✓) = significatività statistica borderline; ✗ = P ≥ 0,05 rispetto a placebo*

Evidenze cliniche per gli attuali trattamenti per la PAH [n. 4]: Inibitori della PDE-5

	Sildenafil		Tadalafil
	SUPER-1 (Galiè et al. 2005; Pepke-Zaba et al. 2008)	**PACES** (Simonneau et al. 2008)	**PHIRST-1** (Galiè et al. 2009; Pepke-Zaba et al. 2009)
N	278	267	406
Durata	12 settimane	16 settimane	16 settimane
Precedente terapia per la PHA*	Nessuna	EPO	il 53% dei pazienti trattati con SIL
FC NYHA/OMS basale	I–IV (II: 39%, III: 58%)	I–IV (II: 25%, III: 66%)	I–IV (II: 32%, III: 65%)
Bracci di trattamento	• SIL 20 mg TID • SIL 40 mg TID • SIL 40 mg TID per 7 giorni, dopodiché 80 mg TID • PBO	• EPO + SIL 20 mg TID per 4 settimane, dopodiché 40 mg TID per 4 settimane, dopodiché 80 mg TID • EPO + PBO	• TAD 2,5, 10, 20 o 40 mg QD • PBO
Idoneità	• IPAH, PAH associata a CHD o CTD, FC OMS I–IV, età ≥18 anni	• IPAH, FPAH, PAH associata a CHD o CTD, età ≥18 anni (16 anni negli USA)	• IPAH, HPAH, PAH associata ad anoressizzante, CHD, CTD, HIV, età ≥12 anni
Significatività rispetto al placebo			
Miglioramento della FC NYHA/OMS	✓	NR	✗
TTCW	✗	✓	TAD 40 mg ✓, altre dosi NR
Variazione nel test 6MWD	✓	✓	TAD 2,5 mg ✗, TAD 10 mg (✓), TAD 20 e 40 mg ✓
PVR	✓	✗	TAD 20 e 40 mg ✓, altre dosi NR
CI	SIL 20 mg (✓), 40 e 80 mg ✓	NR	TAD 40 mg ✓, altre dosi NR
SF-36	PF e GH ✓, V ✓ solo per i dati aggregati su SIL, tutti gli altri domini ✗	PF, GH, V e MH ✓, SF (✓), tutti gli altri domini ✗	PF, RP, BP, GH, V e SF ✓, altri domini ✗

*= endpoint primario; 6MWD = distanza percorsa in 6 minuti; BOS = bosentan; BP = dolore fisico; CI = indice cardiaco; EPO = epoprostenolo; FC = classe funzionale; GH = scala della salute generale; MH = scala della salute mentale; NA = non valutato; NR = non riportato; NYHA = New York Heart Association; PBO = placebo; PF = scala del funzionamento fisico; PVR = resistenza vascolare polmonare; QD = una volta al giorno; RP = scala del ruolo fisico; SF = scala del funzionamento sociale; SF-36 = questionario Short Form 36; SIL= sildenafil; TAD = tadalafil; TID = tre volte al giorno; V = scala della vitalità; * = agente mirato alla PHA (ERA, inibitore della PDE-5, prostanoide); ✓ = P < 0,05 rispetto a placebo; (✓) = significatività statistica borderline; ✗ = P ≥ 0,05 rispetto a placebo*

Evidenze cliniche per gli attuali trattamenti per la PAH [n. 5]: Prostacicline (1)

	Epoprostenolo EV		
	(Rubin et al. 1990)	(Barst et al. 1990)	(Badesch et al. 2000)
N	24	81	111
Durata	8 settimane	12 settimane	12 settimane
Precedente terapia per la PHA*	Nessuna	Nessuna	Nessuna
FC NYHA/OMS basale	II-IV (II: 8%, III: 29%, IV: 63%)	III-IV (III: 74%, IV: 26%)	II-IV (II: 5%, III: 78%, IV: 17%)
Bracci di trattamento	• dose iniziale EPO 1-2 ng/kg/min aumentata fino alla dose massima tollerata • Trattamento standard	• dose iniziale EPO 4 ng/kg/min aumentata fino alla dose massima tollerata • dose iniziale EPO 4 ng/kg/min aumentata fino alla dose massima tollerata E trattamento standard	• dose iniziale EPO 1-2 ng/kg/min aumentata fino alla dose massima tollerata • Trattamento standard
Idoneità	• FPAH, IPAH, FC OMS II–IV, età ≥18 anni	• FPAH, IPAH, FC OMS III–IV, età ≥18 anni	• PAH associata a sclerodermia
Significatività rispetto al comparatore			
Miglioramento della FC NYHA/OMS	✗	✓	NR
TTCW	NA	NA	NA
Variazione nel test 6MWD	✓	✓	✓
PVR	✓	✓	✓
CI	✓	✓	✓
SF-36	NA	NA	NA

■ = endpoint primario; 6MWD = distanza percorsa in 6 minuti; CI = indice cardiaco; EPO = epoprostenolo; FC = classe funzionale; FPAH = PAH familiare; IPAH = PAH idiopatica; NA = non applicabile; NR = non riportato; NYHA = New York Heart Association; PVR = resistenza vascolare polmonare; * = agente mirato alla PAH (ERA, inibitore della PDE-5, prostanoide); trattamento standard = anticoagulanti, vasodilatatori per via orale, diuretici; SF-36 = questionario Short Form 36; TTCW = tempo al peggioramento clinico; ✓ = $P < 0,05$ rispetto a comparatore; ✗ = $P \geq 0,05$ rispetto a comparatore

Evidenze cliniche per gli attuali trattamenti per la PAH [n. 6]: Prostacicline (2)

	Iloprost (per via inalatoria)	Treprostinil (per via inalatoria)	Treprostinil (per via sottocutanea)
	(Olschewski et al. 2002)	(McLaughlin et al. 2010)	(Simmoneau et al. 2002)
N	203	235	469
Durata	12 settimane	12 settimane	12 settimane
Precedente terapia per la PHA*	Nessuna	BOS o SIL, dose stabile da almeno 3 mesi	Nessuna
FC NYHA/OMS basale	II-IV (III: 59%, IV: 41%)	III-IV (III: 98%, IV: 2%)	II-IV (II: 11%, III: 82%, IV: 7%)
Bracci di trattamento	• Iloprost – inalato 6-9 volte al giorno; 2,5 o 5 mcg per inalazione • PBO	• TREP 4 volte al giorno E BOS o SIL • PBO E BOS o SIL	• dose iniziale TREP 1,25 ng/kg/min aumentata fino alla dose massima tollerata E trattamento standard • PBO E trattamento standard
Idoneità	• IPAH, PAH associata a scleroderma, CTEPH • FC OMS III–IV, età ≥18 anni	• FPAH, IPAD, PAH associata ad anoressizzante, CTD, HIV • FC OMS III-IV, età 18-75 anni	• FPAH, IPAH, PAH associata a CHD, CTH
Significatività rispetto al comparatore			
Miglioramento della FC NYHA/OMS	✓	×	NA
TTCW	NA	×	NA
Variazione nel test 6MWD	✓	✓	✓
PVR	✓	✓	✓
CI	✓	✓	✓
SF-36	NA	NA	NA

■ = endpoint primario; 6MWD = distanza percorsa in 6 minuti; BOS = bosentan; CI = indice cardiaco; FC = classe funzionale; FPAH = PAH familiare; IPAH = PAH idiopatica; NA = non applicabile; NR = non riportato; NYHA = New York Heart Association; PBO = Placebo; PVR = resistenza vascolare polmonare; * = agente mirato alla PAH (ERA, inibitore della PDE-5, prostanoide); SF-36 = questionario Short Form 36; SIL = sildenafil; trattamento standard = anticoagulanti, vasodilatatori per via orale, diuretici; TREP = treprostinil; TTCW = tempo al peggioramento clinico; ✓ = $P < 0,05$ rispetto a comparatore; × = $P \geq 0,05$ rispetto a comparatore

Raccomandazione di Nizza[1]

- Le linee guida di Nizza raccomandano che le sperimentazioni di fase III/cardine sulla PAH abbiano un **endpoint primario composito, comprendente la mortalità nonché eventi di morbilità "hard" (ovvero non soggettivi) misurabili** correlati alla PAH:
  - Decesso
  - Trapianto di polmone
  - Ospedalizzazione a causa del peggioramento della PAH (compresa septostomia atriale)
  - Avvio della terapia endovenosa a causa del peggioramento della PAH
  - Peggioramento della funzione (ossia peggioramento della classe funzionale e della capacità di compiere sforzi)
  - Peggioramento dei sintomi della PAH (ossia peggioramento di almeno 2 dei 4 sintomi: dispnea, dolore toracico, capogiri/sincope, stanchezza/livello di attività)

[1] Gomberg-Maitland et al, 2013

Time To Clinical Failure is a composite endpoint and is defined is the first occurrence of any of the following events:

1 Death (all-cause)

2 Hospitalization for worsening PAH (adjudicated), which comprised any of the following:

- Any hospitalization for worsening PAH
- Lung or heart/lung transplant
- Atrial septostomy
- Initiation of parenteral prostanoid therapy

3 Disease progression (adjudicated), defined as follows:

- > 15% decrease from baseline in the 6MWD combined with WHO class III or IV symptoms (at 2 consecutive post baseline clinic visits separated by ≥ 14 days)

4 Unsatisfactory long-term clinical response (adjudicated), which comprised all 3 of the following criteria:

- Receiving ≥ 1 dose of randomized treatment and in the study for ≥ 6 months
- A decrease from baseline in 6MWD at 2 consecutive post baseline clinic visits separated by ≥ 14 days
- WHO class III symptoms assessed at 2 clinic visits separated by ≥ 6 months

SINGLE CLINICAL ENDPOINT

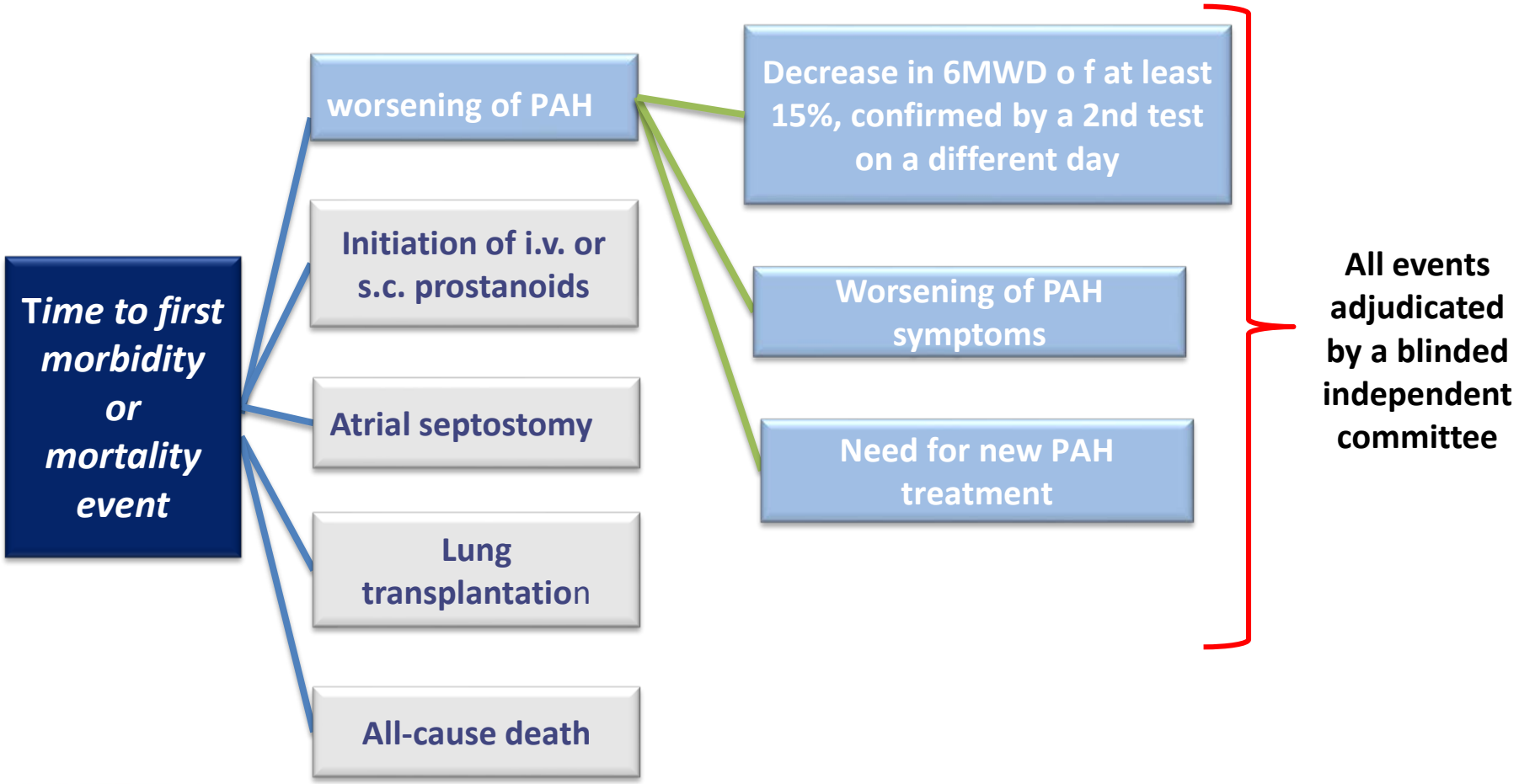
COMPOSITE ENDPOINT

PRIMARY ENDPOINT IN CLINICAL TRIAL

Seraphin

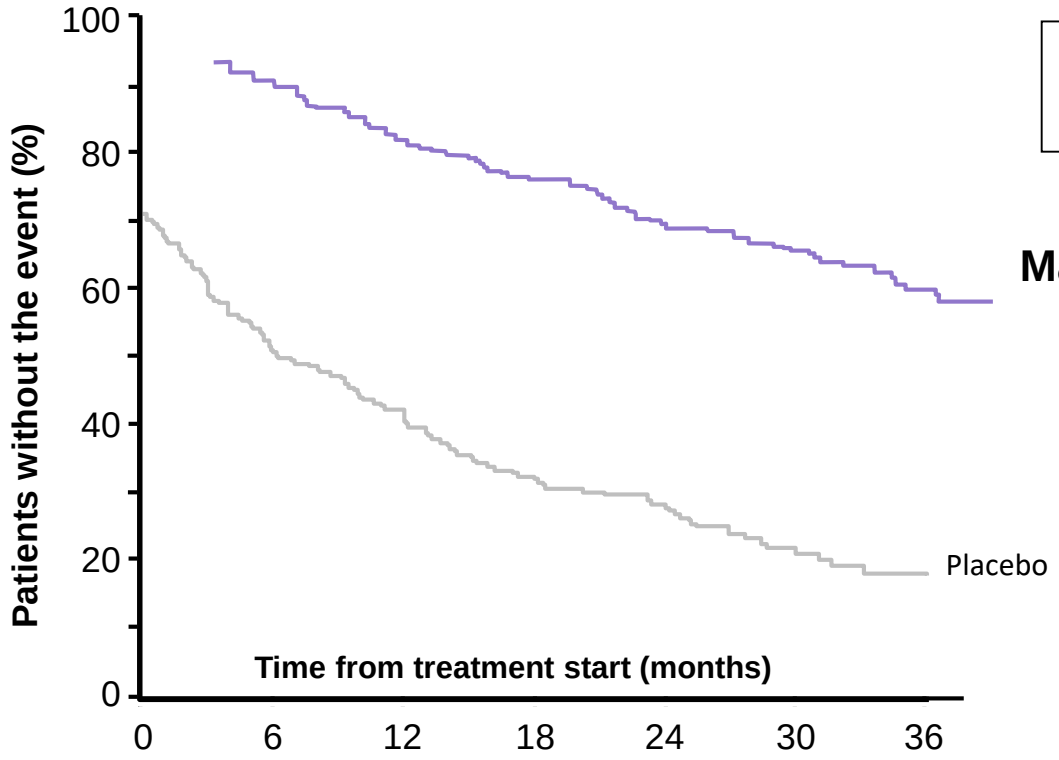
Study with Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome

Seraphin : Morbidity and mortality primary endpoint



Pulido T, *et al. N Engl J Med* 2013

Primary endpoint: Time to the first morbidity and mortality event



Risk reduction of primary endpoint event vs placebo

Macitentan 10 mg: 45%

Treatment difference	10 mg
Hazard ratio (HR)	0.55
Log-rank *p*-value	< 0.001

Patients at risk

242	208	187	171	155	91	41	Macitentan 10 mg
250	188	160	135	122	64	23	Placebo

Pulido T, *et al. N Engl J Med* 2013.

Relative Risk Reduction (RRR)

It is calculated by HR

It reflects the reduction that an end-point will be happen

HR = drug events/placebo events

RRR=1-HR

HR=55/100=0,55

RRR=1-0,55=0,45

45% RRR

Pulido et al. N Engl J Med 2013; 369: 809-818

Relationship between 6MWD and long-term outcome Evidence from the SERAPHIN trial*

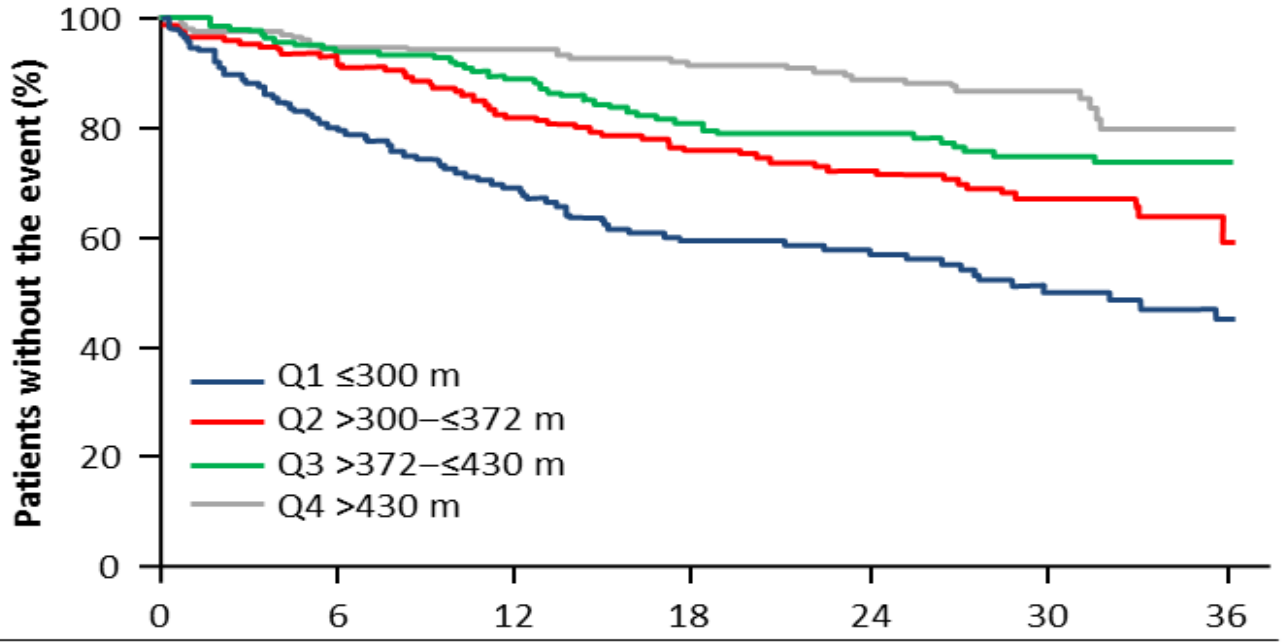
The relationship between 6WMD and long-term outcome was investigated in 595 patients with available data included in the Seraphin trial*

Hazard ratios were calculated to determine the association between PAH-related Death or Hospitalisation at the EOT and between all cause death up to EOS with

- Baseline 6MWD
- Absolute 6MWD reached at month 6
- Change in 6MWD from baseline to month 6

Pulido T et al. New Engl J Med.2013

PAH related death or hospitalization



Quartile	Patients at risk						
Q1 ≤300 m	197	130	102	82	72	43	22
Q2 >300–≤372 m	179	148	124	109	101	57	25
Q3 >372–≤430 m	182	157	139	120	109	64	26
Q4 >430 m	181	164	154	146	133	61	19

Recent morbidity-mortality trials in PAH

TRIAL	Inclusion Period	Maximum Follow-up
Seraphin (n=742) : Primary end-point met Macitentan vs placebo 64% pre- treated with PDE5-inh or Prostanoids	1.5 year	3 years
Griphon (n=1156) : Primary end-point met Selexipag vs placebo 80% treated with PDE5-in and or ERA	3.5 years	3 years
Ambition (n=605) : Primary end-point met Ambrisentan+Tadalafil vs monotherapy	3.8 years	3 years

Composite Endpoints - a Dilemma

Which should be the duration of the exposure to the risk of developing the endpoint condition?

1. DB treatment period?
2. Time span of the study disregarding the actual DB treatment period?

How to handle a study of a second in class treatment when patients, after stopping DB treatment, switch to another same class treatment? Are these data still interpretable?

Summary (1)

- Changes in 6MWD have served as primary E-P in many pivotal RCTs of PAH

- More of 10 drugs are currently approved in PAH. So, the level of requirement for the approval of new drugs need to be markedly increased

- PAH is a chronic life-threatening disease and recent proceedings and guidelines support the use of long-term outcome studies to assess the effects of novel therapies on disease progression

Summary (2)

- Since PAH is a progressive disease, death is rarely the first recorded event and generally preceded by a clinical deteriorarion
- In morbidity- mortality trials the treatment effect for the primary end-point is mainly driven by the rates of worsening events
- In Seraphin, when death is analyzed at the EOT or EOS there were trends toward risk reduction of deaths with macitentan 10 mg
- With Seraphin, Griphon and Ambition trials, we are entering a new era for drug evaluation in PAH

Thank You


E.R.
E' IN STATO COMATOSO!
DOBBIAMO RIANIMARLO!
RONF RONF ZZZZZZ