

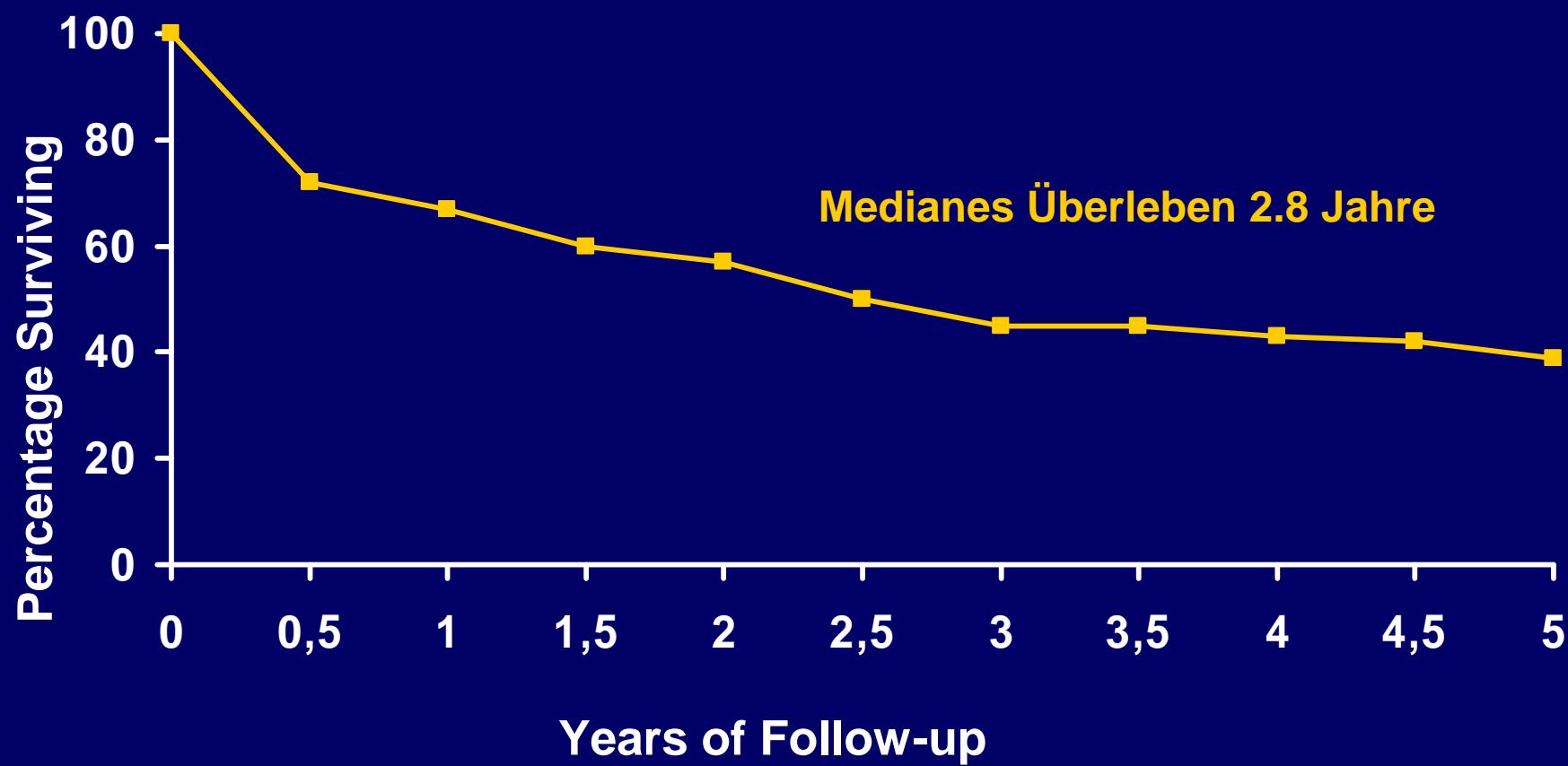
# **Therapie des Lungenhochdrucks Sicht des Klinikers**

---

H.A. Ghofrani  
Department of Internal Medicine  
University of Giessen Lung Center (UGLC)

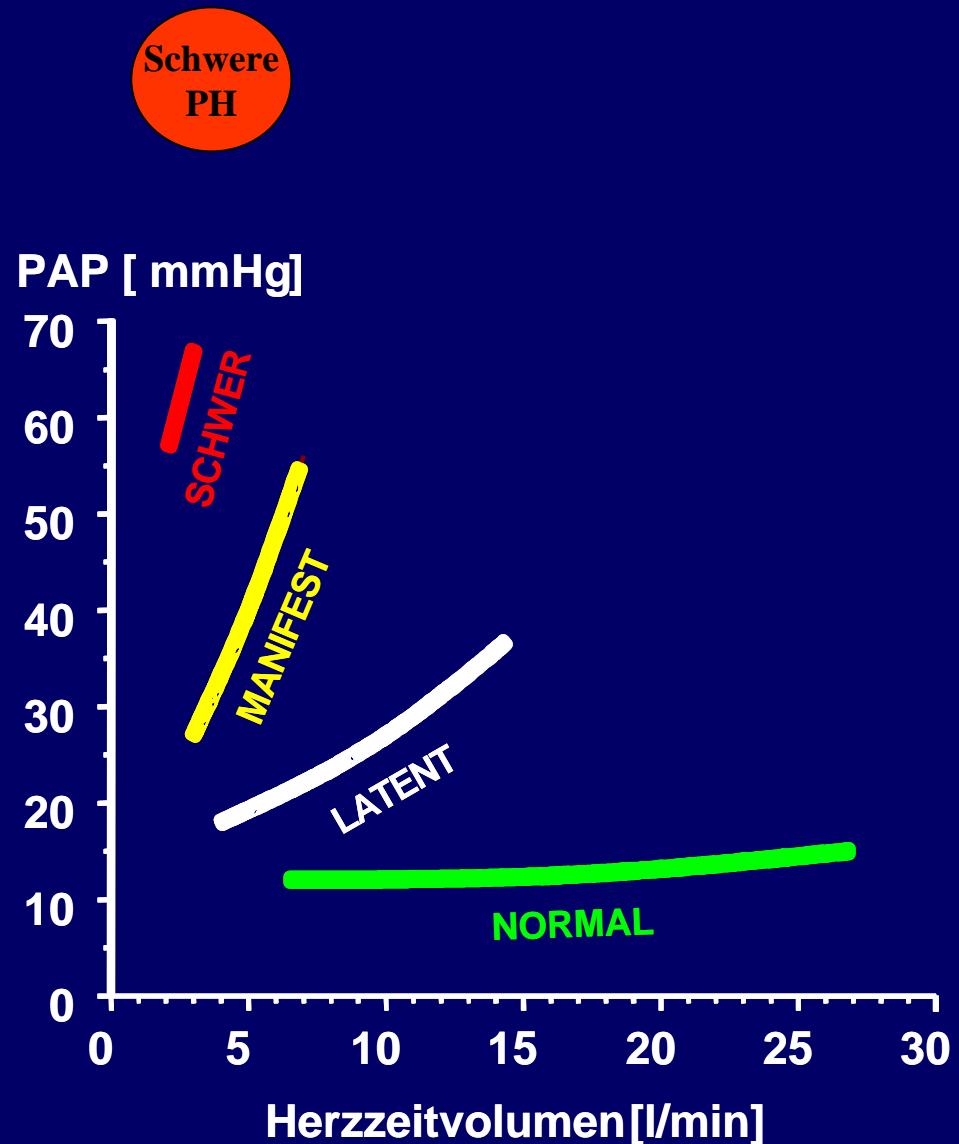
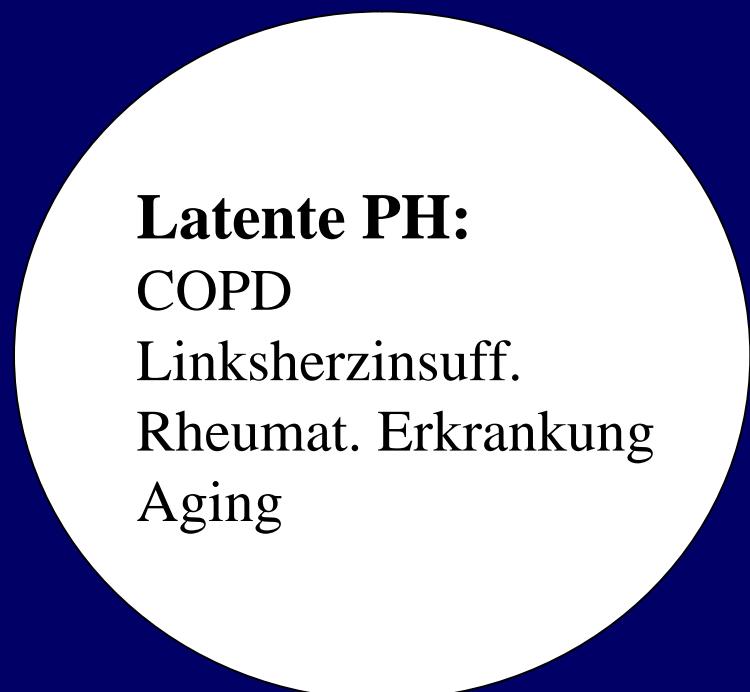
[ardeschir.ghofrani@innere.med.uni-giessen.de](mailto:ardeschir.ghofrani@innere.med.uni-giessen.de)

# Überlebenszeit mit schwerer Pulmonaler Hypertonie

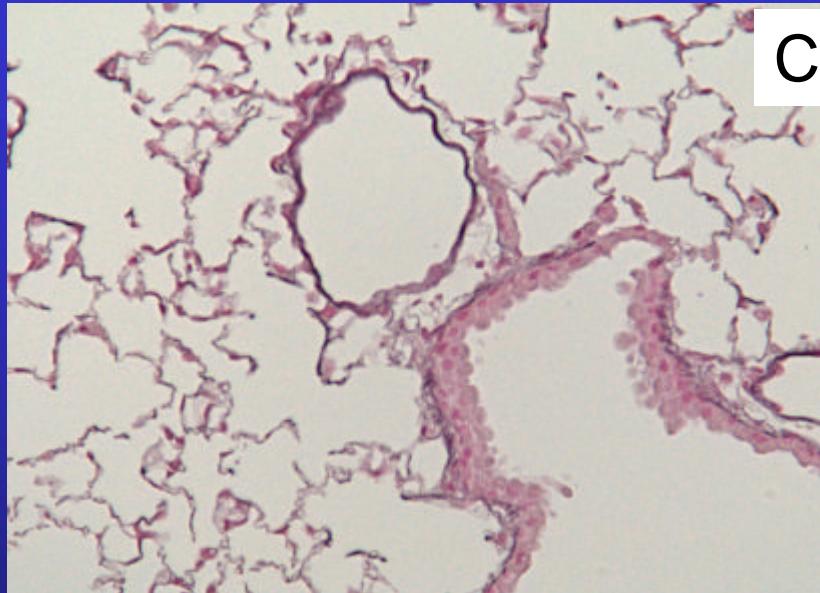


D'Alonzo et al. Ann Int Med 1991

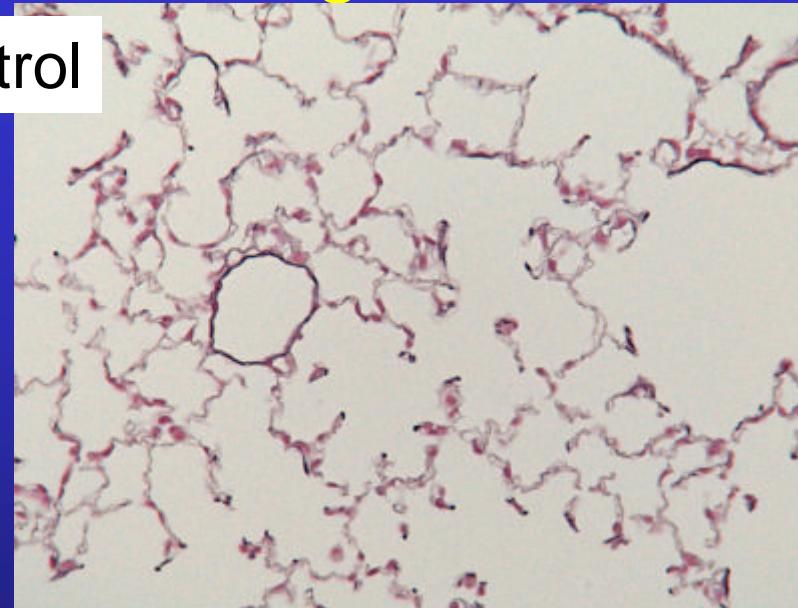
# Relative Häufigkeiten der pulmonalen Hypertonie



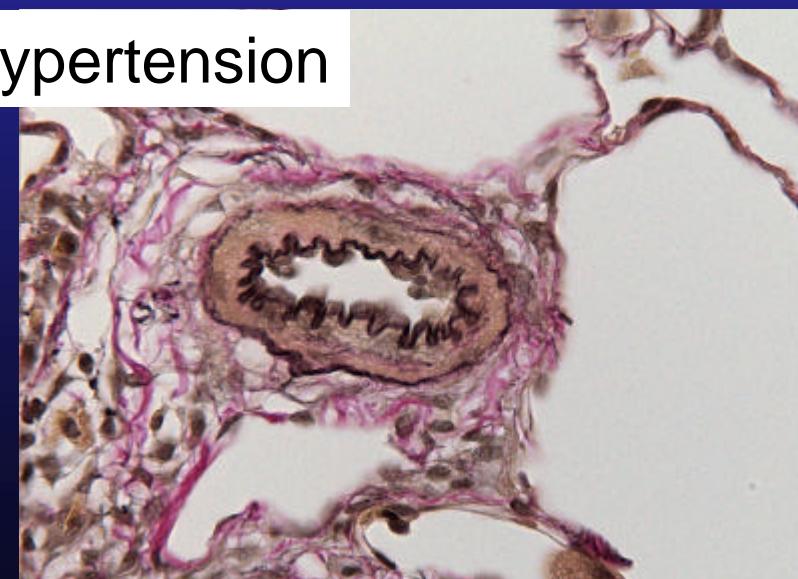
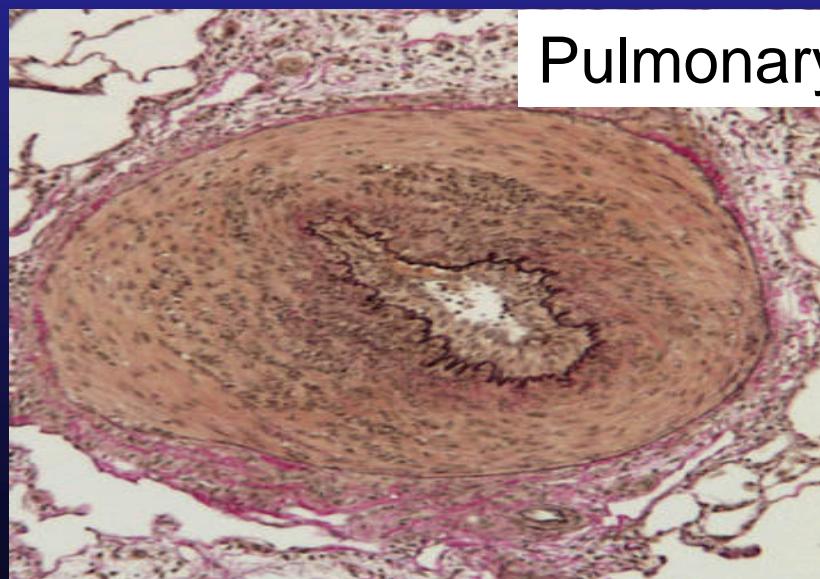
# Pathohistology: Vascular remodeling



Control



Pulmonary hypertension



# Diagnostische Klassifikation der Pulmonalen Hypertonie (Venedig 2003)

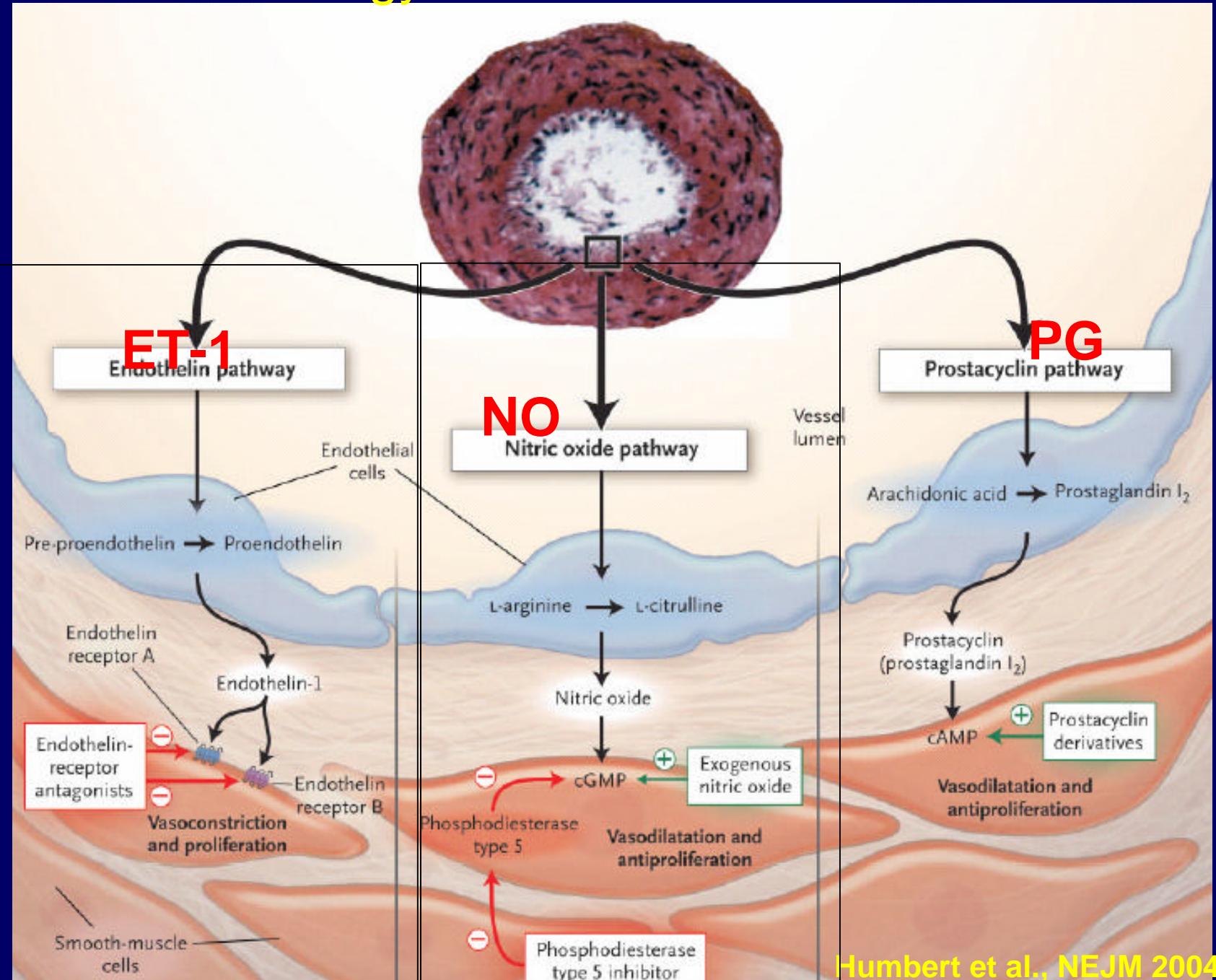
---

- 1 Pulmonal Arterielle Hypertonie
- 2 Pulmonal Venöse Hypertonie
- 3 PH assoziiert mit Lungenkrankheiten
- 4 PH infolge chronisch thromboembolischer Ereignisse
- 5 PH infolge von Erkrankungen, die direkt die Lungengefäße erfassen

# Ziele?

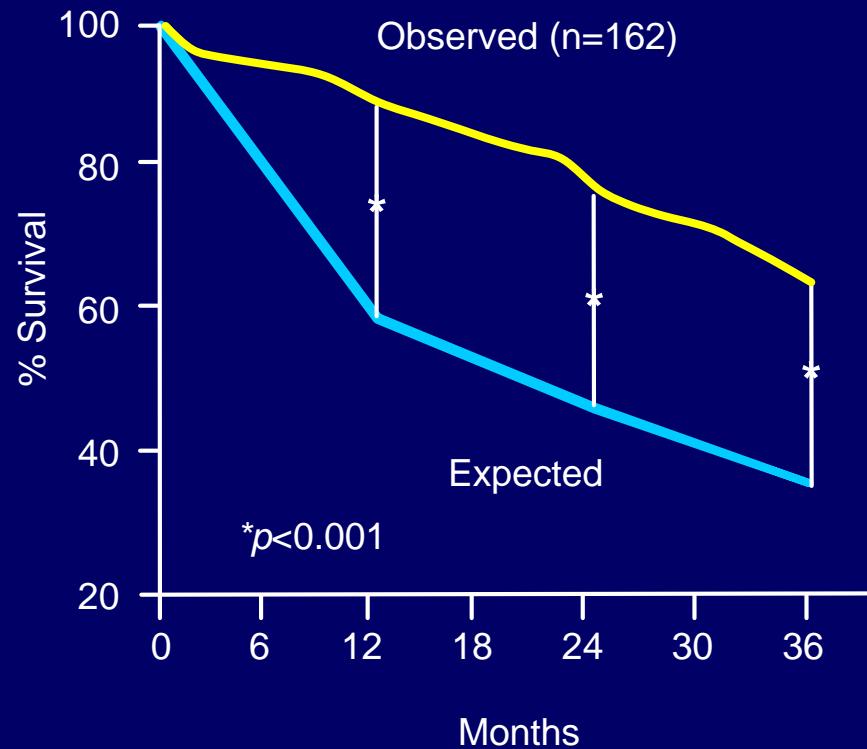
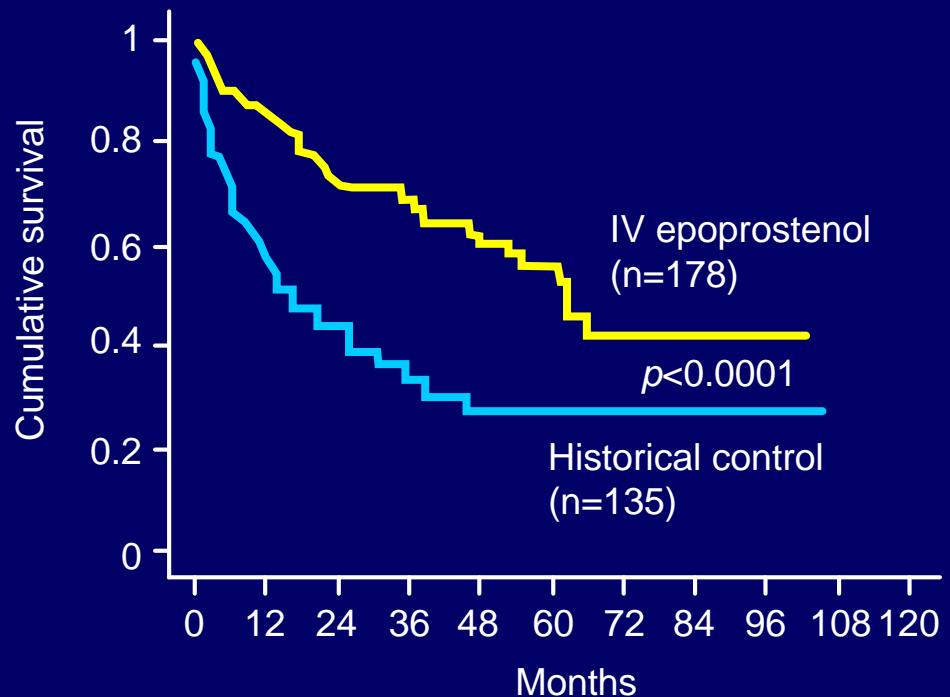
Verbesserung der Lebensqualität  
Verbesserung der Prognose  
Individualisierte Therapie

# Molecular Pathology: Imbalance of vasoactive mediators



Humbert et al., NEJM 2004

# Long-term Outcome in IPAH With Epoprostenol

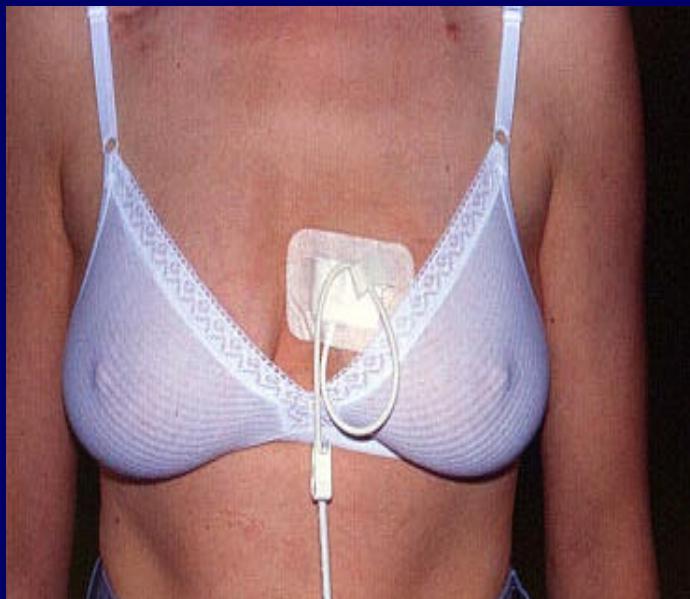


Sitbon O et al. *J Am Coll Cardiol.*  
2002;40:780-788.

McLaughlin VV et al.  
*Circulation.*  
2002;106:1477-1482.

# THERAPIE DER PAH

## Komplikationen von i.v. PGI<sub>2</sub>



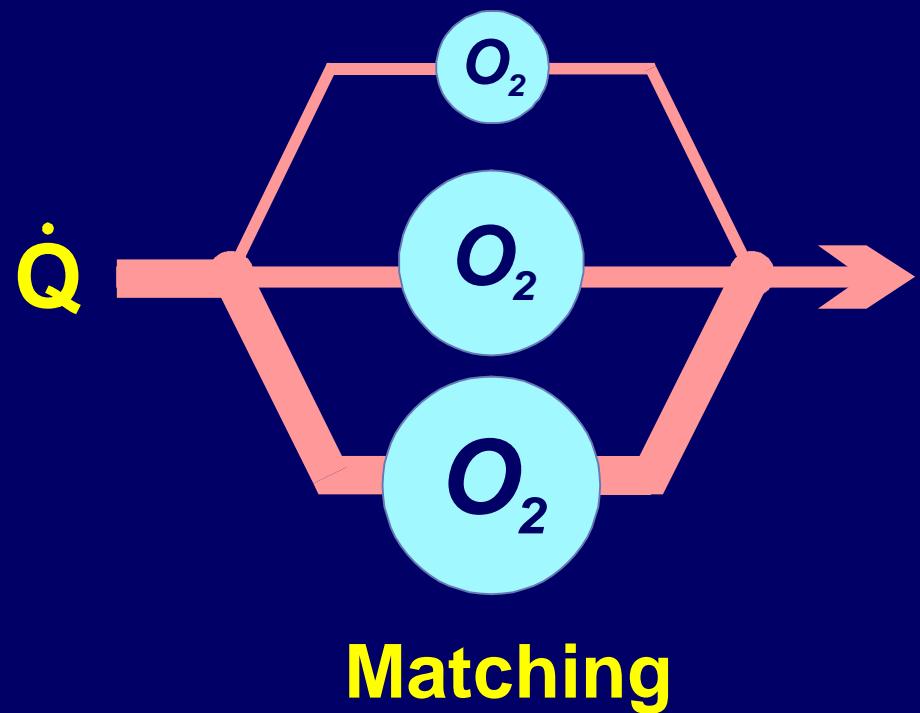
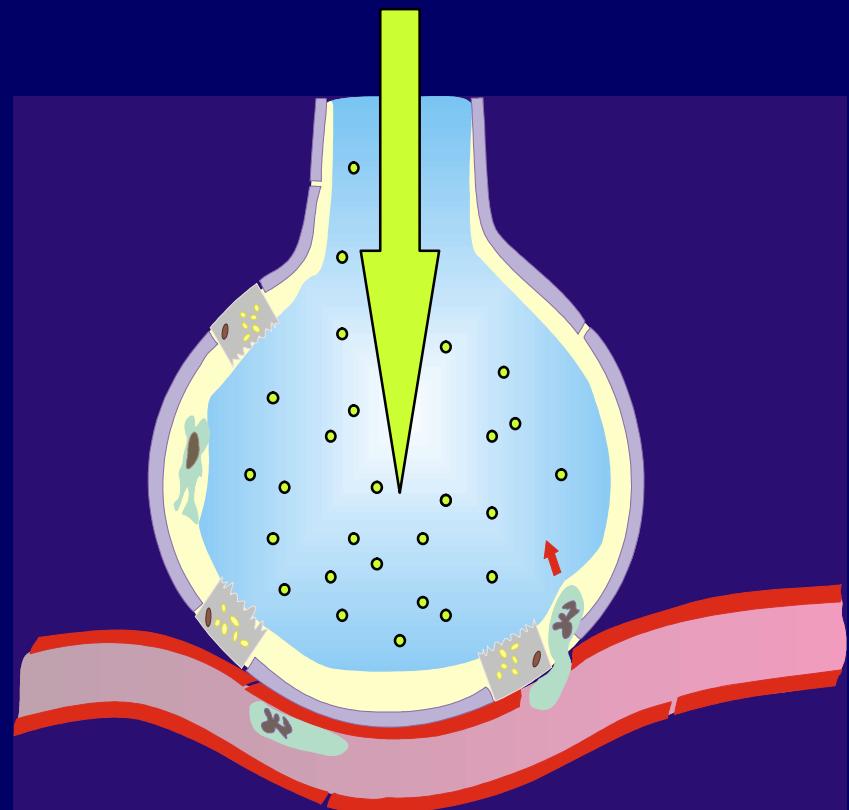
System-  
bezogen

- Infektionen
- Thrombosen
- Ausfall der Pumpe
- Katheter Dislokation

## Inhalierte Vasodilatoren:

- 1.pulmonale Selektivität
- 2.intrapulmonale Selektivität

### Vasodilatanz



**Matching**

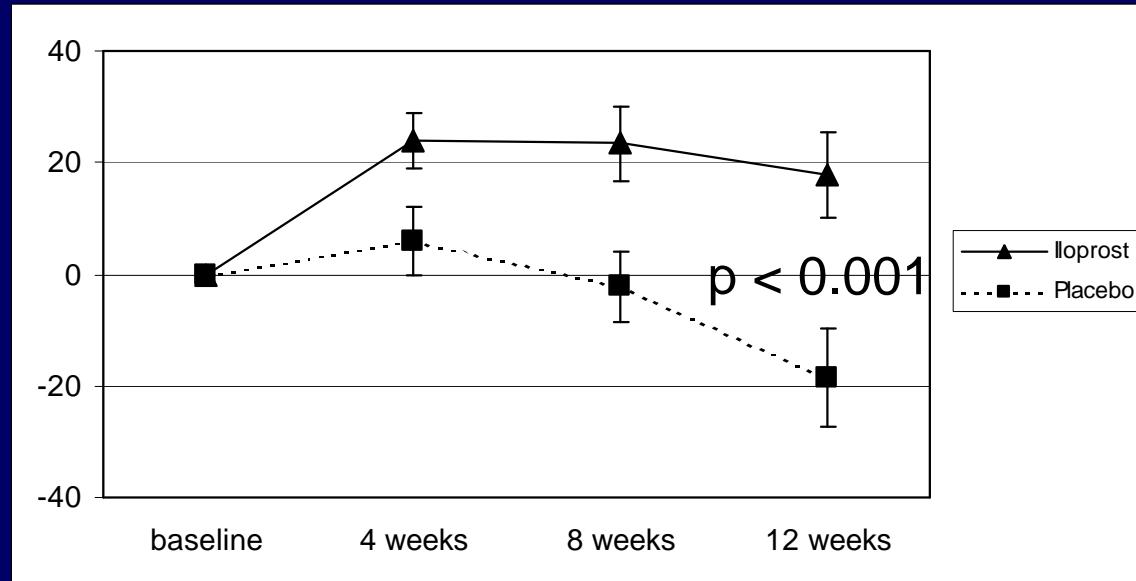


N Engl J Med, Vol. 347, No. 5 • August 1, 2002

# The New England Journal of Medicine

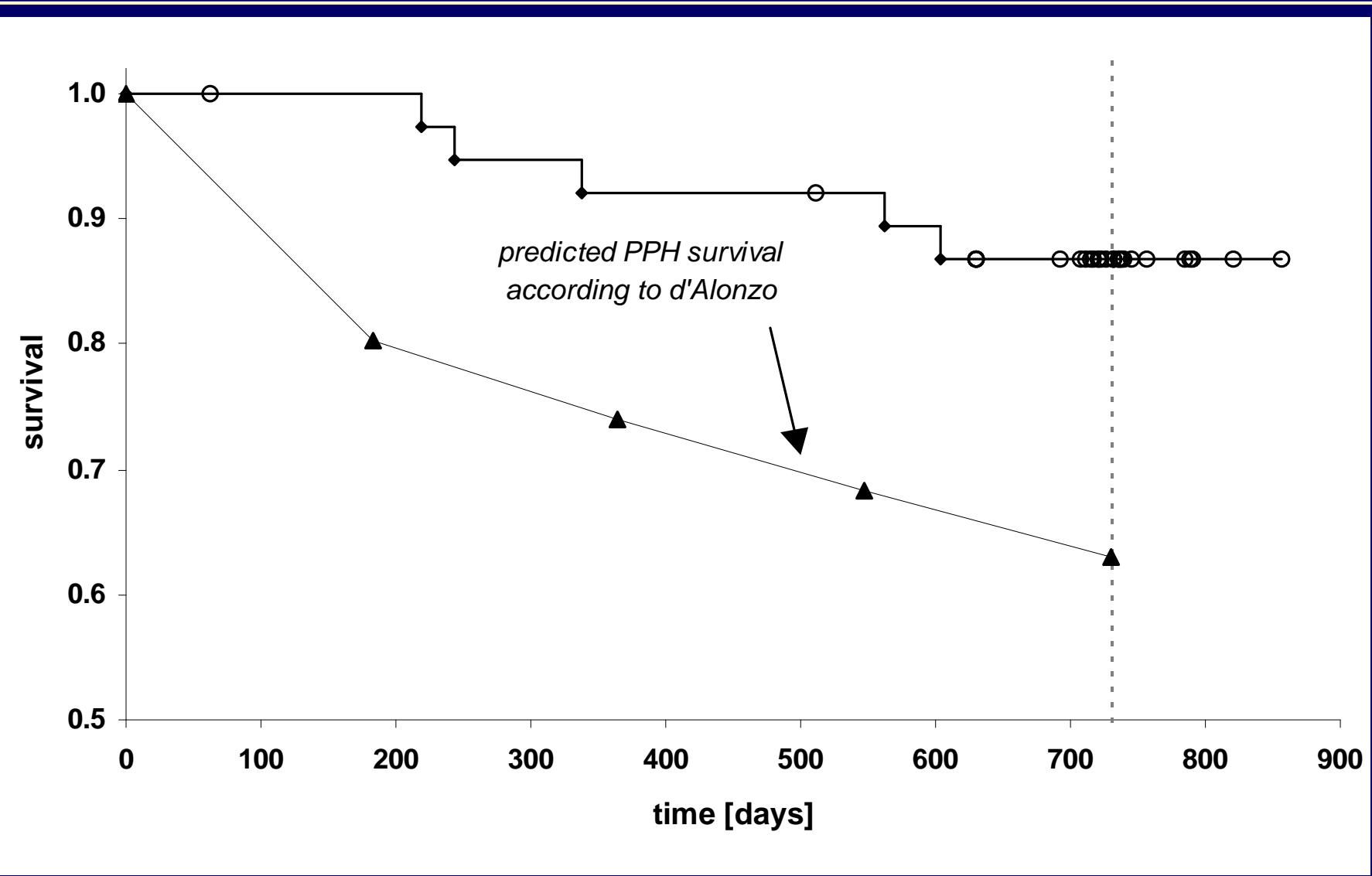
## INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION

HORST OLSCHEWSKI, M.D., GERALD SIMONNEAU, M.D., NAZZARENO GALIE, M.D., TIMOTHY HIGENBOTTAM, M.D.,  
ROBERT NAEIJE, M.D., LEWIS J. RUBIN, M.D., SYLVIA NIKKHO, M.D., RUDOLF SPEICH, M.D., MARIUS M. HOEPER, M.D.,  
JÜRGEN BEHR, M.D., JÖRG WINKLER, M.D., OLIVIER SITBON, M.D., VLADIMIR POPOV, M.D.,  
H. ARDESCHIR GHOFRANI, M.D., ALESSANDRA MANES, M.D., DAVID G. KIELY, M.D., RALPH EWERT, M.D.,  
ANDREAS MEYER, M.D., PAUL A. CORRIS, F.R.C.P., MARION DELCROIX, M.D., MIGUEL GOMEZ-SANCHEZ, M.D.,  
HARALD SIEDENTOP, DIPL.STAT., AND WERNER SEEGER, M.D.,  
FOR THE AEROSOLIZED ILOPROST RANDOMIZED STUDY GROUP\*



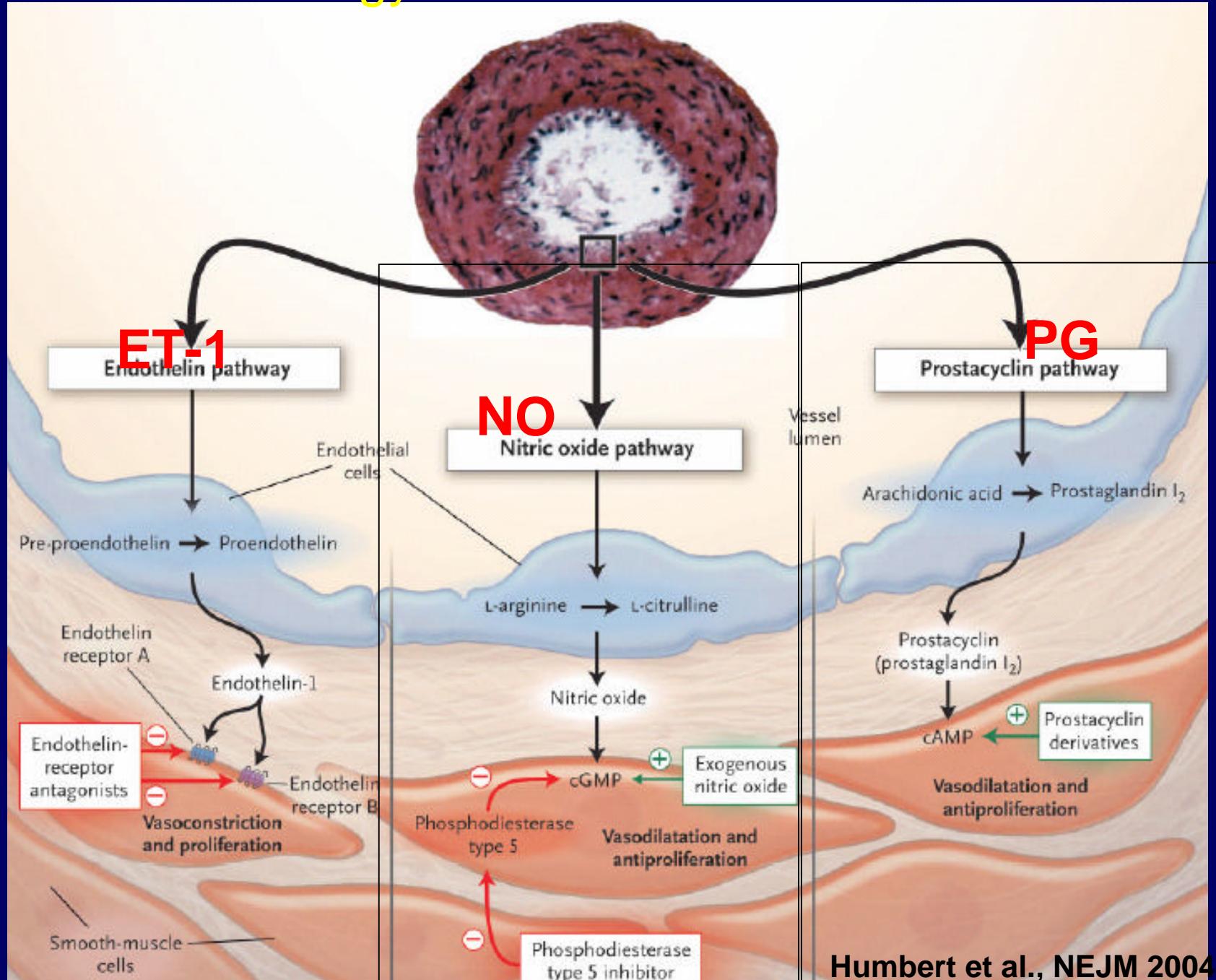
Inhaliertes Iloprost effektiv und sicher zur  
Behandlung der chron. PHT

# Inhaled Iloprost improves prognosis (AIR2)



Kaplan-Meier estimators for survival; all PPH (n=39) with d'Alonzo predictor; follow-up information included

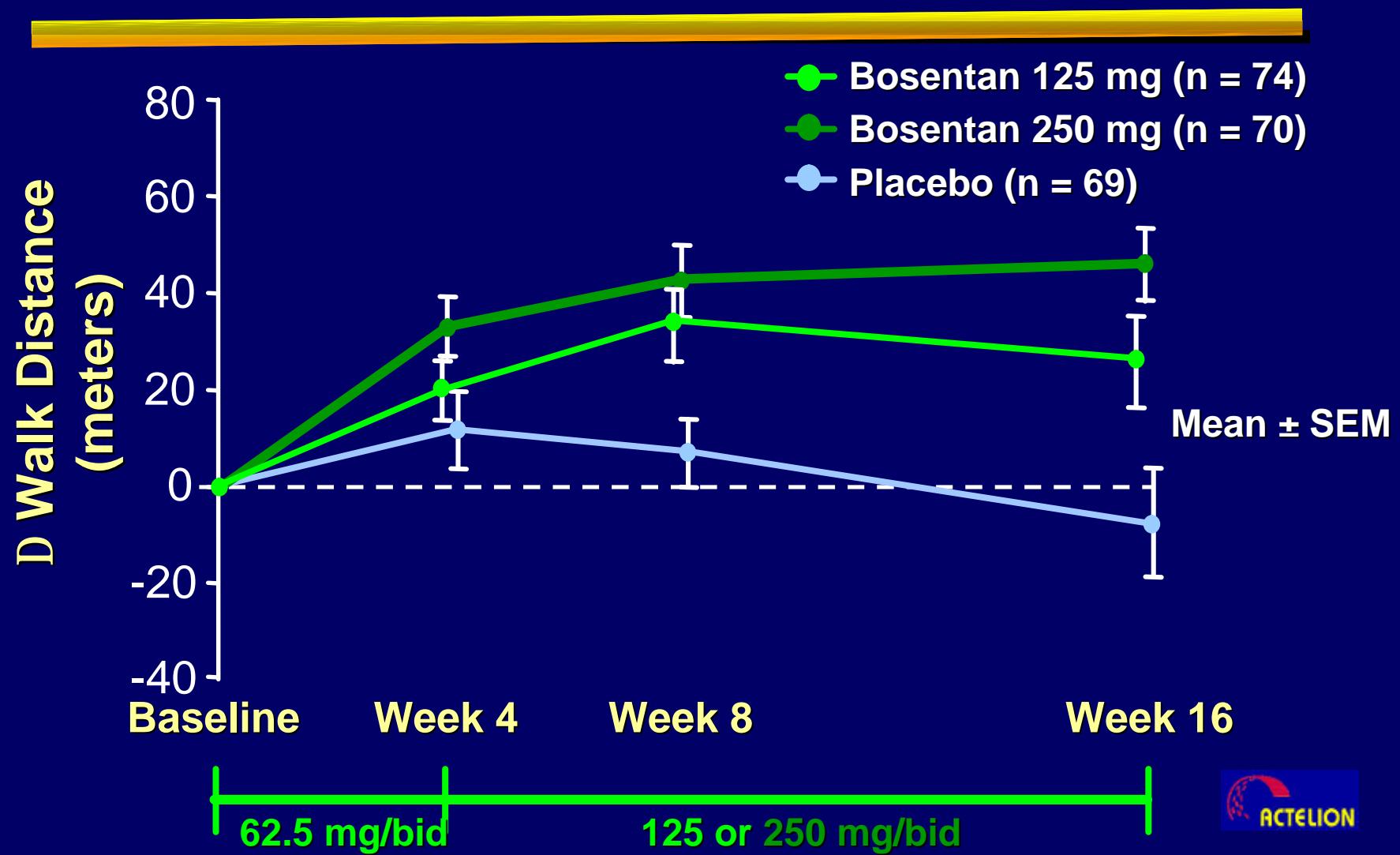
# Molecular Pathology: Imbalance of vasoactive mediators



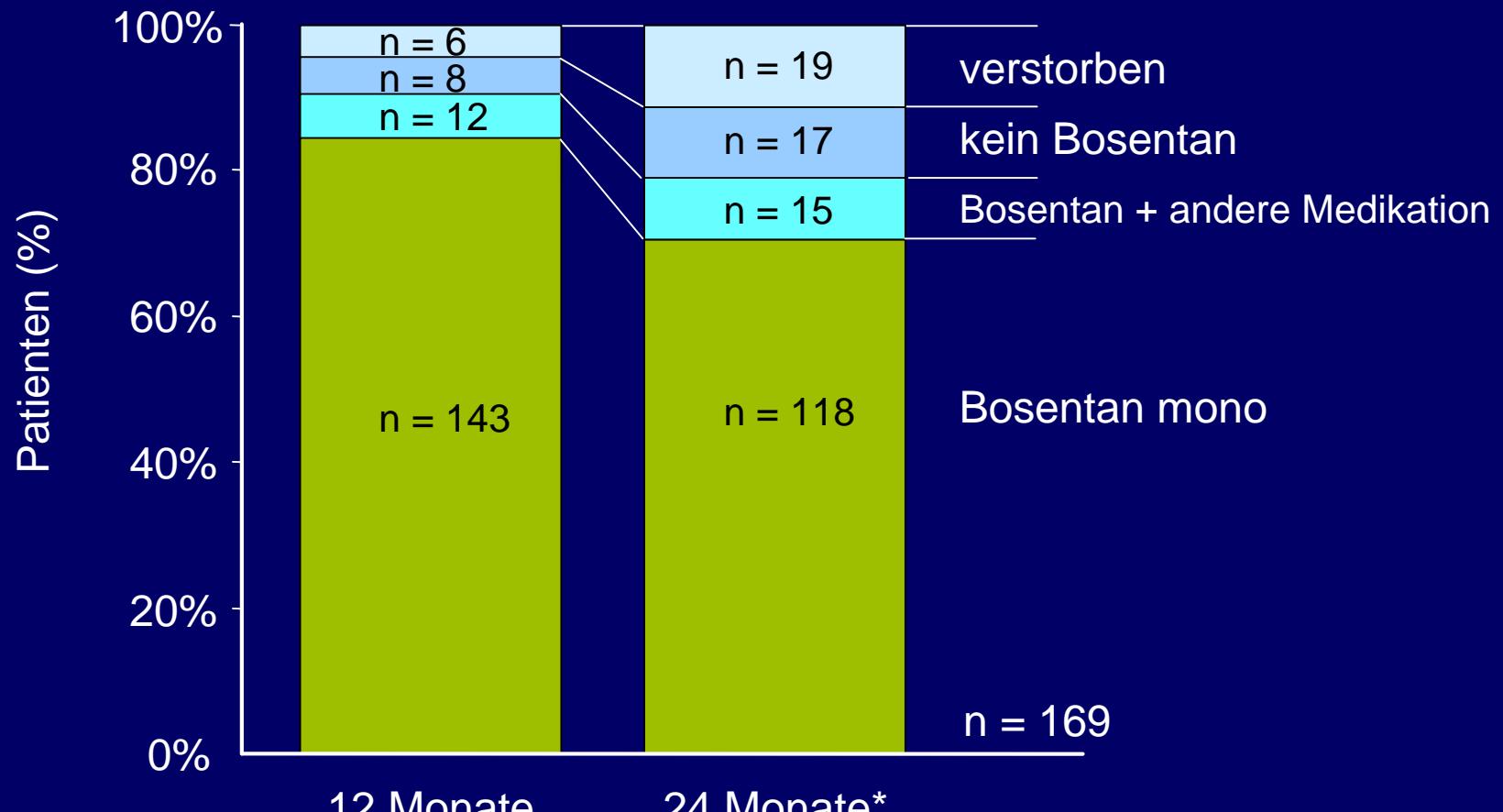
Humbert et al., NEJM 2004

# Walk Test ITT

## Change From Baseline to Week 16



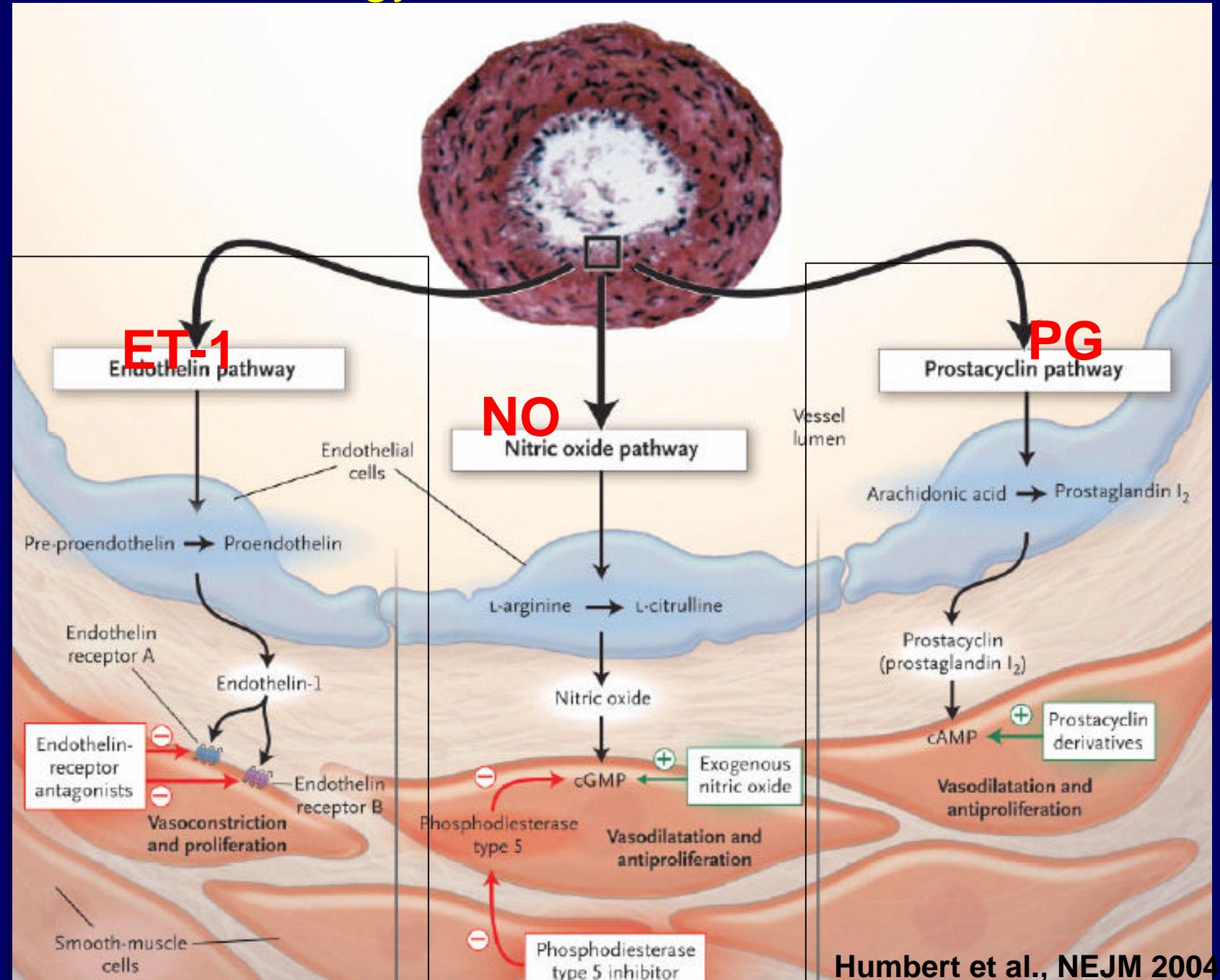
# Langzeitwirksamkeit von Bosentan



\* einschließlich Daten von 23 Patienten, die nicht über den gesamten Zeitraum von 24 Monaten beobachtet wurden



# Molecular Pathology: Imbalance of vasoactive mediators



Humbert et al., NEJM 2004

# Warum PDE-5 Inhibitoren bei Lungenhochdruck?

- Orales Medikament
- Gutes Sicherheitsprofil
- Pulmonale Selektivität

Ghofrani et al., Annals Int Med 2002

- Intrapulmonale Selektivität

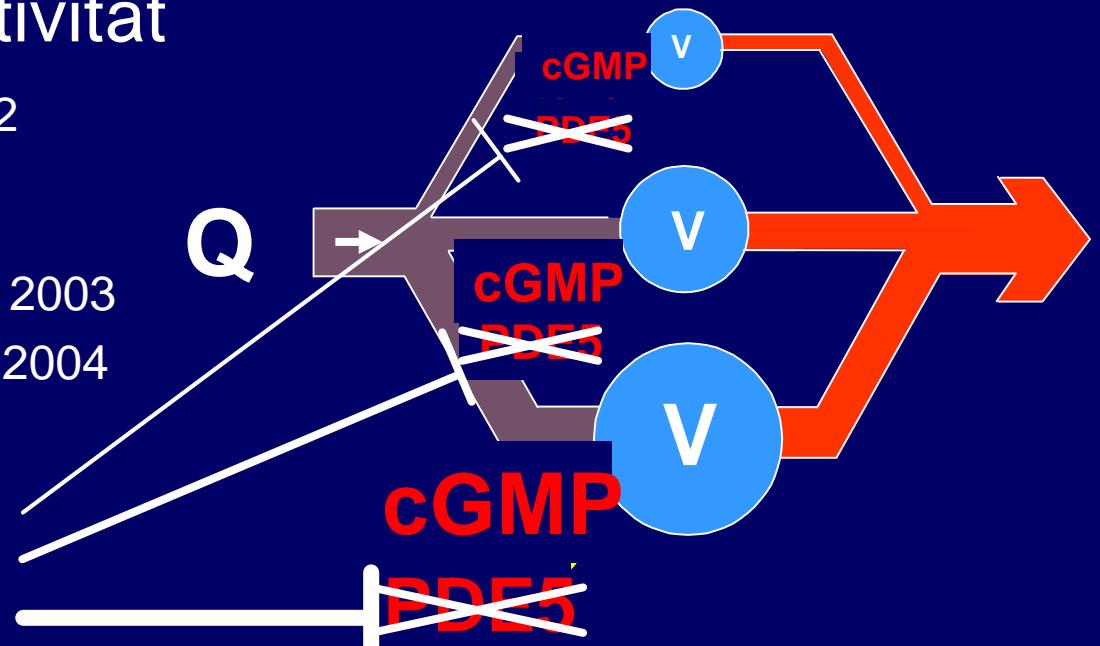
Ghofrani et al., Lancet 2002

- Antiproliferativ

Schermuly et al., AJRCCM 2003

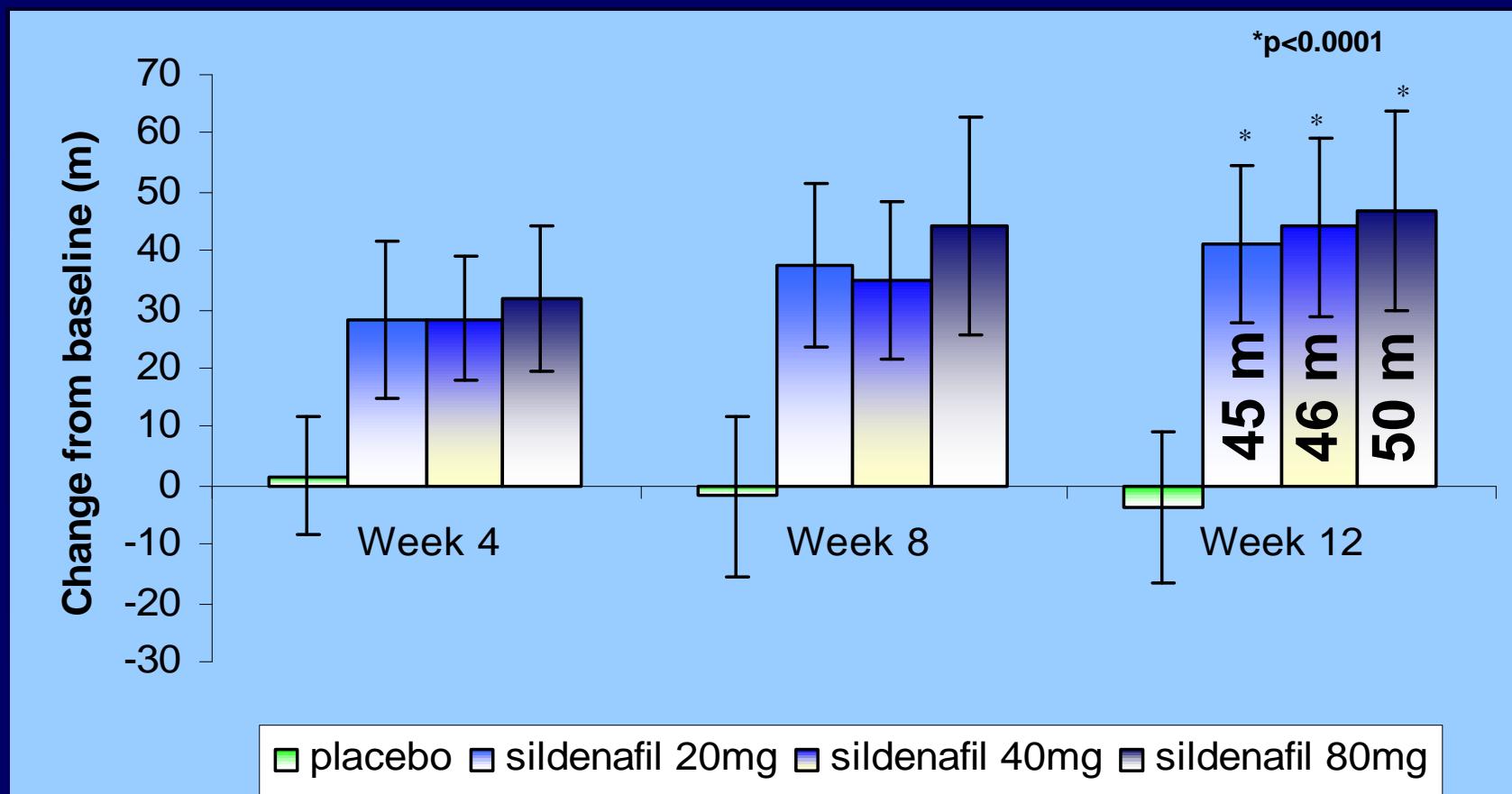
Rondelet et al., Circulation 2004

**Sildenafil**



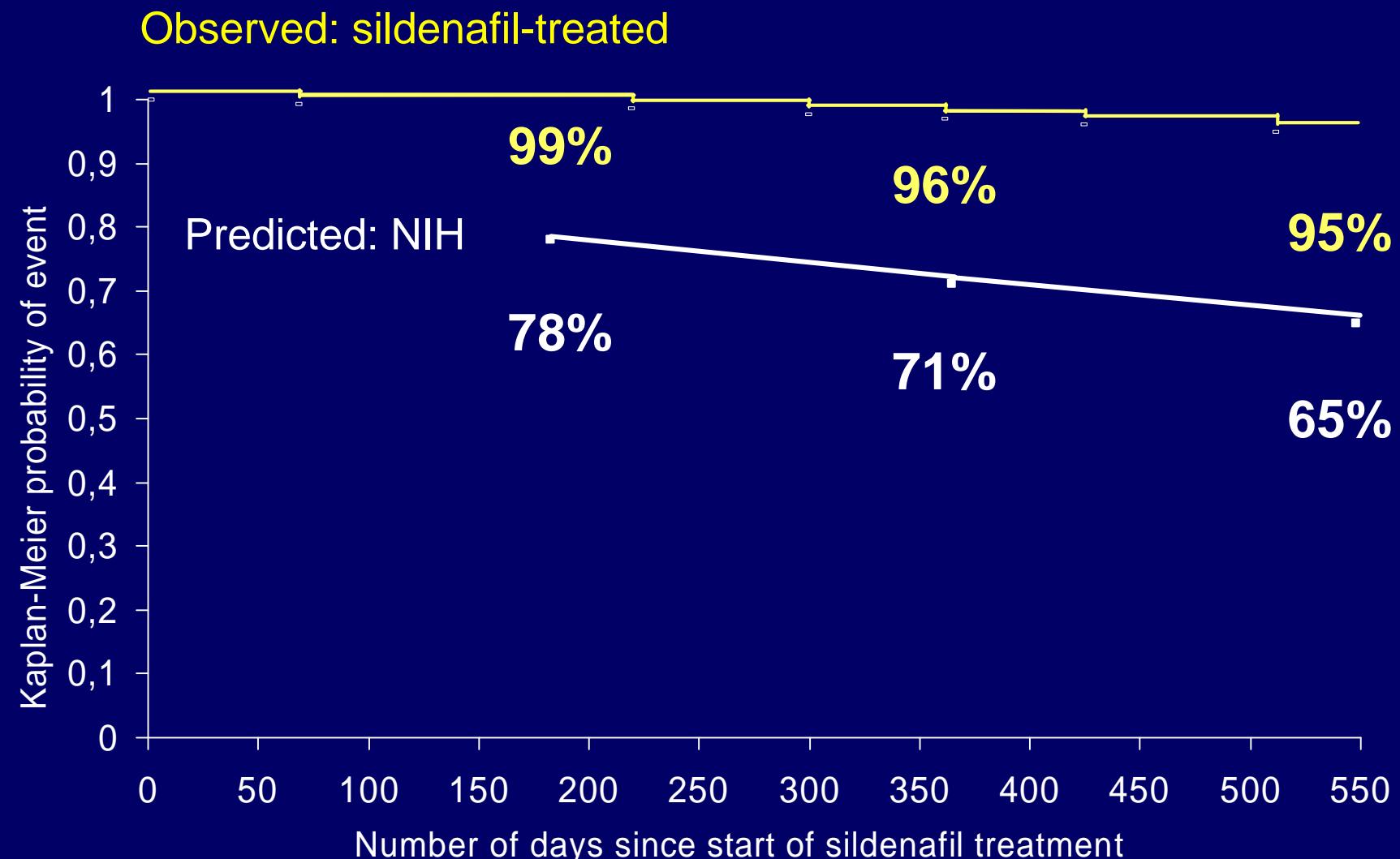
# SUPER-1

## Sildenafil verbessert körperliche Belastbarkeit



N Engl J Med 2005

# Sildenafil bei PAH: Langzeitüberleben (SUPER-2 Studie) (n=141)



NEJM 2005

## Ausblick: *Individualisierte Therapie*

**Identifikation von Patienten „at Risk“**

**Identifikation von “Respondern“**

**Frühe Identifikation potentieller Therapieversager**

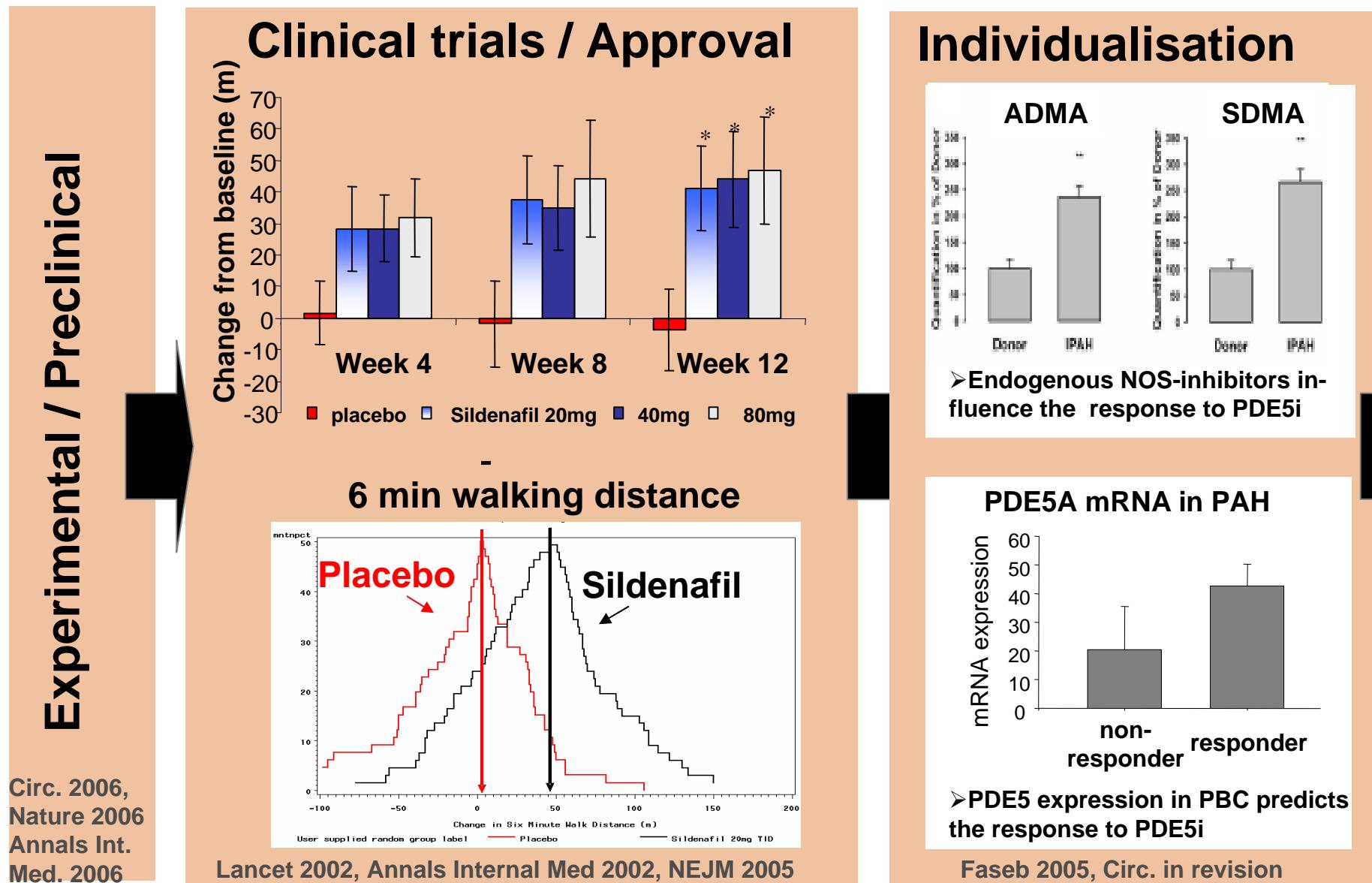
### **Individualisierte gezielte Therapie**

**Welches Medikament für wen, wann und welche Kombinationen?**



**ECCPS**  
EXCELLENCE CLUSTER  
CARDIO-PULMONARY  
SYSTEM

# Individualisierte Therapie: Beispiel Translationaler Forschung



RESEARCH AREAS

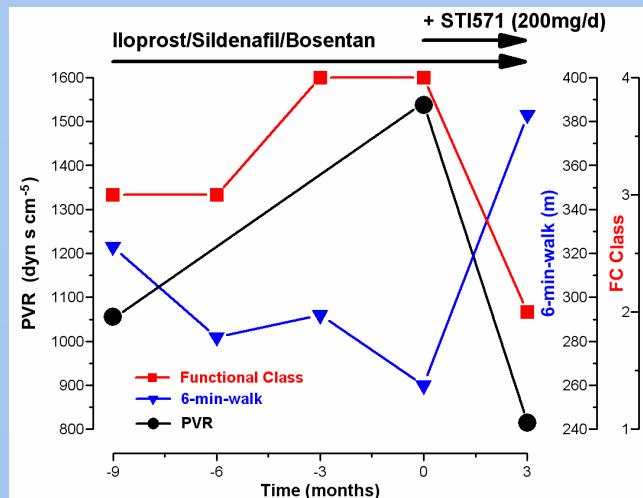
# Individualisierte Therapie: Beispiel Translationaler Forschung

## Experimental / Preclinical

J. Clin.  
Invest. 2005

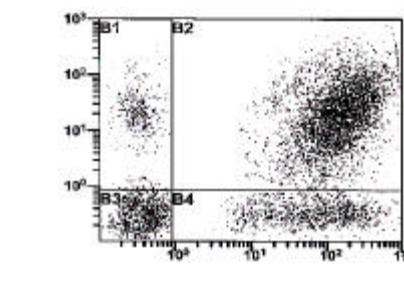
## Clinical trials

### Clinical trial: Tyrosine kinase inhibition by STI571 in patients with PAH



NEJM 2005

## Individualisation



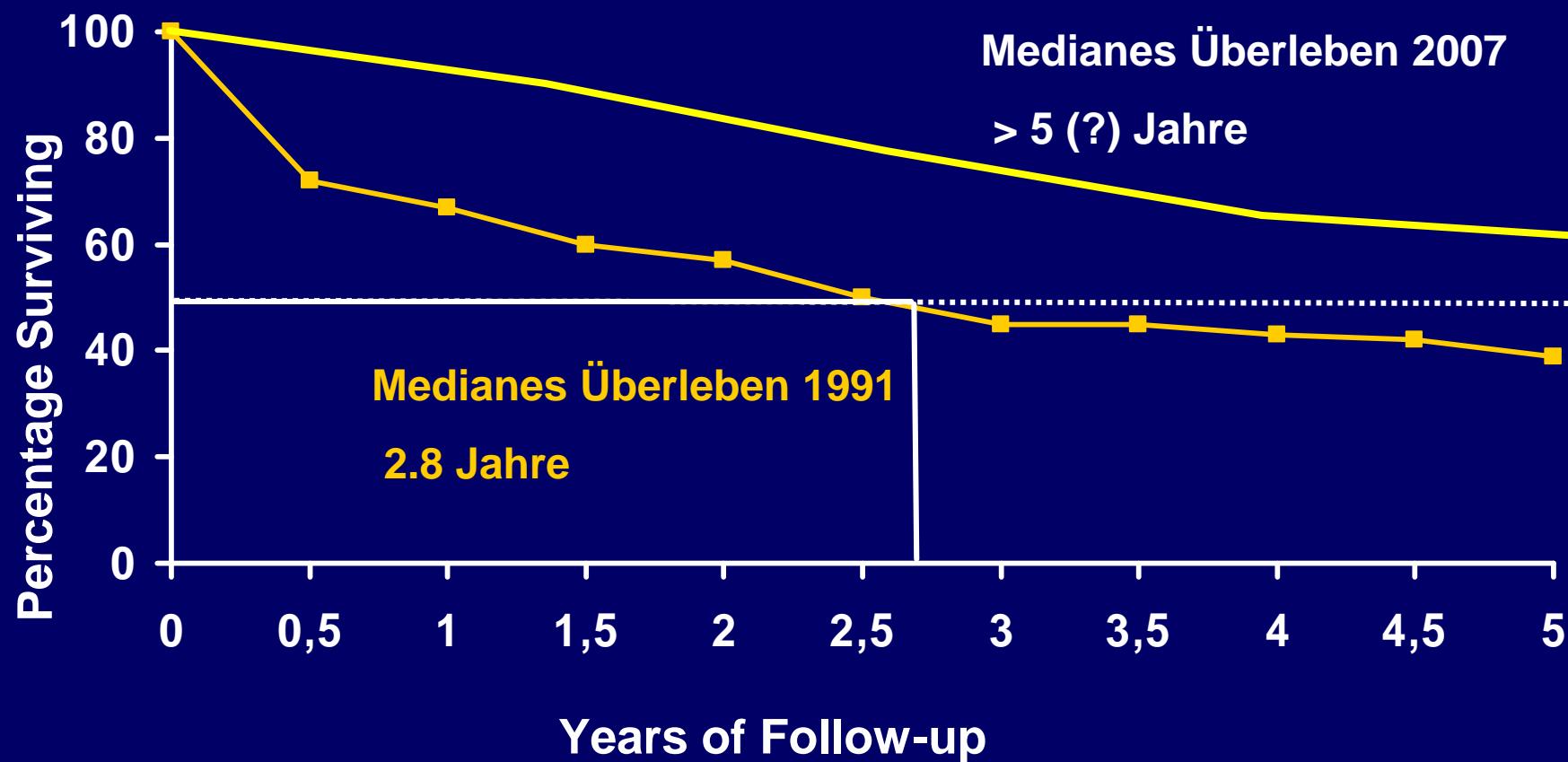
- CD34+ p-tyrosine content predicts good responses in CML
- Analysis of circulating EPC in PHT



- RV myocardial biopsy
- Identification of predictive factors
- Differential display analysis pre-post treatment

RESEARCH AREAS

# Überlebenszeit mit schwerer Pulmonaler Hypertonie



# University of Giessen Lung Center (UGLC)



- F. Grimminger
- W. Seeger
- R.T. Schermuly
- N. Weissmann
- H.Olschewski
- R. Voswinckel
- O. Eickelberg
- S. Pulamsetti
- A. Sydykov
- B. Egemnazarov
- R. Dumitrasco
- B. Enke
- F. Reichenberger
- H. Gall
- B. Karadas

**Supported by:**  
•DFG SFB 547  
•Klifo Resp. Insuff.  
•BMBF  
•EU FP6 „Pulmotension“

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- Bayer Pharma
- Schering
- Novartis
- Actelion