

Pulmoner Hipertansiyon Tedavisi

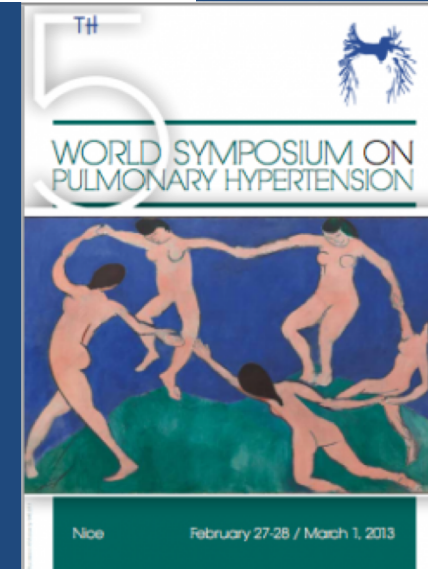
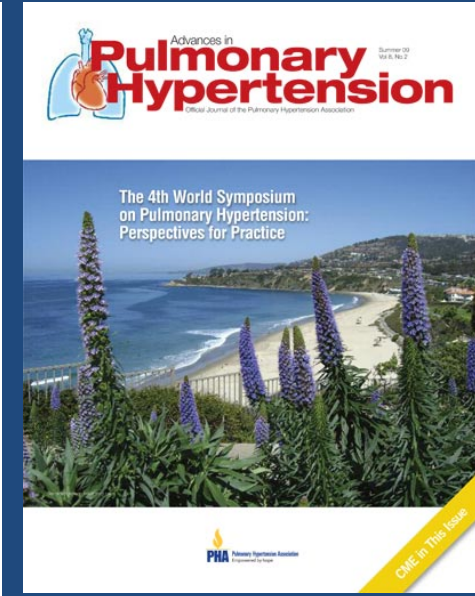
Dr. Kürşat Uzun

PAH Hastalarım

- 3 hasta yoğun bakımda evre 4 hasta ex
- 2 sistemik sklerosis (65-70y, 2 K, ex)
- 1 hasta 2004 yılında egzersiz testi ile sonra tedavi stop
- 2 KTEPH
 - 1 E 55y kombinasyon
 - 1 K 30y monoterapi
- 6 IPAHA
 - 1 K, ex 65y
 - 2 K 25-35y, kombinasyon tedavisi
 - 1 K 45-55y, monoterapi
 - 1 K 35-40y, takip dışı
 - 1 K 34Y, Behçet hast, KTEPH

Tedavideki Gelişme

- 1998 Evian, Fransa (2. WSPH)
 - Ca kanal blokörü, oral
 - Epopostenol, iv
- 2003, Venedik, İtalya (3. WSPH)
 - ERA, oral
 - Prostanoidler, iv, sc, inhaler
 - PDE-5i, oral
- 2008, Dana Point, California, USA (4. WSPH)
 - 4 ek ilaç eklendi
 - Sitexentan çekildi
- 2013, Nice, France (5. WSPH)
 - Yeni tedavi seçenekleri



Tedavi Amacı

- Semptomların giderilmesi
- Egzersiz kapasitesinin artırılması
- Yaşam kalitesinin artırılması
- Hayatta kalma süresinin uzatılması

Tedavi Prensipleri



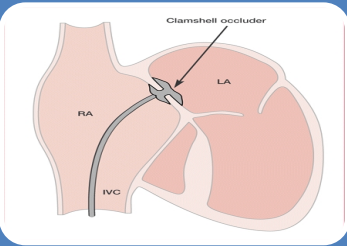
Genel prensipler

- Rehabilitasyon (egzersiz, psikososyal destek, gebelik, aşı)
- Destek tedavisi (diüretikler, antikoagülasyon, digital, O₂)
- Referans merkezler (kronik, fatal, pahalı, disfonksiyonel, tedavi edilebilir)



Başlangıç Tedavi

- Monoterapi
- Kombinasyon



İnvaziv İşlemler

- Balon atriyal septostomi
- Akciğer Transplantasyonu

PAH Sınıflandırılması

Grup 1

- Pulmonary arterial hypertension
 - İdiopatik PAH
 - Kalıtsal PAH
 - BMPR2
 - ALK-1, ENG, SMAD9, CAV1, KCNK3
 - Bilinmeyen

Sağ kalp kateteri ve adenozin testi

- İlişkili olduğu hastalıklar
 - Bağ dokusu hastalıkları
 - HIV
 - Portal hipertansiyon
 - Konjenital kapak hastalıkları
 - Schistosomiasis

Grup 2

- Sol kalp hastalıkları nedenli PAH
 - Sol ventrikül sistolik disfonksiyonu
 - Sol ventrikül diyastolik disfonksiyonu
 - Kapak hastalıkları
 - Kardiyomiyopatiler ve diğerleri

PAH sınıflandırma

Grup 3

- Akciğer hastalıkları ve hipoksi
 - KOAH
 - İAH
 - Diğer restriktif ve obstrüktif
 - Uykuda solunum bozuklukları
 - Alveoler hipoventilasyon send
 - Yüksek rakım
 - Gelişimsel akciğer hastalıkları

Grup 4

- Kronik tromboembolik pulmoner hipertansiyon (CTEPH)

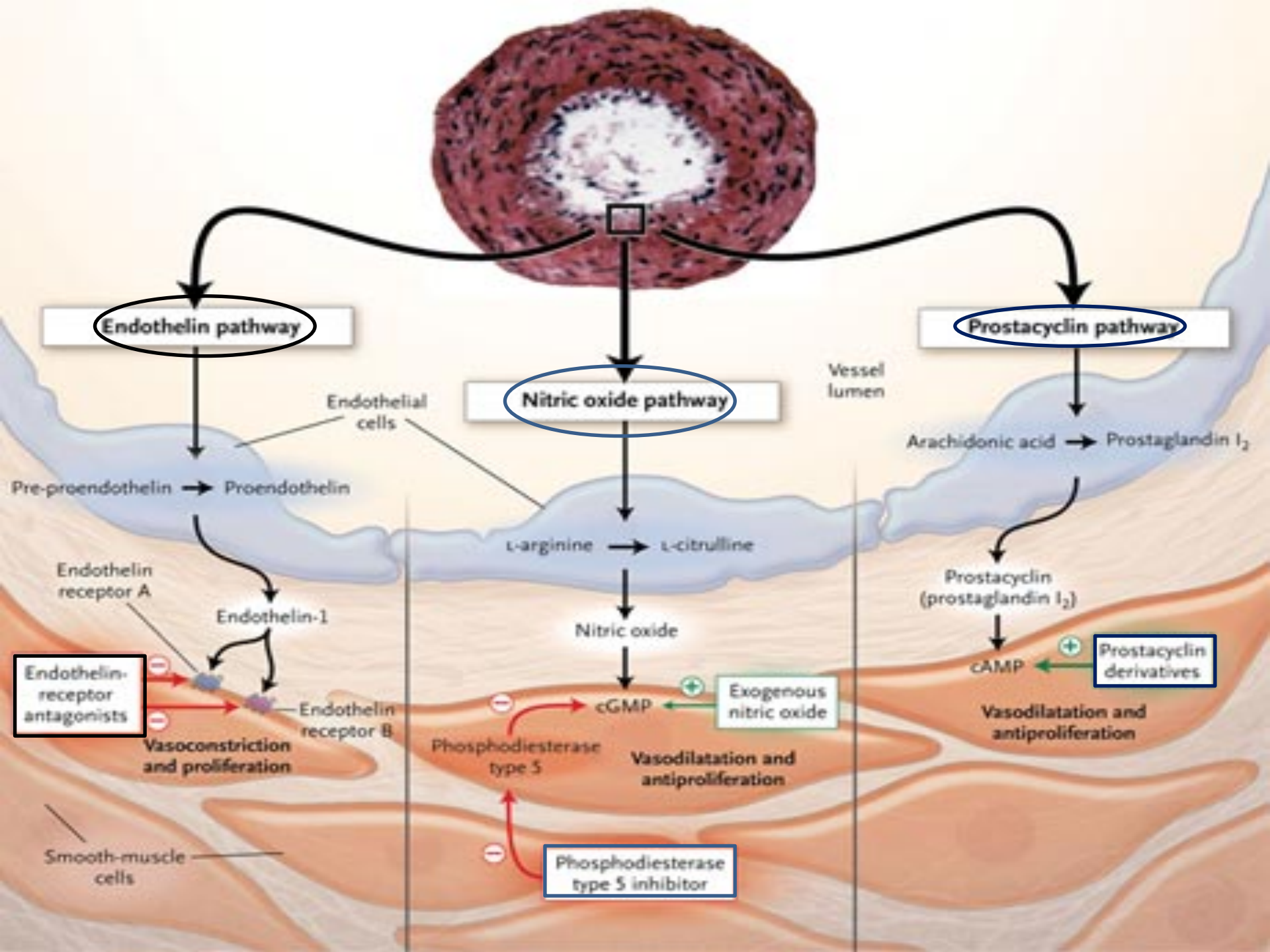
PAH sınıflandırma

Grup 5

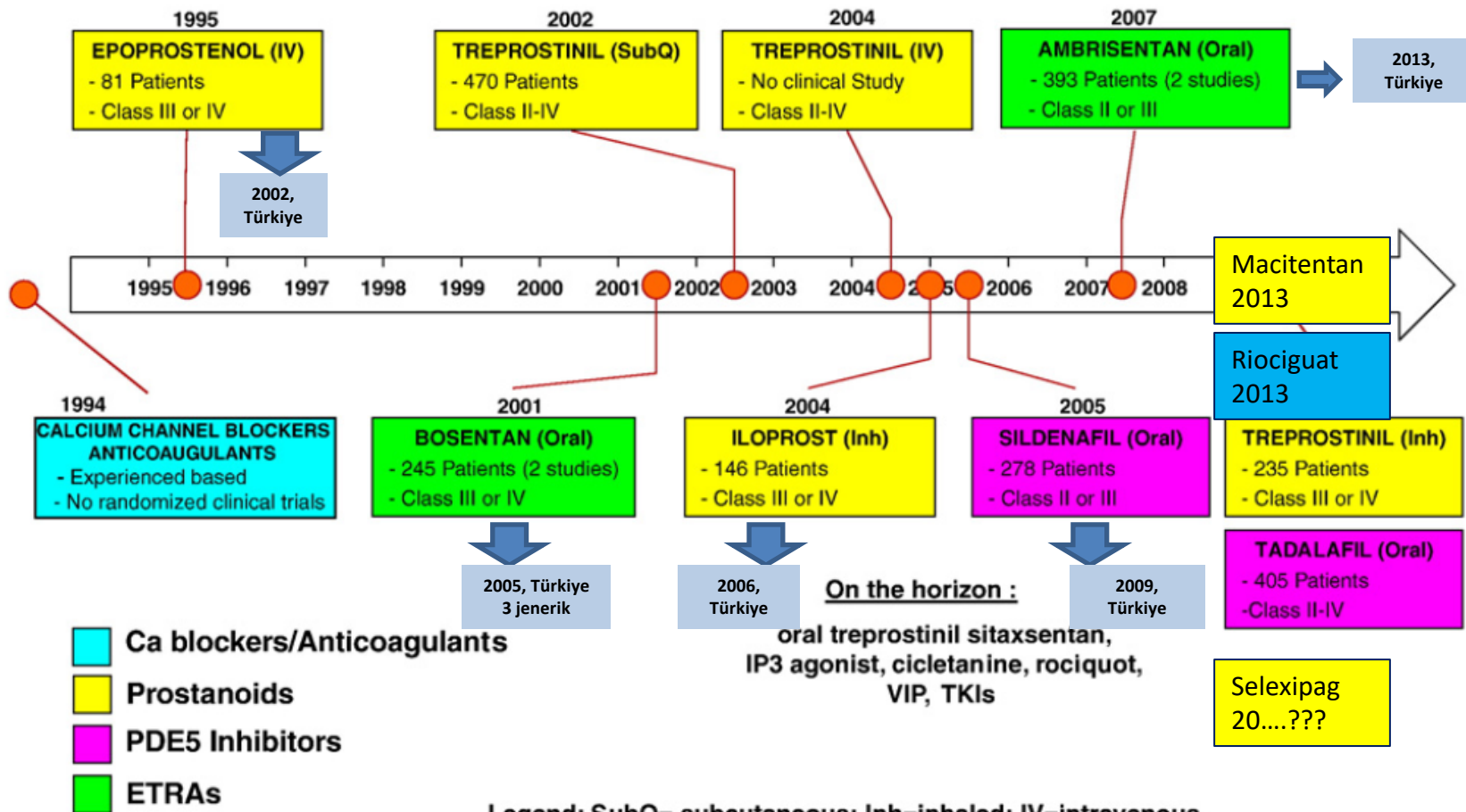
- Bir çok nedenli PAH
 - Hematolojik hastalıklar
 - Kr. Hemolitik anemiler
 - MDS
 - Splenektomi
 - Sistemik hastalıklar
 - Sarkoidozis
 - Pulmoner histiyositozis
 - lymphangioleiomyomatosis
 - Metabolik hastalıklar
 - Glycogen depo hast,
 - Gaucher hast,
 - Tiroid hast
 - Diğerleri
 - Tümör obst
 - Fibrozan mediastenit
 - KBY

Pulmoner hipertansiyon fonksiyonel sınıflandırması

- **Sınıf I**
 - Fiziksel aktivite kısıtlanması olmayan hastalar.
 - Olağan fiziksel aktiviteler belirtilere neden olmaz.
- **Sınıf II**
 - Hafif fiziksel aktivite kısıtlanması olan hastalar.
 - Hasta dinlenme sırasında rahattır.
 - Olağan fiziksel aktiviteler belirtilere neden olur.
- **Sınıf III**
 - Fiziksel aktivite kısıtlanması olan hastalar.
 - Hasta dinlenme sırasında rahattır.
 - Olağan düzeyin altında fiziksel aktivite belirtilere neden olur.
- **Sınıf IV**
 - Semptomlar gelişmeden hiçbir fiziksel aktivitede bulunamayan hastalar.
 - Bu hastalarda sağ kalp yetersizliği bulguları vardır.
 - Dispne ve/veya halsizlik dinlenme sırasında bile gözlemlenebilir.
 - Her türlü fiziksel aktivitede rahatsızlık artar.



İlaç Gelişimi



KKB

- Başlangıçtaki kalp hızı önemli
 - Bradikardi olanlarda nifedipin ve amlodipin,
 - Taşikardi bulunanlarda diltizem
- Nifedipin 120–240 mg/gün (2x1, 30 mg)
- Diltizem 240–720 mg/gün (3x1, 60 mg)
- Amlodipin 2.5-20 mg (1x1, 2.5 mg)
- Doz artırımında sınırlandırıcı faktörler
 - Sistemik hipotansiyon ve alt ekstremitelerde periferik ödem
- Etkinlik takip edilmeli
 - İlk değerlendirme tedavinin 3.–4. ayında

Adenozin testi pozitif Grup 1 hastalarda

KKB

- DSÖ-FS 1 veya 2 hastalarda yeterli yanıt alınmazsa
 - PAH tedavisine diğer ilaçlar ile devam etmek
- KKB tedavisi başlanılmamalı
 - Vazoreaktivite değerlendirmesi yapılmayan
 - Negatif sonuç alınan hastalarda
 - Şiddetli olabilecek yan etkilere (örn. hipotansiyon, senkop ve RV yetersizliği) yol açabileceği

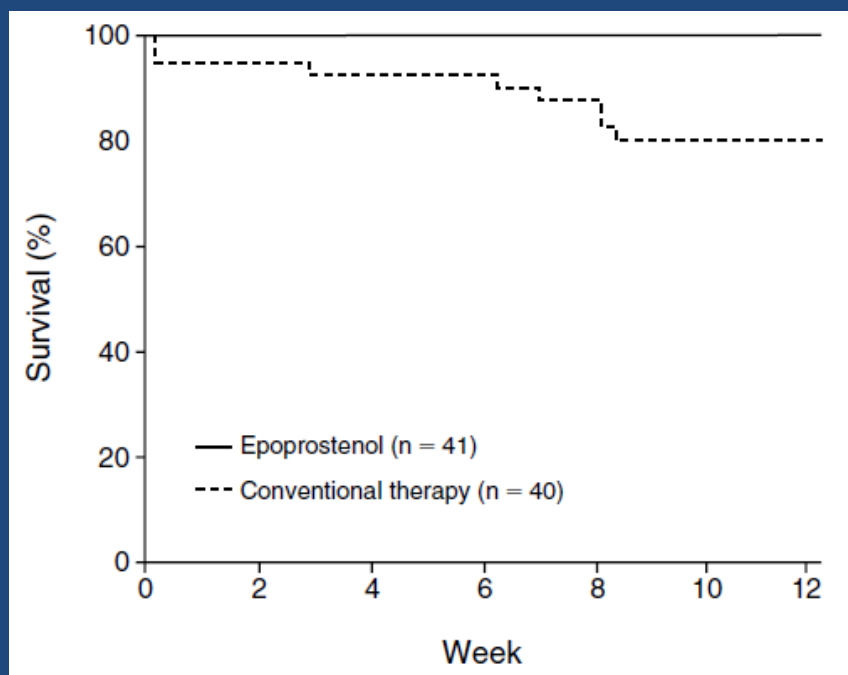
Prostonoidler

- Endotel fonksiyonu
 - Vazodilatasyon
 - Plt agregasyonu inh
 - Antiproliferasyon
- Epoprostenol, iv
 - (Glisin-Manitol)
- Epoprostenol AM
 - (Arginin-Manitol)
- Treprostinil, iv
- Treprostinil, sc
- Treprostinil, inhale
- İnhaler iloprost
- Beraprost

Epoprostenol, iv

- Hızlı metabolize olur
- Taşiflaksi gelişir
 - Aylar içinde doz artırılır
- Yarılanma ömrü 6dk↓
 - İnfüzyonun kesilmemesi
- Kateter problemleri
 - Enfeksiyon
 - %41.5
 - Tromboz
- Minör yan etkiler
 - Çene ağrısı, baş ağrısı, flushing, bulantı-kusma, ishal
- Soğukta muhafaza edilmesi gerekir
- 1-2 ng/kg/dk (25-40ng/kg)
- 1990 yıllarında PAH tedavisinde
 - Hemodinamide
 - Fonksiyonel kapasitede
 - Semptomlarda düzelme
- Oda sıcaklığında muhafaza edilen yeni formül
 - Eporostenol AM
 - Arginine ve manitol

A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION



In conclusion, the continuous intravenous infusion of epoprostenol plus conventional therapy for primary pulmonary hypertension resulted in better hemodynamics, exercise endurance, quality of life, and survival than conventional therapy alone. Although we did not address the long-term effects of therapy, our previous study suggests that the beneficial effects of epoprostenol on hemodynamics and exercise capacity persist with long-term therapy.¹⁶

Table 3. Effects on the Quality of Life of Treatment with Epoprostenol as Compared with Conventional Therapy.*

TREATMENT EFFECT	CHANGE FROM BASE LINE					
	EPOPROSTENOL		CONVENTIONAL THERAPY		HODGES-LEHMANN ESTIMATE†	95% CONFIDENCE INTERVAL‡
	no. of patients	median change	no. of patients	median change		
Chronic Heart Failure Questionnaire§						
Dyspnea	35	8.0	26	0.0	7.0	4.0 to 10.0
Fatigue	39	5.0	31	0.0	5.0	3.0 to 7.0
Emotional function	38	6.0	30	-1.0	7.0	3.0 to 10.0
Mastery¶	39	3.0	30	-0.5	2.5	1.0 to 4.0
Nottingham Health Profile						
Emotional reaction	37	-10.0	31	0.0	-14.7	-24.5 to
Energy	39	-36.8	31	0.0	-36.8	-4.9
Pain	39	0.0	31	0.0	0.0	-60.8 to 0.0
Physical mobility	39	-11.2	30	-6.4	-9.2	-5.8 to 0.0
Sleep	41	-16.1	31	0.0	-21.7	-19.9 to 2.0
Social isolation	40	0.0	31	0.0	0.0	-34.3 to -9.1
						-20.1 to 0.0
Dyspnea-Fatigue Rating§	41	1.0	31	0.0	2.0	1.0 to 3.0

The continuous intravenous infusion of epoprostenol may be useful in the management of severe primary pulmonary hypertension when it is refractory to conventional medical therapy.

İnhale iloprost

- Nebulizatör ile
- 6x1 veya 9x1 alınması gerekiyor
 - 2.5-5 µg/her nebülde
- Monoterapi ve Kombinasyon tedavilerinde

TABLE 4. INCIDENCE OF SERIOUS AND OTHER ADVERSE EVENTS.*

VARIABLE	ILOPROST GROUP (N= 101)	PLACEBO GROUP (N= 102)	P VALUE
	no. of patients (%)		
Serious adverse event			
Any event	28 (27.7)	25 (24.5)	0.63
Right ventricular failure and edema	4 (4.0)	10 (9.8)	0.16
Syncope	5 (5.0)	0	0.03
Other†	33 (32.7)	35 (34.3)	0.88
Adverse event‡			
Any event	91 (90.1)	90 (89.2)	0.82
Increased cough	39 (38.6)	26 (25.5)	0.05
Headache	30 (29.7)	20 (19.6)	0.11
Flushing	27 (26.7)	9 (8.8)	0.001
Influenza-like syndrome	14 (13.9)	10 (9.8)	0.39
Peripheral edema	13 (12.9)	16 (15.7)	0.69
Nausea	13 (12.9)	8 (7.8)	0.26
Jaw pain	12 (11.9)	3 (2.9)	0.02
Hypotension	11 (10.9)	6 (5.9)	0.22
Diarrhea	9 (8.9)	11 (10.8)	0.81
Vertigo	7 (6.9)	11 (10.8)	0.46
Syncope	8 (7.9)	5 (4.9)	0.41
Other adverse events§	296	277	

INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION

HORST OLSCHESKI, M.D., GERALD SIMONNEAU, M.D., NAZZARENO GALIÈ, 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., WLADIMIR 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*

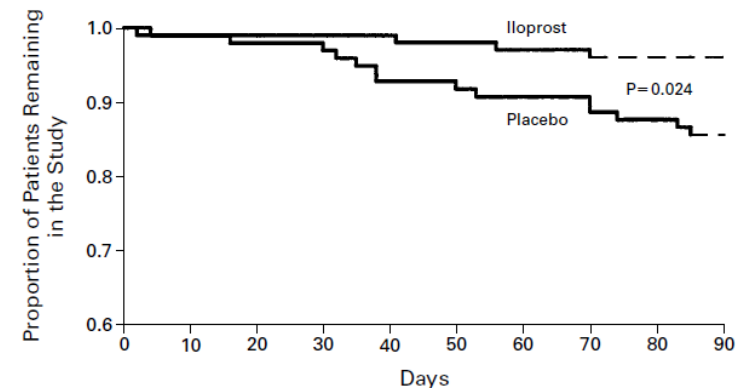
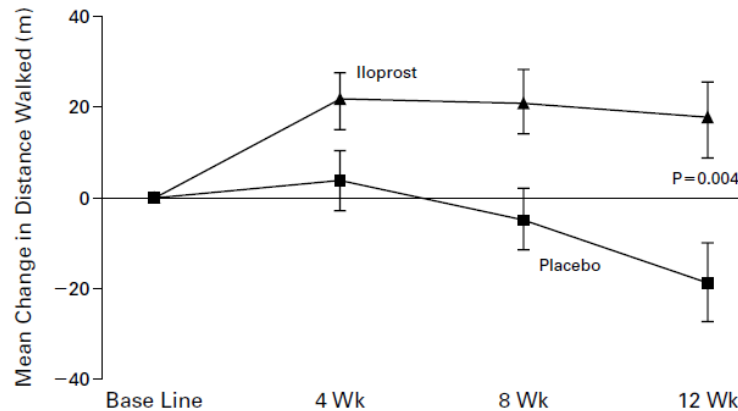


TABLE 3. MEAN ($\pm$ SD) CHANGE FROM BASE LINE IN HEMODYNAMIC VALUES DURING 12 WEEKS OF THERAPY WITH INHALED ILOPROST OR PLACEBO.*

VARIABLE	PLACEBO GROUP	ILOPROST GROUP	
		BEFORE INHALATION	AFTER INHALATION
		mean $\pm$ SD	
Pulmonary-artery pressure (mm Hg)	-0.2 ± 6.9	-0.1 ± 7.3	$-4.6 \pm 9.3^\dagger$
Cardiac output (liters/min)	$-0.19 \pm 0.81^\ddagger$	$+0.05 \pm 0.86$	$+0.55 \pm 1.1^\dagger$
Pulmonary vascular resistance (dyn $\cdot$ sec $\cdot$ cm $^{-5}$)	$+96 \pm 322^\ddagger$	$-9 \pm 275^\S$	$-239 \pm 279^\dagger$
Systemic arterial pressure (mm Hg)	-0.2 ± 12.4	-1.7 ± 12.8	$-4.3 \pm 13.6^\ddagger$
Right arterial pressure (mm Hg)	$+1.4 \pm 4.8^\ddagger$	$+0.5 \pm 4.6$	-0.8 ± 4.6
Pulmonary-artery wedge pressure (mm Hg)	$+0.7 \pm 3.6$	$+1.1 \pm 4.7^\ddagger$	$+1.8 \pm 5.3^\ddagger$
Arterial oxygen saturation (%)	$-1.6 \pm 4.4^\ddagger$	-0.4 ± 3.7	$-1.4 \pm 3.7^\ddagger$
Mixed venous oxygen saturation (%)	$-3.2 \pm 6.7^\dagger$	-1.1 ± 7.6	$+1.8 \pm 8.3$
Heart rate (beats/min)	-1.2 ± 9.5	-1.8 ± 12.4	-2.25 ± 12.6

TABLE 2. EFFECTS OF 12 WEEKS OF THERAPY WITH INHALED ILOPROST OR PLACEBO ON THE NEW YORK HEART ASSOCIATION (NYHA) CLASS AND THE SIX-MINUTE WALK TEST.

VARIABLE	ILOPROST GROUP			PLACEBO GROUP		
	ALL PATIENTS	PATIENTS WITH PRIMARY PULMONARY HYPERTENSION	PATIENTS WITH NONPRIMARY PULMONARY HYPERTENSION	ALL PATIENTS	PATIENTS WITH PRIMARY PULMONARY HYPERTENSION	PATIENTS WITH NONPRIMARY PULMONARY HYPERTENSION
percentage of patients						
Change in NYHA class						
Improved by 2 classes	1.0*	1.9	0.0	0.0	0.0	0.0
Improved by 1 class	23.8*	22.6	25.0	12.7	7.3	19.1
Unchanged	64.4	66.0	62.5	65.7	69.1	61.7
Worsened	5.9	3.8	8.3	7.8	10.9	4.3
Data missing	1.0	1.9	0.0	0.0	0.0	0.0
Noncompletion of study	4.0	3.8	4.2	13.7	12.7	14.9
Death	1.0	1.9	0.0	3.9	3.6	4.3
Other	3.0†	1.9	4.2	9.8‡	9.1	10.6
Change in 6-minute walk distance						
$\geq 10\%$ increase	37.6§	49.1	25.0	25.5	30.9	19.1
$< 10\%$ increase to $< 10\%$ decrease	42.6	37.7	47.9	32.4	20.0	46.8
$\geq 10\%$ decrease	13.9	5.7	22.9	25.5	32.7	17.0
Data missing	5.9	7.5	4.2	16.7	16.4	17.0
Combined end point	16.8¶	20.8	12.5	4.9	5.5	4.3

Long-term therapy with inhaled iloprost in patients with pulmonary hypertension[☆]

Horst Olschewski^{a,b,*}, Marius M. Hoeper^c, Juergen Behr^d, Ralf Ewert^{e,f},
Andreas Meyer^g, Mathias M. Borst^{h,i}, Jörg Winkler^j, Michael Pfeifer^k,
Heinrike Wilkens^l, Hossein Ardeschir Ghofrani^a, Sylvia Nikkho^m,
Werner Seeger^a



Thirty-six patients completed at least 630 days of therapy (25 IPAH, 11 PHother), 19 patients dropped out prematurely and 8 patients died (3 IPAH, 5 PHother). There were no drug-induced toxicities and only mild to moderate side effects. The most common side effects were coughing and flushing. Two-year survival was estimated at 85% (IPAH group 91%, PHother 78%). A modified analysis was performed to correct for differential drop-out. It included follow-up data from the premature discontinuations and revealed a 2-year survival of 87% [95% CI, 76%–98%] in the IPAH group while the predicted survival was 63%. The iloprost dose increased by 16% over 2 years.

Conclusion: Inhaled iloprost is well tolerated as long-term therapy and no substantial dose increase is required. Although uncontrolled, the data suggest a long-term clinical benefit from continued therapy with inhaled iloprost.

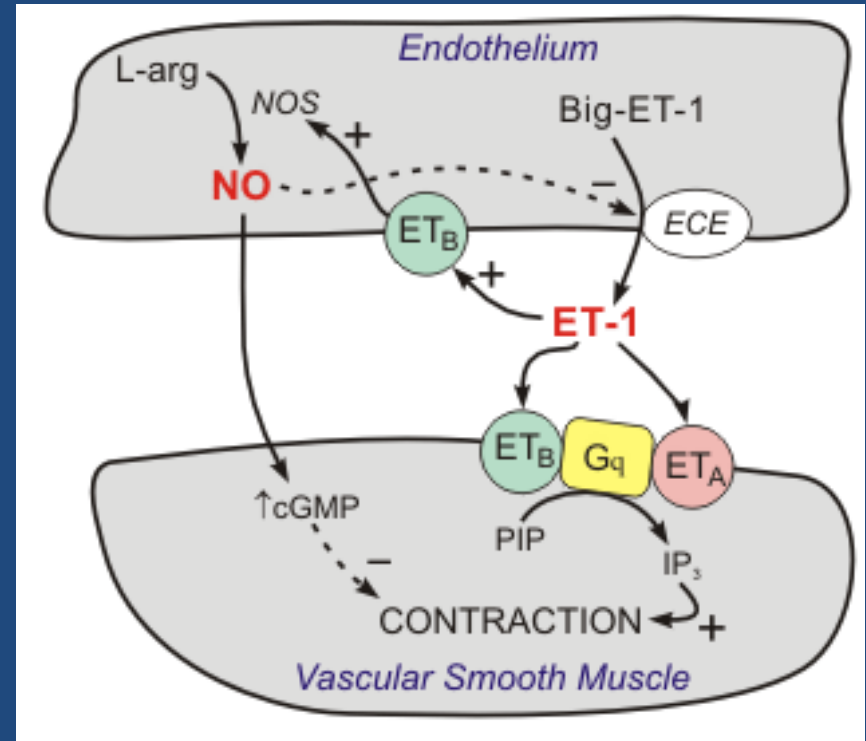
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Treprostinil

- Oda sıcaklığında stabil
- Yarı ömrü 4.5 saat
- İv, sc ve oral tb
- Evre 4 hastalarda derialtı formu orta düzeyde etkiye sahip
- Kateter komplikasyonlarına alternatif
- Derialtı uygulamasında ağrı
 - %85

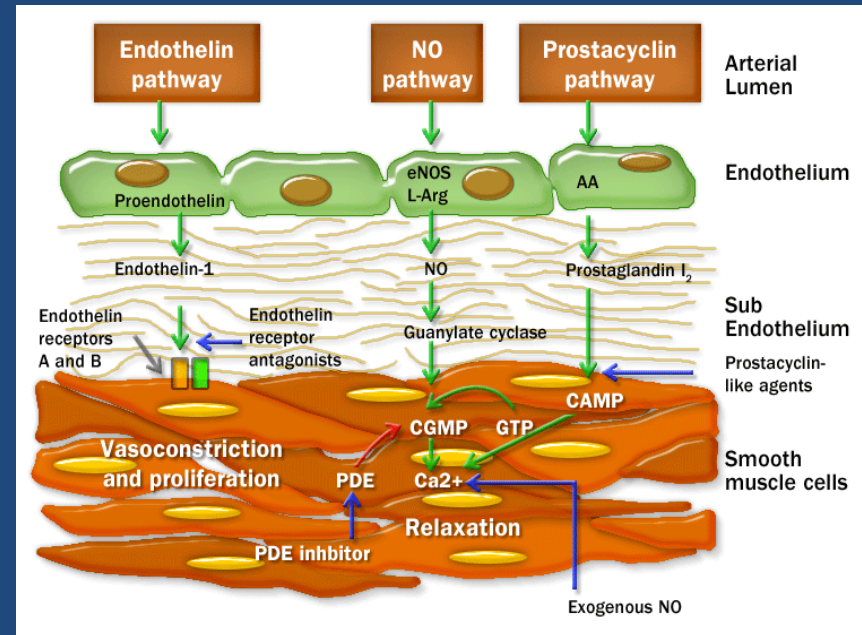
Endotelin Reseptör Antagonistleri

- Endotel hücreleri tarafından
 - 21aa peptid
 - ET-1
 - Vazokonstriktör
 - Mitojen
 - Endotelin reseptörleri
 - ET-A
 - Düz kas ve kalp hücresi
 - ET-B
 - Damar endoteli ve düz kas hücresi



Endotelin Reseptör Antagonistleri

- Non-selektif dual etki
 - Bosentan
 - Masitentan
- Selektif ET-A R antagonisti
 - Ambresentan
 - Sitaksentan
 - Ölümcü yan etki (2010)



Long-term outcome and effects of oral bosentan therapy in Taiwanese patients with advanced idiopathic pulmonary arterial hypertension

Patient no.	Gender	Age (yr)	MPAP (mm Hg)	NYHA FC
1	Female	29	72	IV
2	Female	24	49	IV
3	Female	40	51	III
4	Female	37	68	III
5	Female	41	52	III
6	Female	42	51	III
7	Female	17	75	III
8	Male	14	80	IV
9	Female	51	65	III
10	Female	57	40	IV
11	Female	33	66	IV
12	Female	43	41	IV

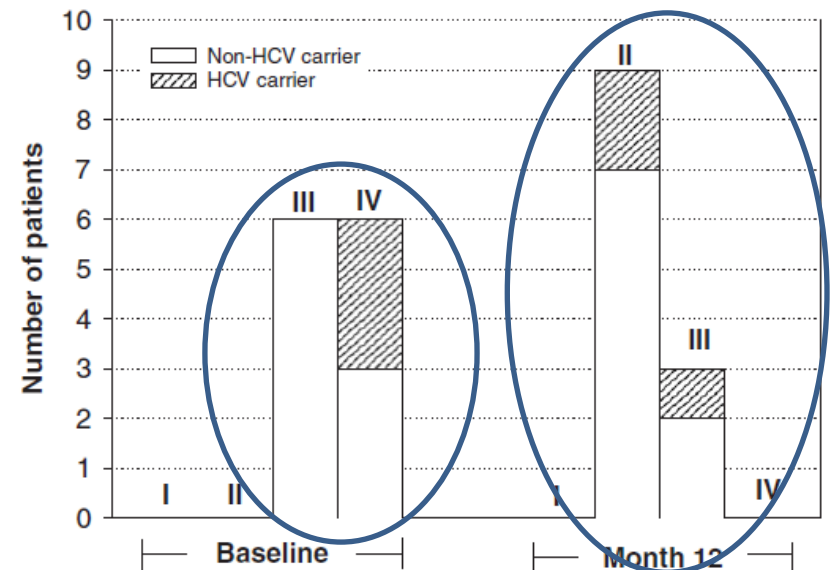


Table 2 Variables before bosentan treatment and at end of observation (12 months).

	Baseline	End of observation	<i>p</i> value
NYHA FC	3.5 ± 0.52	2.25 ± 0.45	0.002
6-MWD (m/6 min)	326 ± 138	446 ± 119	0.002
RVEF (%)	31.0 ± 17.1	54.5 ± 12.2	0.004
Cardio-thoracic ratio	0.551 ± 0.066	0.508 ± 0.049	0.019
FVC (% predicted)	84.2 ± 14.7	95.3 ± 16.1	0.003
FEV ₁ (% predicted)	77.1 ± 17.7	84.0 ± 17.0	0.019

Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial

N Galiè, L J Rubin, M M Hoeper, P Jansa, H Al-Hiti, G M B Meyer, E Chiossi, A Kusic-Pajic, G Simonneau

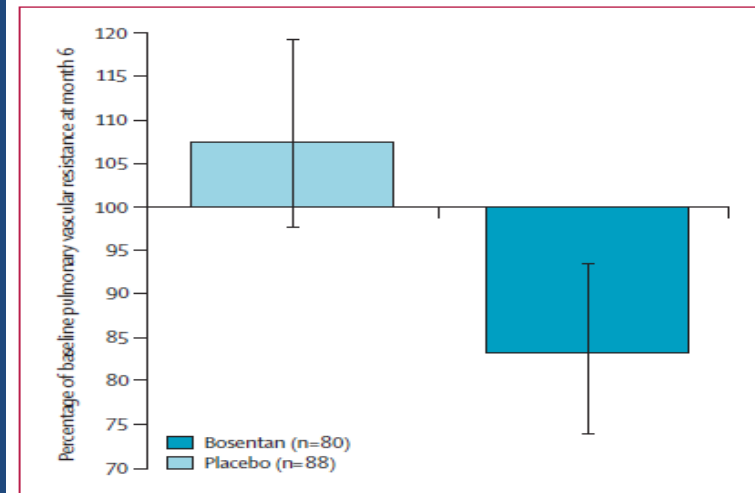
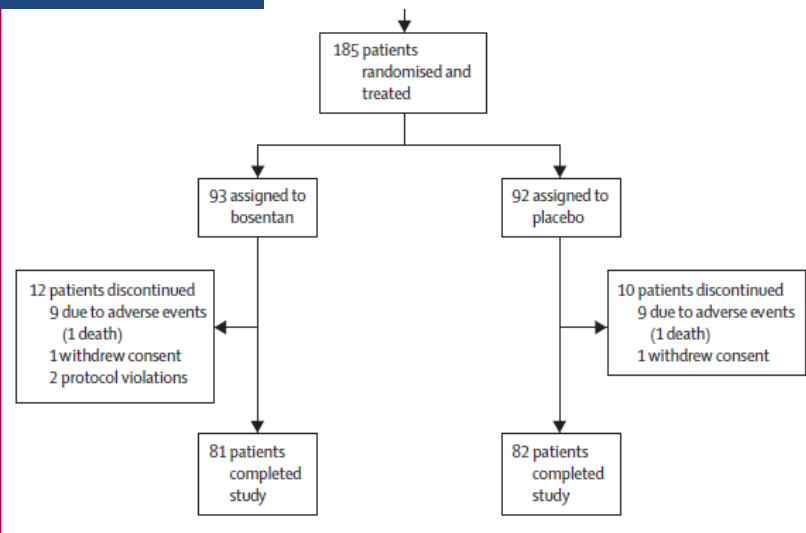
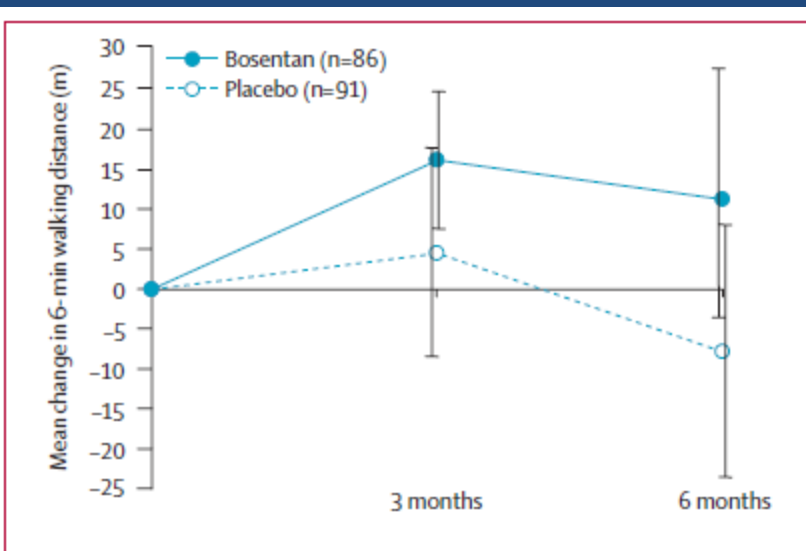
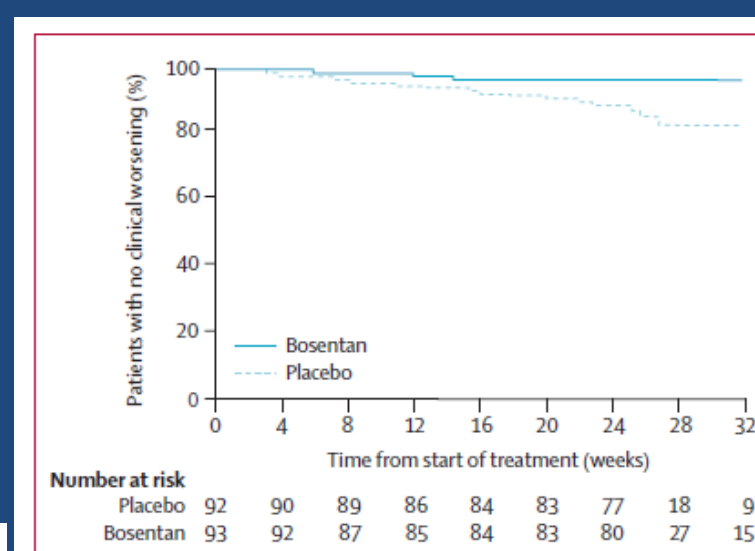


Figure 2: Percentage of baseline pulmonary vascular resistance at 6 months. Error bars are 95% CI.



Lancet 2008; 371: 2093-100



Number at risk

Placebo	92	90	89	86	84	83	77	18	9
Bosentan	93	92	87	85	84	83	80	27	15

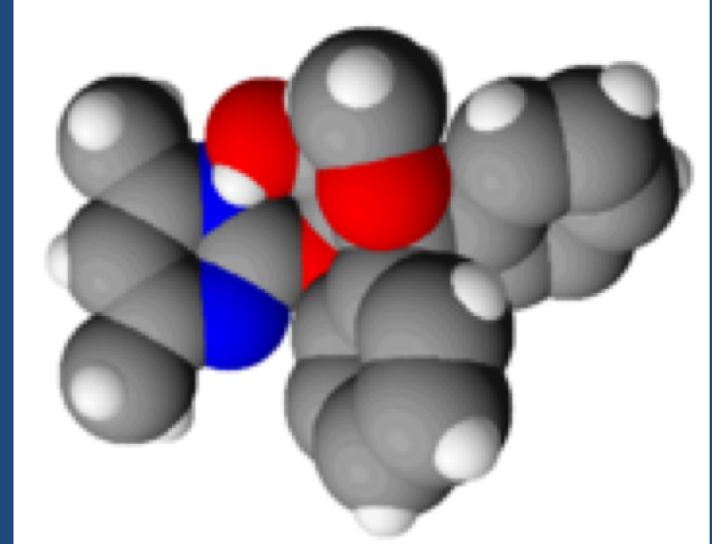
Yan etkileri

Bosentan

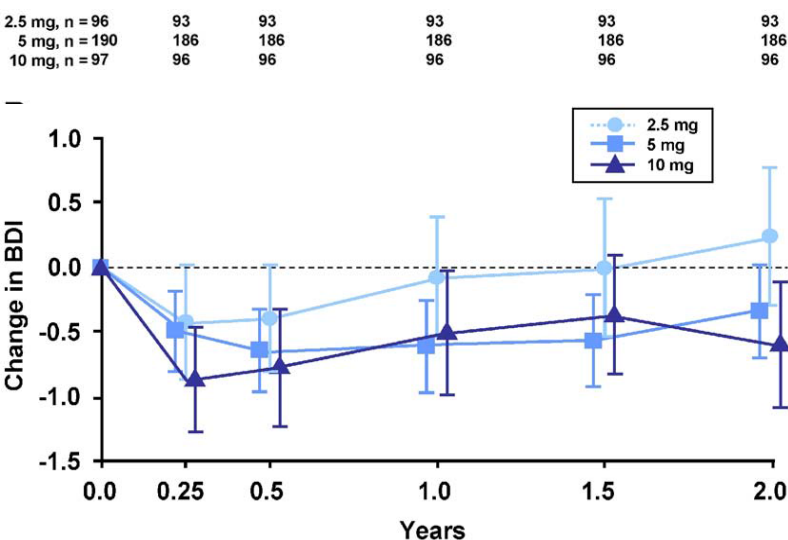
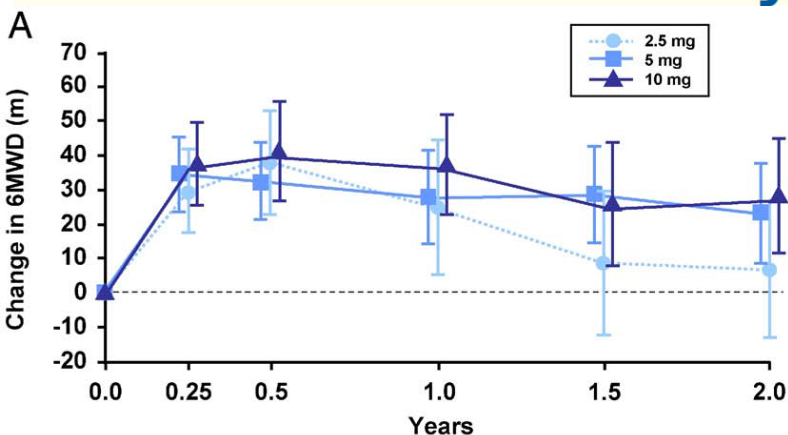
- Gıdalar ile etkilenmiyor
- Böbrek yetmezliğinde etkilenmiyor
- ALT ve AST düzeylerinde artma
 - %2 hastada kesiliyor
 - İlk 16 hf da %12.7 hastada 3 kat artış mg
 - Genellikle geçici artış
- Tedavinin ilk 5 hf da Hb düzeylerinde 0.9 g/dL azalma mg
- Alt ekstremitelerde ödem
 - %13.9 (plasebo %8.8)
 - Diüretik tedaviye cevap
- Nazofaranjit
 - Nazal streoid
 - İn hale ipratropiyum
- Teratojeniktir
- Warfarin doz ayarlaması yapılabilir
 - Metabolizmayı artırdığından

Ambrisentan

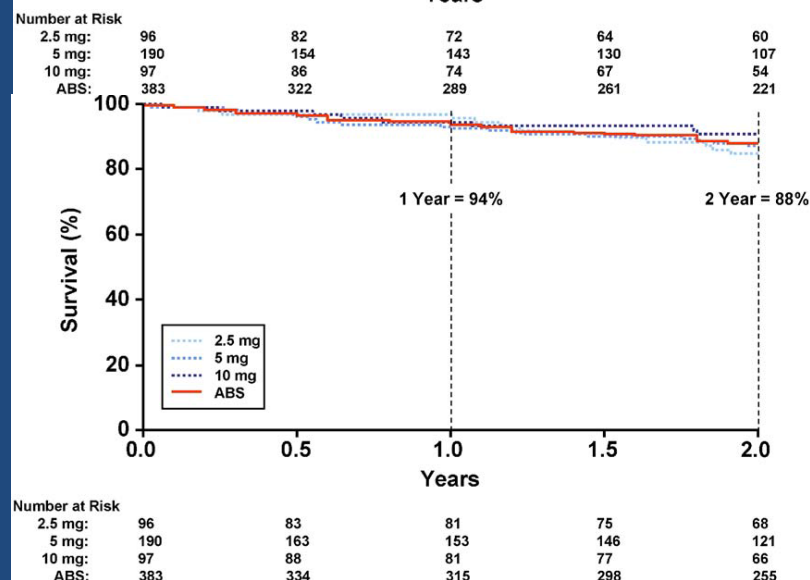
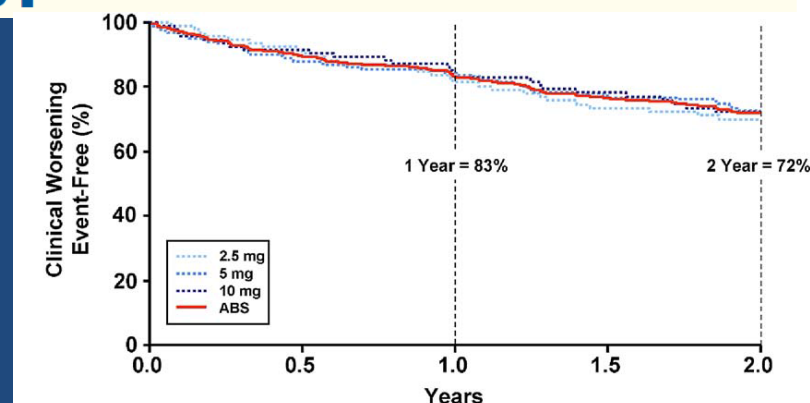
- 2007 yılında
- Spesifik ET_A reseptör anatgonisti
 - ET_A'ya afinitesi >4000 (ET_B'ye göre)
- Evre II ve III hastalarda
- Oral tb (1x1) (5-10mg)
- Böbrek yetmezliğinde etkilenmiyor (hafif-orta)
- Orta-ağır KC yetm'de tavsiye edilmiyor
- Teratojenik (rat)
- Anne sütü yasak
- Warfarin ile etkileşimi yok doz ayarlanmasına gerek yok



Long-Term Ambrisentan Therapy for the Treatment of Pulmonary Arterial Hypertension

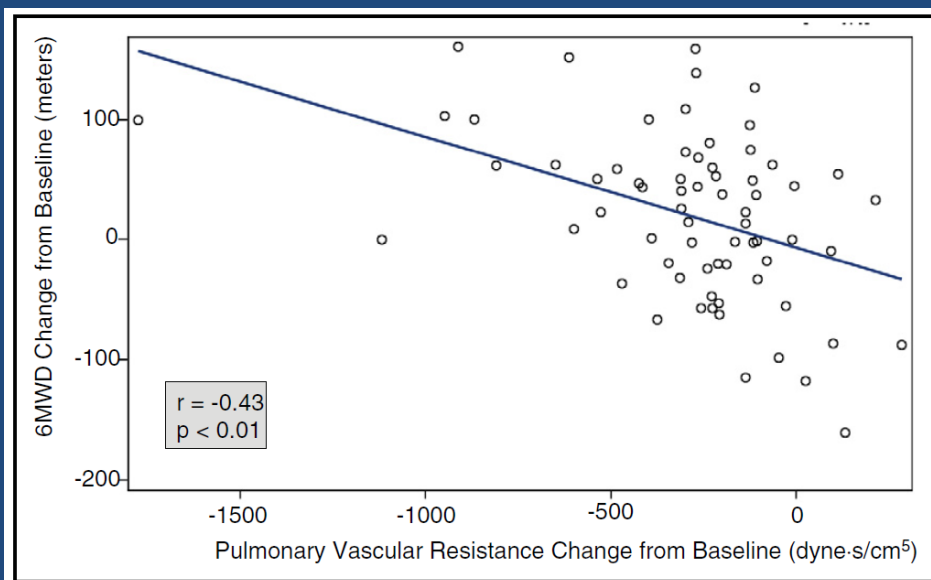
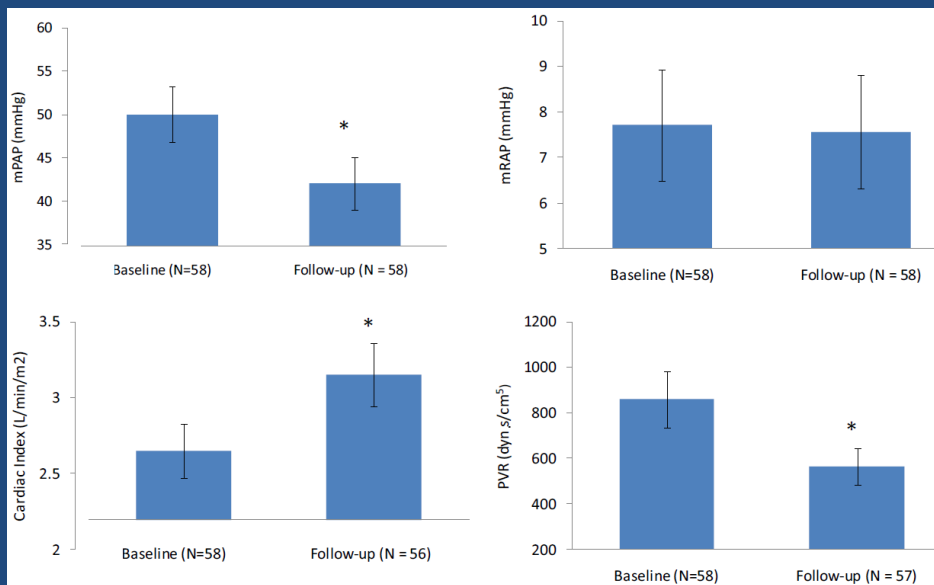


- 383 hasta
- 2yıl takip
- Evre 2 ve 3
- 2.5mg
- 5mg
- 10mg
- IPAH
- APAH



Long-Term Pulmonary Hemodynamic Effects of *Ambrisentan* in Pulmonary Arterial Hypertension

James R. Klinger, MD^{a,*}, Ronald J. Oudiz, MD^b, Rebecca Spence, PhD^c, Darrin Despain, MS^c, and Christopher Dufton, PhD^c



Frequency of Edema in Patients With Pulmonary Arterial Hypertension Receiving Ambrisentan

Shelley Shapiro, MD, PhD^{a,*}, David M. Pollock, PhD^b, Hunter Gillies, MD^c, Noreen Henig, MD^c,
Martine Allard, PhD^c, Christiana Blair, MSc^c, Crystal Anglen, PhD^c, and
Donald E. Kohan, MD, PhD^d

Ödem %23, plasebo %14
%76 Evre 3 ve 4, ödem+
%56 Evre 3 ve 4 ödem –
Daha yaşlı hastalar
Belirgin olarak BNP
düzeylerinde azalmaya
neden olduğu

Edema is a common side effect of endothelin receptor antagonists. Ambrisentan is an endothelin type A-selective endothelin receptor antagonist approved for the treatment of pulmonary arterial hypertension. We examined the clinical outcomes of patients who developed edema with and without ambrisentan treatment in 2 phase III, randomized placebo-controlled trials, ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2 (ARIES-1 and ARIES-2) (n = 393). Edema-related adverse events were extracted using broad adverse event search terms. The present post hoc analysis included 132 placebo patients and 261 ambrisentan patients. Of these patients, 14% of the placebo patients and 23% of the ambrisentan patients experienced edema-related adverse events. Overall, the patients who experienced edema tended to have a worse baseline World Health Organization (WHO) functional class (edema 76%, WHO functional class III-IV; no edema 56%, WHO functional class III-IV). In the ambrisentan patients, those with edema were older (mean age 58 ± 13 years) and heavier (mean weight 75 ± 19 kg) than those without edema (mean age 49 ± 15 years; mean weight 70 ± 17 kg). At week 12 of treatment, the ambrisentan patients had significantly increased their 6-minute walk distance (6MWD) by 34.4 m compared to the placebo patients in whom the 6MWD had deteriorated by -9.0 m ($p < 0.001$). Among the ambrisentan patients, those without edema had a 6MWD increase of 38.9 m and those with edema had a 6MWD increase of 19.4 m. Ambrisentan significantly improved the brain natriuretic peptide levels by -34% compared to the brain natriuretic peptide levels in the placebo group that had worsened by $+11\%$ ($p < 0.001$). Ambrisentan reduced the brain natriuretic peptide concentrations similarly in patients with and without edema. In conclusion, the present subanalysis of patients with pulmonary arterial hypertension has revealed that ambrisentan therapy provides clinical benefit compared to placebo, even in the presence of edema. Published by Elsevier Inc. (Am J Cardiol 2012;110:1373–1377)

Treatment of Idiopathic Pulmonary Fibrosis With Ambrisentan: A Parallel, Randomized Trial

Ganesh Raghu, MD; Juergen Behr, MD; Kevin K. Brown, MD; Jim J. Egan, MD; Steven M. Kawut, MD; Kevin R. Flaherty, MD; Fernando J. Martinez, MD; Steven D. Nathan, MD; Athol U. Wells, MD; Harold R. Collard, MD; Ulrich Costabel, MD; Luca Richeldi, MD; Joao de Andrade, MD; Nasreen Khalil, MD; Lake D. Morrison, MD; David J. Lederer, MD; Lixin Shao, MD; Xiaoming Li, PhD; Patty S. Pedersen, BSN; A. Bruce Montgomery, MD; Jason W. Chien, MD; Thomas G. O'Riordan, MD, and the ARTEMIS-IPF Investigators*

The study was terminated after enrollment of 492 patients (75% of intended enrollment; mean duration of exposure to study medication, 34.7 weeks) because an interim analysis indicated a low likelihood of showing efficacy for the end point by the scheduled end of the study. Ambrisentan-treated patients were more likely to meet the prespecified criteria for disease progression (90 [27.4%] vs. 28 [17.2%] patients; $P = 0.010$; hazard ratio, 1.74 [95% CI, 1.14 to 2.66]). Lung function decline was seen in 55 (16.7%) ambrisentan-treated patients and 19 (11.7%) placebo-treated patients ($P = 0.109$). Respiratory hospitalizations were seen in 44 (13.4%) and 9 (5.5%) patients in the ambrisentan and placebo groups, respectively ($P = 0.007$). Twenty-six (7.9%) patients who received ambrisentan and 6 (3.7%) who received placebo died ($P = 0.100$). Thirty-two (10%) ambrisentan-treated patients and 16 (10%) placebo-treated patients had pulmonary hypertension at baseline, and analysis stratified by the presence of pulmonary hypertension revealed similar results for the primary end point.

Conclusion: Ambrisentan was not effective in treating IPF and may be associated with an increased risk for disease progression and respiratory hospitalizations.

Macitentan

- Oral dual ERA antagonisti
- Sürekli reseptör bağlanır
- Doku penetresyonu daha güçlü
- İlaç-ilaç etkileşimi daha düşük

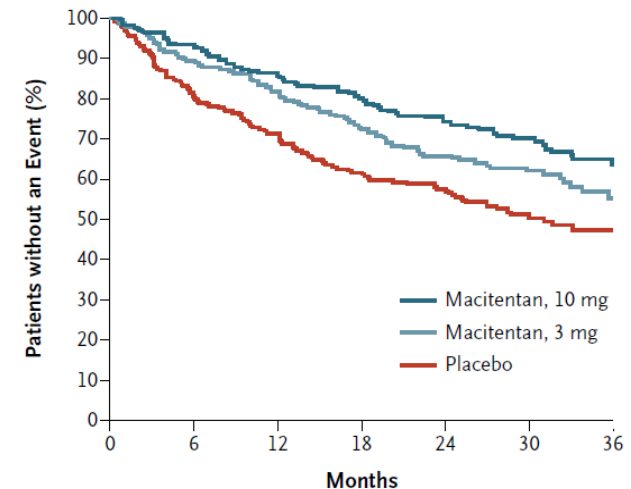
ORIGINAL ARTICLE

Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

SERAPHIN çalışmasında mortalite ve morbiditeyi azalttığı ve yan etki olarak baş ağrısı, faranjit ve anemi plasebo grubuna göre daha fazla

Table 2. Primary and Secondary End Points for Events Related to Pulmonary Arterial Hypertension and Death.*

End Point	Placebo (N = 250)	Macitentan, 3 mg (N = 250)	Macitentan, 10 mg (N = 242)	Macitentan, 3 mg, vs. Placebo		Macitentan, 10 mg, vs. Placebo	
				Hazard Ratio (97.5% CI)	P Value	Hazard Ratio (97.5% CI)	P Value
number of patients (percent)							
Event related to PAH or death as the first event							
All events	116 (46.4)	95 (38.0)	76 (31.4)	0.70 (0.52–0.96)	0.01	0.55 (0.32–0.76)	<0.001
Worsening of PAH	93 (37.2)	72 (28.8)	59 (24.4)				
Death from any cause†	17 (6.8)	21 (8.4)	16 (6.6)				
Prostanoid initiation	6 (2.4)	1 (0.4)	1 (0.4)				
Lung transplantation	0	1 (0.4)	0				
Death due to PAH or hospitalization for PAH as the first event							
All events	84 (33.6)	65 (26.0)	50 (20.7)	0.67 (0.46–0.97)	0.01	0.50 (0.34–0.75)	<0.001
Hospitalization for PAH	79 (31.6)	56 (22.4)	45 (18.6)				
Death due to PAH‡	5 (2.0)	9 (3.6)	5 (2.1)				
Death from any cause	19 (7.6)	21 (8.4)	14 (5.8)	0.97 (0.48–1.98)	0.92	0.64 (0.29–1.42)	0.20
Death due to PAH§	14 (5.6)	14 (5.6)	7 (2.9)	0.87 (0.37–2.04)	0.72	0.44 (0.16–1.25)	0.07
Death from any cause by the end of the study¶	44 (17.6)	47 (18.8)	35 (14.5)	1.05 (0.65–1.67)	0.83	0.77 (0.46–1.28)	0.25



No. at Risk

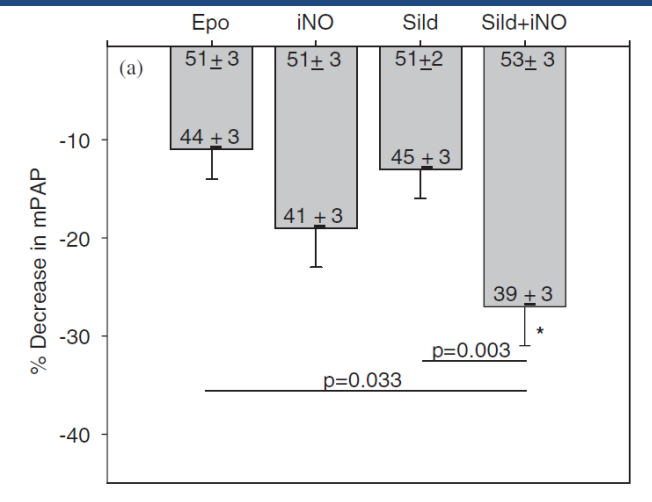
Placebo	250	188	160	135	122	64	23
Macitentan, 3 mg	250	213	188	166	147	80	32
Macitentan, 10 mg	242	208	187	171	155	91	41

Fosfodiesteraz-5 inhibitörleri

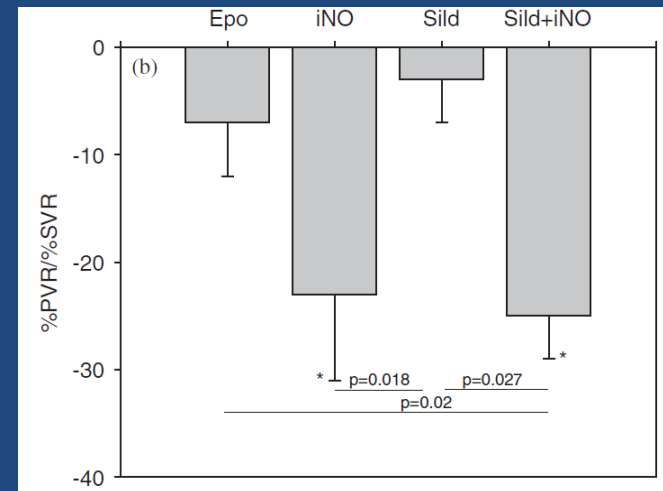
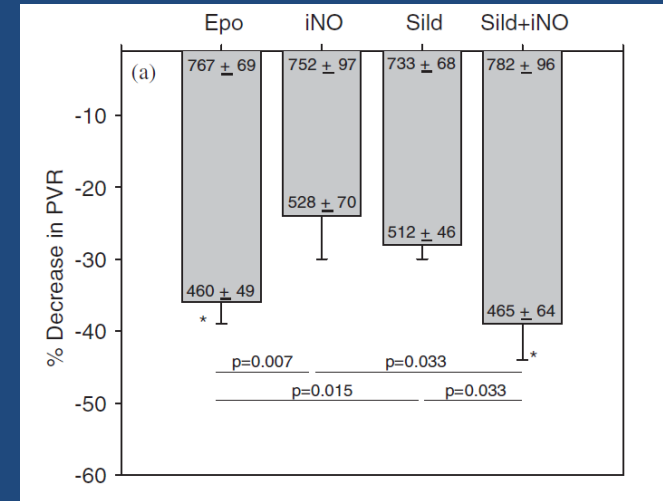
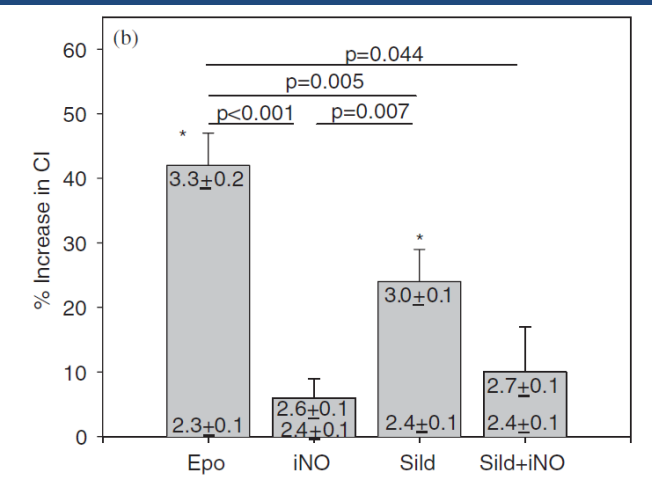
- Sildenafil
- Tadalafil
- Vardenafil
- Baş ağrısı
- Flushing
- Dispepsi
- Myalji
 - tadalafil
- Bulanık görme
- Işığa hassasiyet
- Ani işitme kaybı

Acute and chronic effects of sildenafil in patients with pulmonary arterial hypertension

Ioana R. Preston*, James R. Klinger, Jeanne Houtches, David Nelson, Harrison W. Farber, Nicholas S. Hill



- 20 hasta
- Akut ve kronik etki
- Akut vazodilatasyon yaptığı
- Uzun süreli tek başına veya kombinasyon ile etkili ve güvenilir bir ilaç



Selexipag

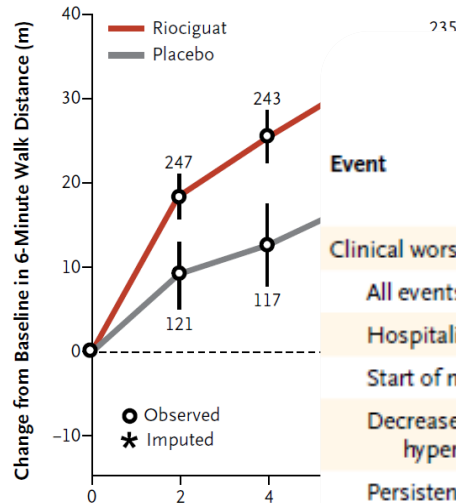
- Oral prostosiklin (IP) reseptör agonisti
- Güçlü vazodilatör
- Faz 3 GRIPHON çalışması devam ediyor
- Faz 2 çalışması
 - PVR azalma
 - 6 dk yürüme testinde düzelme
 - %30.3 tedavi etkinliği
 - İyi tolere güvenli

Riociguat

- Soluble guanylate cyclase uyarıcı
- cGMP üretimini artırıyor
- Dual etki
 - eNO ile sinerjik etkileşim
 - sGC uyarısı
- Deneysel olarak
 - Güçlü vazodilatör
 - Güçlü Remodellingi geri çevirme özelliği
- Faz 1 ve 2 çalışmalarda
 - Hemodinamik parametrelerinde düzeltme

ORIGINAL ARTICLE

Riociguat for the Treatment of Pulmonary Arterial Hypertension



Event

Clinical worsening

All events

Hospitalization

Start of new treatment

Decrease in 6-minute walk distance

hypertension

Persistent worsening of pulmonary hypertension

Death

PATE

ve se

Adverse events

Any	108 (86)	227 (89)	58 (92)
Headache	25 (20)	69 (27)	20 (32)
Dyspepsia	10 (8)	48 (19)	8 (13)
Peripheral edema	14 (11)	44 (17)	14 (22)
Nausea	16 (13)	40 (16)	10 (16)
Dizziness	15 (12)	40 (16)	15 (24)
Diarrhea	13 (10)	35 (14)	6 (10)
Vomiting	11 (9)	26 (10)	7 (11)
Nasopharyngitis	14 (11)	26 (10)	6 (10)
Hypotension	3 (2)	25 (10)‡	2 (3)
Anemia	3 (2)	21 (8)	1 (2)
Palpitations	6 (5)	20 (8)	5 (8)
Chest pain	11 (9)	18 (7)	4 (6)
Dyspnea	14 (11)	16 (6)	4 (6)
Gastroesophageal reflux disease	4 (3)	14 (6)	4 (6)
Cough	13 (10)	12 (5)	3 (5)
Nasal congestion	3 (2)	11 (4)	4 (6)
Tachycardia	7 (6)	9 (4)	0
Pyrexia	4 (3)	8 (3)	6 (10)
Fatigue	8 (6)	7 (3)	0
Chest discomfort	11 (9)	6 (2)	4 (6)
Flushing	7 (6)	5 (2)	2 (3)
Gastritis	0	4 (2)	4 (6)
Syncope	5 (4)	3 (1)	0

Event	P Value†
Any	<0.001
Headache	<0.001
Dyspepsia	<0.001
Peripheral edema	<0.001
Nausea	0.003
Dizziness	0.002
Diarrhea	0.07
Vomiting	0.002
Nasopharyngitis	<0.001
Hypotension	<0.001
Anemia	0.07
Palpitations	<0.001
Chest pain	0.07
Dyspnea	<0.001
Gastroesophageal reflux disease	0.08
Cough	<0.001
Nasal congestion	<0.001
Tachycardia	0.07
Pyrexia	<0.001
Fatigue	0.08
Chest discomfort	<0.001
Flushing	<0.001
Gastritis	<0.001
Syncope	<0.001

ORIGINAL ARTICLE

Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

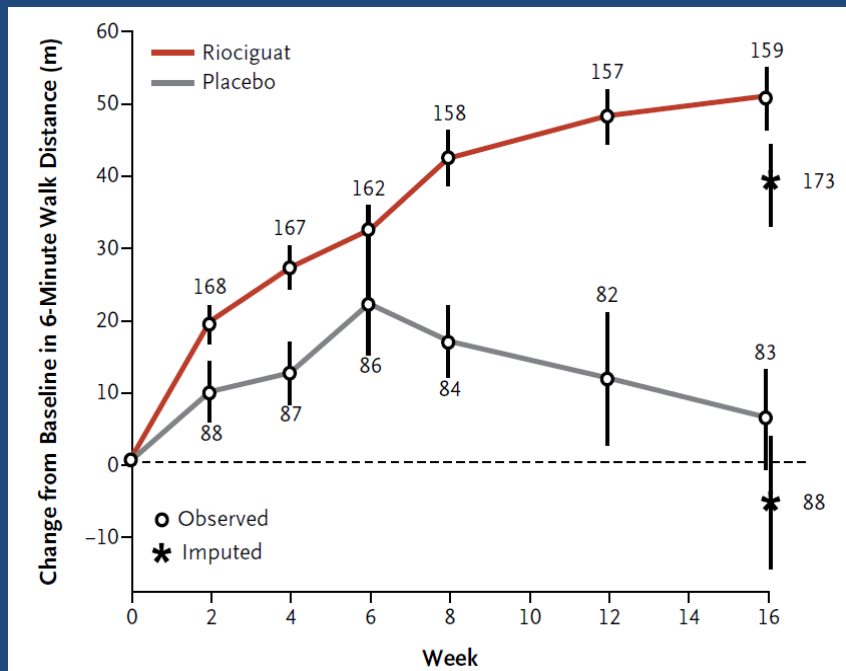


Table 2. Change from Baseline to End of Week 16 in Primary and Secondary End Points and in Hemodynamic Variables.*

End Point	Placebo			Riociguat			Least-Squares Mean Difference (95% CI)	P Value†
	No. of Patients	Baseline	Change	No. of Patients	Baseline	Change		
Primary end point								
6-Min walk distance (m)‡	88	356±75	-6±84	173	342±82	39±79	46 (25 to 67)	<0.001
Secondary end points								
Pulmonary vascular resistance (dyn·sec·cm ⁻⁵)	82	779±401	23±274	151	791±432	-226±248	-246 (-303 to -190)	<0.001
NT-proBNP (pg/ml)	73	1706±2567	76±1447	150	1508±2338	-291±1717	-444 (-843 to -45)	<0.001
WHO functional class§	87	0 patients in class I, 25 (29%) in class II, 60 (69%) in class III, 2 (2%) in class IV	13 patients (15%) moved to lower class (indicating improvement), 68 (78%) stayed in same class, 6 (7%) moved to higher class	173	3 patients (2%) in class I, 55 (32%) in class II, 107 (62%) in class III, 8 (5%) in class IV	57 patients (33%) moved to lower class (indicating improvement), 107 (62%) stayed in same class, 9 (5%) moved to higher class	—	0.003
Borg dyspnea score¶	88	4±2	0.2±2.4	173	4±2	-0.8±2	—	0.004
EQ-5D score**	87	0.66±0.25	-0.08±0.34	172	0.64±0.24	0.06±0.28	0.13 (0.06 to 0.21)	<0.001
LPH score††	86	46±23	-2±19	170	41±22	-7±19	-6 (-10 to -1)	0.1
Hemodynamic variables‡‡								
Pulmonary-artery pressure (mm Hg)	84	44±10	0.8±7.3	156	45±13	-4±7	-5 (-7 to -3)	<0.001
Mean arterial pressure (mm Hg)	78	95±11	-0.3±11.8	155	95±12	-9±12	-9 (-12 to -6)	<0.001
Right atrial pressure (mm Hg)	84	9±6	-0.6±5.2	157	9±5	-1±5	-0.6 (-1.7 to 0.6)	0.4
Cardiac output (liters/min)	83	4±1	-0.03±1.07	155	4±1	0.8±1.1	0.9 (0.6 to 1.1)	<0.001
Pulmonary-capillary wedge pressure (mm Hg)	83	9±4	0.2±4.3	151	9±3	0.6±3.7	0.6 (-0.4 to 1.5)	0.2
Arterial oxygen saturation (%)	87§§	94±2	-3±8	172¶¶	94±3	-2±4	—	—

CHEST-1 çalışmasında Egzersiz kapasitesini ve PVR azalttığı gösterilmiştir

Gebelikten kaçının (I-C)
İnfluenza ve pnömokok aşısı (I-C)
Gözetimli rehabilitasyon (IIa-B)
Psikososyal destek (IIa-C)
Aşırı fiziksel aktiviteden kaçının (III-C)

Genel önlemler ve destek tedavisi

Uzmana Sevk (I-C)

Akut vazoreaktivite testi
(İPAH için I-C)
(APAH için IIb-C)

Diüretikler (I-C)
Oksijen* (I-C)
Oral antikoagülanlar:
İPAH, kalıtsal PAH ve anoreksijenlere
bağlı PAH (IIa-C)
APAH (IIb-C)
Digoksin (IIb-C)

VAZOREAKTİF

VAZOREAKTİF DEĞİL

DSÖ-FS I-III
KKB (I-C)

Kalıcı yanıt
(DSÖ-FS I-II)

Var

Yok

KKB'yi sürdürün

İLK TEDAVİ

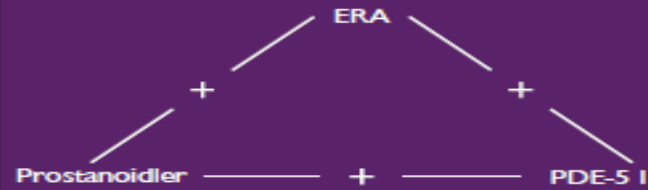
Tavsiye-Kanıt	DSÖ-FS II	DSÖ-FS III	DSÖ-FS IV
I-A	Ambrisentan, Bosentan Sildenafil	Ambrisentan, Bosentan, Sitaksentan, Sildenafil Epoprostenol i.v., İloprost inhale	Epoprostenol i.v.
I-B	Tadalafil†	Tadalafil† Treprostinil subkütan, inhale†	
IIa-C	Sitaksentan	İloprost i.v., Treprostinil i.v..	Ambrisentan, Bosentan, Sitaksentan, Sildenafil, Tadalafil†, İloprost inhale ve i.v. Treprostinil subkütan, i.v., inhale† Başlangıçta kombinasyon tedavisi
IIb-B		Beraprost	

KLİNİK YANIT YETERSİZ

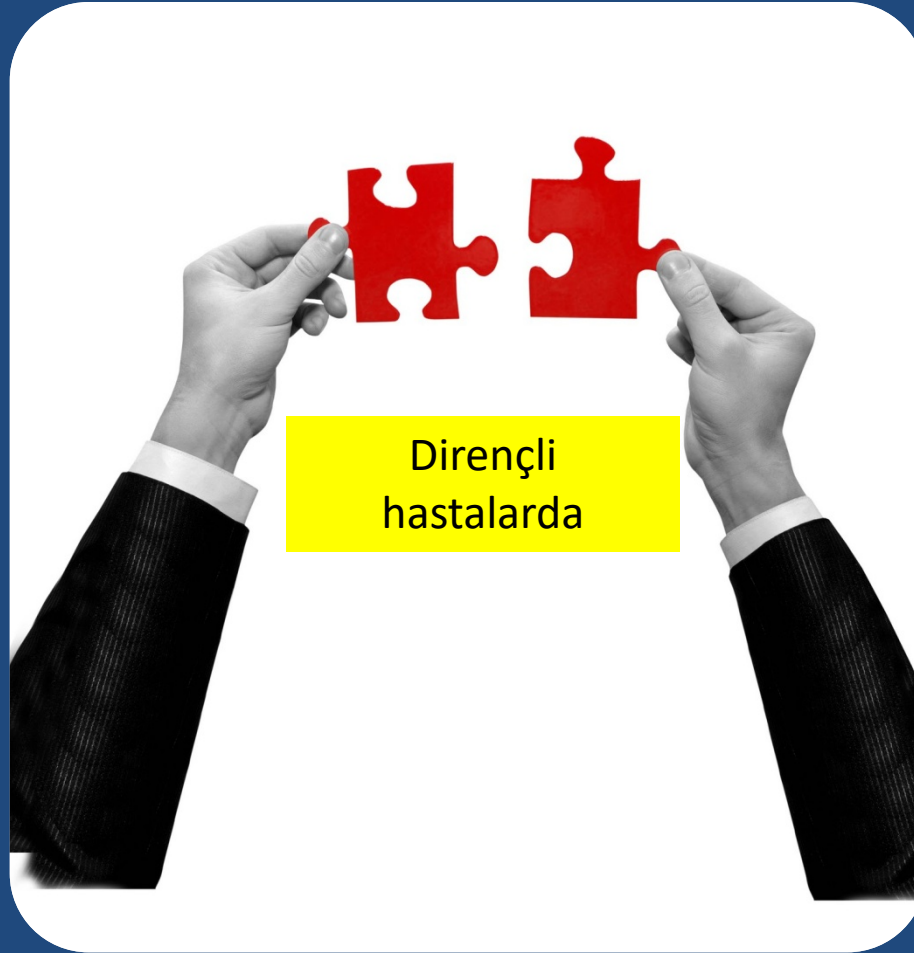
KLİNİK YANIT YETERSİZ

BAS (I-C) ve/veya Akciğer
transplantasyonu (I-C)

Ardışık kombinasyon tedavisi (IIa-B)§



Kombinasyon Tedavileri

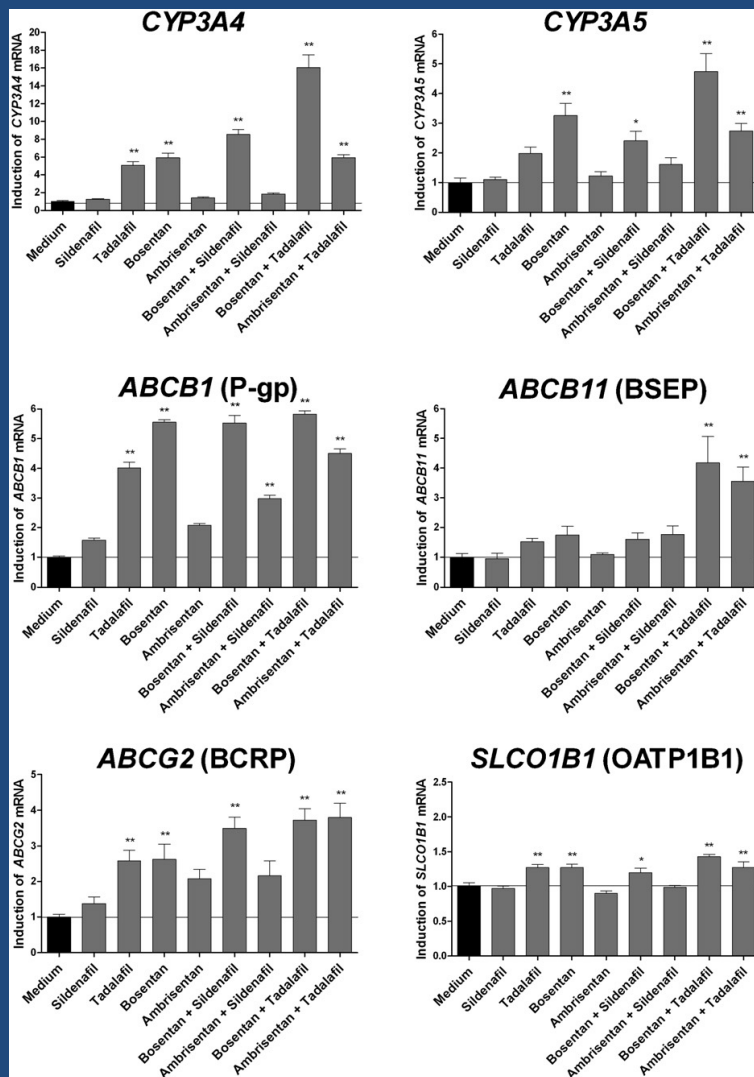


Kombinasyon

- 2 veya daha fazla ilaç
- 3-6 ay sonra değerlendirme
- Klinik cevap yeterli değilse
- İlk tedavi olarak başlanılabilir (evre 4)
- Çoğunlukla ardışık olarak

Influence of sildenafil and tadalafil on the enzyme- and transporter-inducing effects of bosentan and ambrisentan in LS180 cells

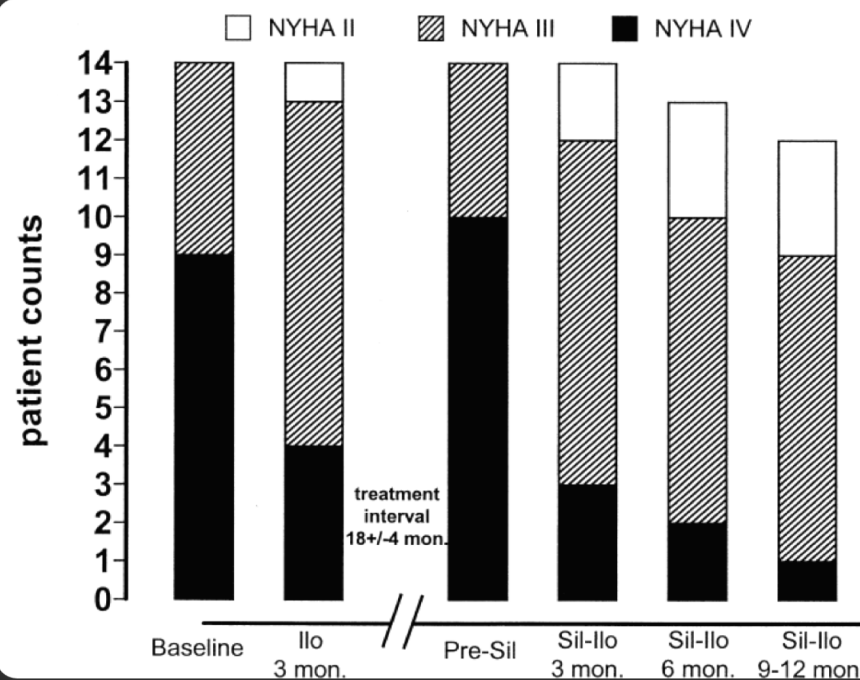
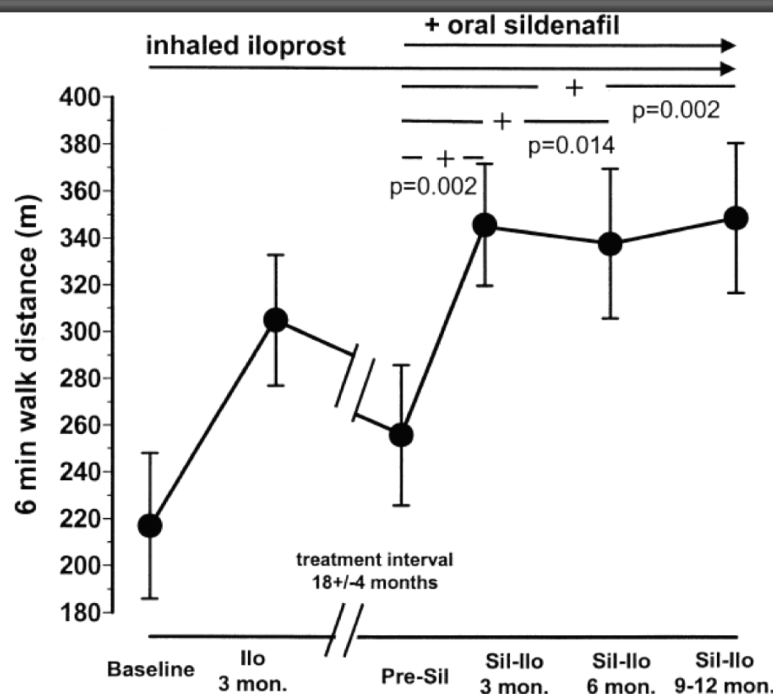
Johanna Weiss*, Dirk Theile, Adriana Spalwisch, Jürgen Burhenne, Klaus-Dieter Riedel, Walter Emil Haefeli



- Kombinasyon tedavisinde ilaçlar birbirlerini etkilese bile invitro ve klinik olarak etkilerini azalttığı gösterilememiştir.

Oral Sildenafil as Long-Term Adjunct Therapy to Inhaled Iloprost in Severe Pulmonary Arterial Hypertension

Hossein A. Ghofrani, MD, Frank Rose, MD, Ralph T. Schermuly, PhD, Horst Olschewski, MD, Ralph Wiedemann, MD, André Kreckel, MD, Norbert Weissmann, PhD, Stefanie Ghofrani, MD, Beate Enke, MD, Werner Seeger, MD, Friedrich Grimminger, MD, PhD
Giessen, Germany

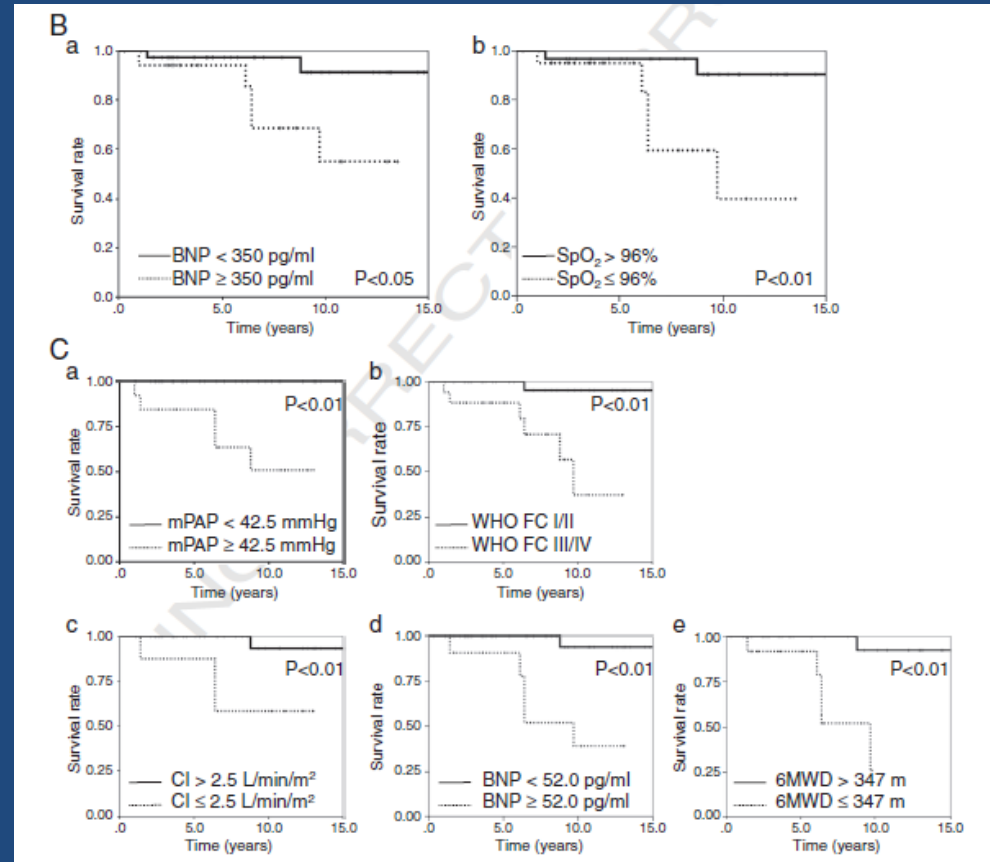
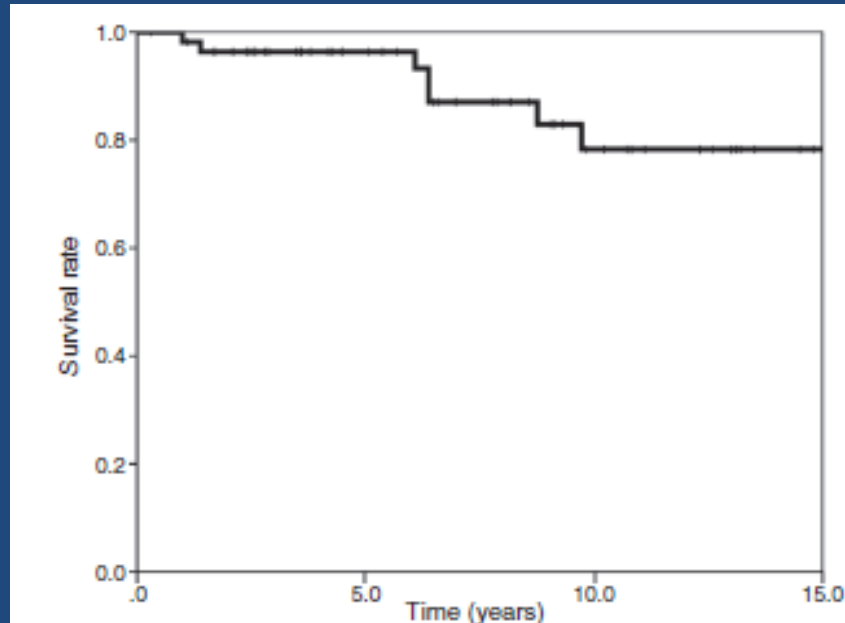


Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan

Aiko Ogawa^a, Kentaro Ejiri^b, Hiromi Matsubara^{a,b,*}

^a Department of Clinical Science, National Hospital Organization Okayama Medical Center, Okayama, Japan

^b Division of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan



Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan

Aiko Ogawa^a, Kentaro Ejiri^b, Hiromi Matsubara^{a,b,*}

^a Department of Clinical Science, National Hospital Organization Okayama Medical Center, Okayama, Japan

^b Division of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan

Table 1

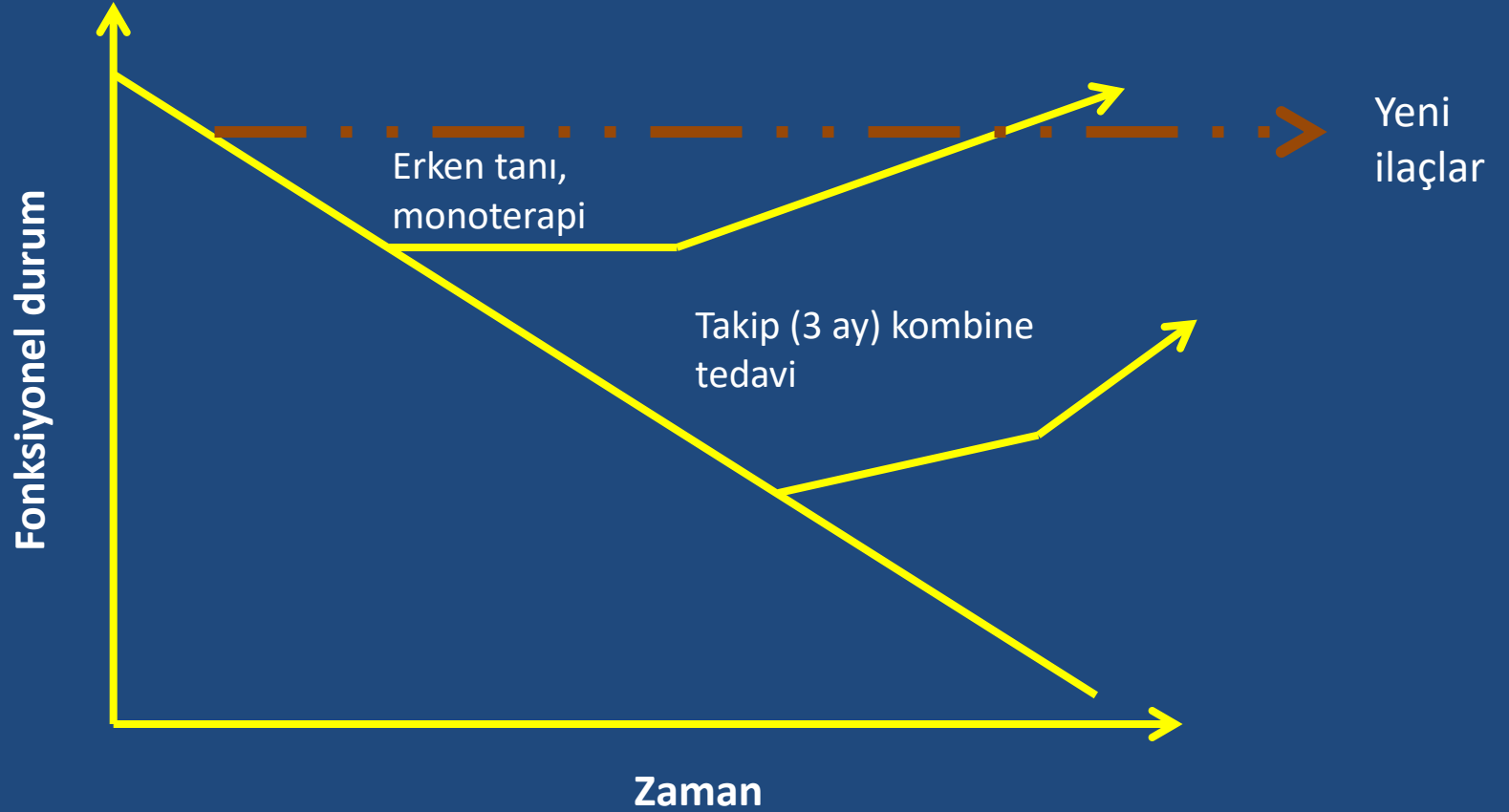
Clinical and hemodynamic data of survivors and non-survivors at baseline.

	Survivor (n = 49)	Non-survivor (n = 7)	P
Age, years	33 ± 18	25 ± 10	0.26
Male, n (%)	14 (29)	1 (14)	0.43
HPAH, n (%)	10 (20)	0 (0)	0.41
WHO functional class (I/II/III/IV)	3 (0/2/34/13)	4 (0/0/2/5)	<0.01
6MWD (m)	257 ± 166	103 ± 179	<0.05
BNP (pg/mL)	260 ± 307	705 ± 556	<0.01
Uric acid (mg/dL)	6.3 ± 2.0	6.7 ± 1.0	0.66
mPAP (mm Hg)	61 ± 17	62 ± 14	0.95
RAP (mm Hg)	8 ± 4	13 ± 9	<0.05
PCWP (mm Hg)	9 ± 3	10 ± 5	0.82
SvO ₂ (%)	66.1 ± 8.7	65.4 ± 10.1	0.86
Cardiac index (L/min/m ²)	2.4 ± 0.9	2.4 ± 0.9	0.82
PVR (dyns/cm ⁵)	1391 ± 615	1375 ± 537	0.96
Heart rate (bpm)	74 ± 16	86 ± 15	0.07
SpO ₂ (%)	97 ± 3	95 ± 3	0.08
Treatment			
Oral PGI ₂	9 (18)	0 (0)	0.22
IV PGI ₂	37 (76)	6 (86)	0.55
Dose of epoprostenol (ng/kg/min)	79.6 ± 43.2	54.0 ± 47.8	0.19
ERA	34 (69)	4 (57)	0.52
PDE5 inhibitor	28 (57)	1 (14)	<0.05
Monotherapy	10 (20)	3 (43)	0.24
Combination therapy	38 (78)	4 (57)	0.24
Number of PAH-targeted drugs: 2	16 (33)	4 (57)	0.21
Number of PAH-targeted drugs: 3	22 (45)	0 (0)	<0.05
Warfarin	11 (22)	2 (29)	0.72
Oxygen therapy	46 (94)	7 (100)	0.50

Clinical and hemodynamic data before and after treatment.

	Baseline	Follow-up	P
Age, years	32 ± 17		
WHO functional class (I/II/III/IV)	3 (0/1/38/17)	2 (0/38/15/3)	<0.01
6MWD (m)	234 ± 174	378 ± 114	<0.01
BNP (pg/mL)	313 ± 372	67 ± 156	<0.01
Uric acid (mg/dL)	6.4 ± 1.9	6.2 ± 1.7	0.70
mPAP (mm Hg)	63 ± 15	35 ± 10	<0.01
RAP (mm Hg)	8 ± 4	5 ± 4	<0.01
PCWP (mm Hg)	9 ± 3	8 ± 4	0.31
SvO ₂ (%)	66.2 ± 8.9	77.2 ± 5.7	<0.01
Cardiac index (L/min/m ²)	2.3 ± 0.8	3.5 ± 0.9	<0.01
PVR (dyns/cm ⁵)	1473 ± 600	481 ± 421	<0.01
Heart rate (bpm)	76 ± 17	82 ± 18	0.09
SpO ₂ (%)	97 ± 3	98 ± 3	0.14

Amaç



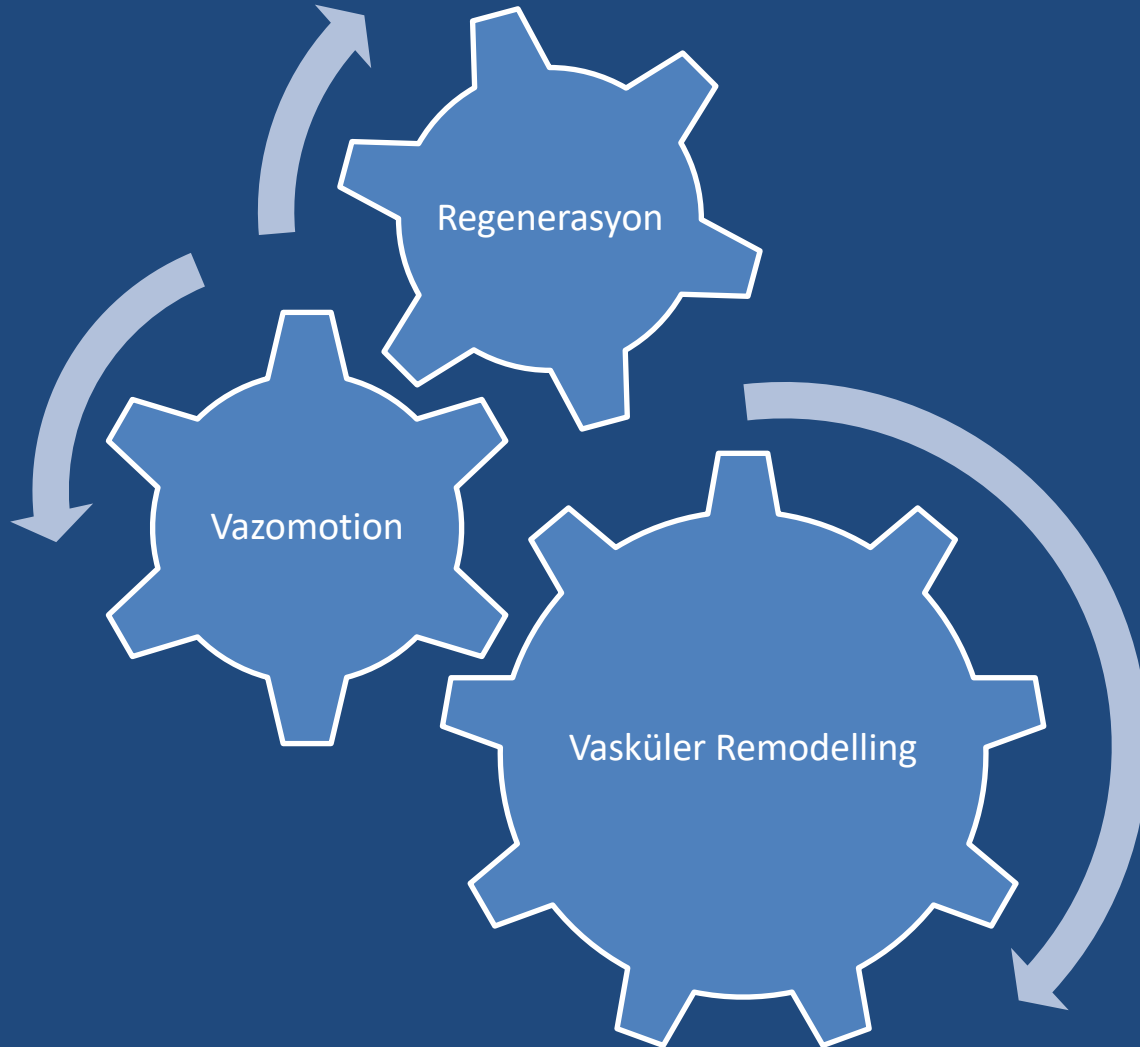
Tedavi

- Akciğer transplantasyonu
- Atriyal septostomi
 - Medikal tedavi uygun değilse palyatif olarak
 - Transplantasyon bekleyen hastalarda
 - Maksimal tedaviye rağmen kötüleşen hastalarda ara tedavi olarak
 - Balon atriyal septostomi teknik olarak
 - Sağ atriyum basıncı >20 mmHg ve $\text{satO}_2 < 85$ ise yapılmamalı

Tedavi Prensipleri

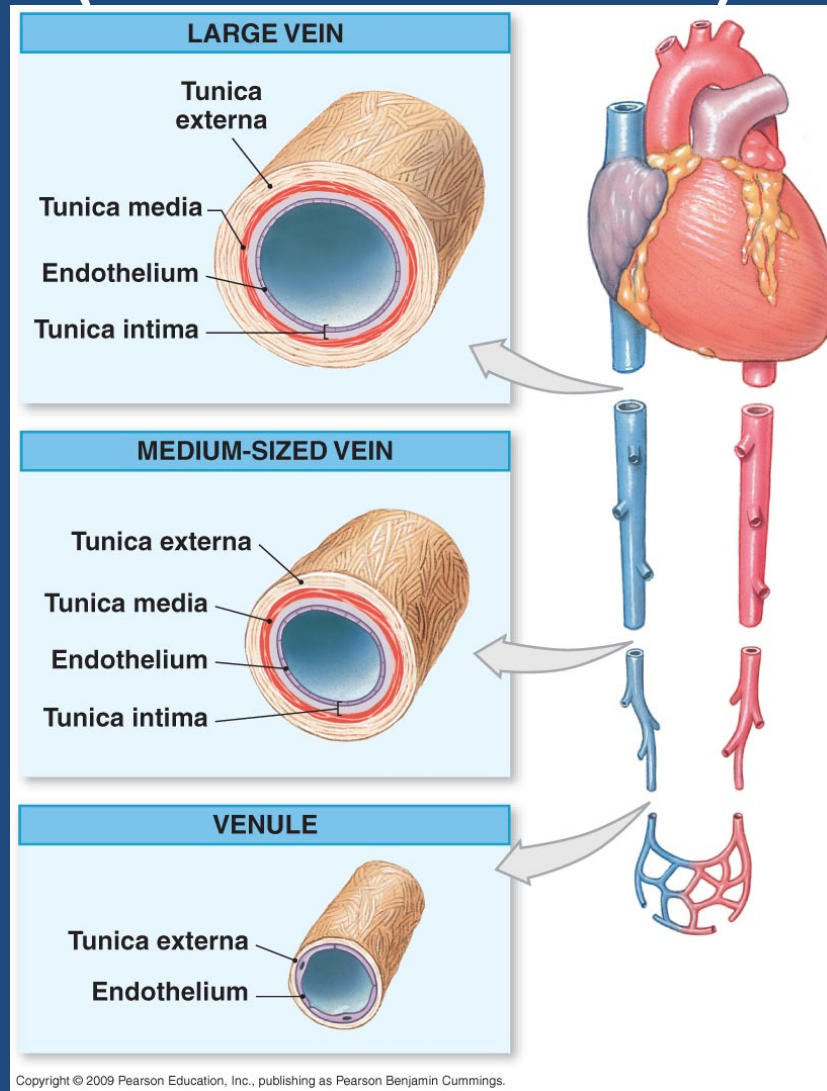
- Genel prensiplerin uygulanması
- Tecrübeli merkezlere hastanın gönderilmesi
- Vazoreaktivite testi (grup1 hastalarda)
 - Vazoreaktif hastalar KKB ile tedavi edilmeli
 - Non-vazoreaktif WHO-2 hastalar oral bir ilaç ile
 - Vazoreaktif fakat WHO-3 de kalanlar oral ilaç ile
- Devamlı iv epoprostenol WHO-4 de ilk seçenek
- WHO-4 hastalarda ilk seçenek olarak kombinasyon tedavisi uygulanabilir
- Cevap yoksa ardışık kombinasyon 3'lü olarak
 - Riociguat ve PDE-5i kombinasyonu kontrendike
- Akciğer transplantasyonu
- Atriyal septostomi

Tedavideki gelişmeler



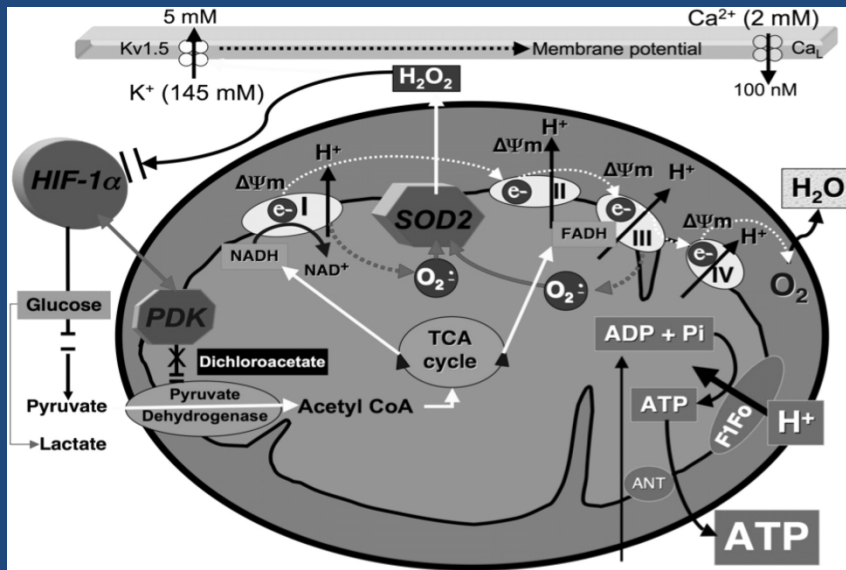
HEDEF-1

(Damar tonüsü)

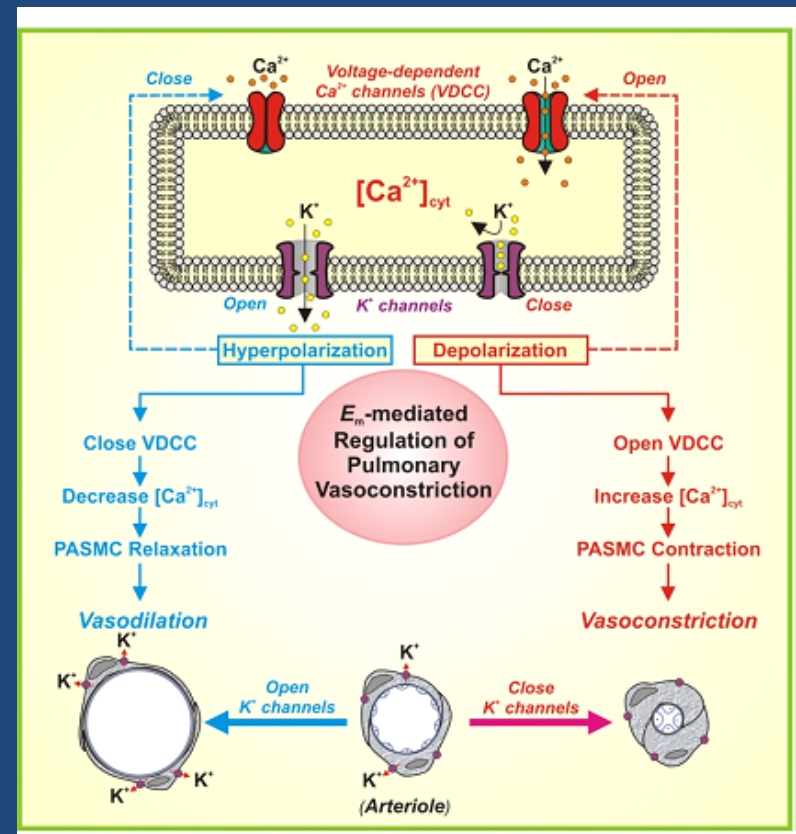


HEDEF-1

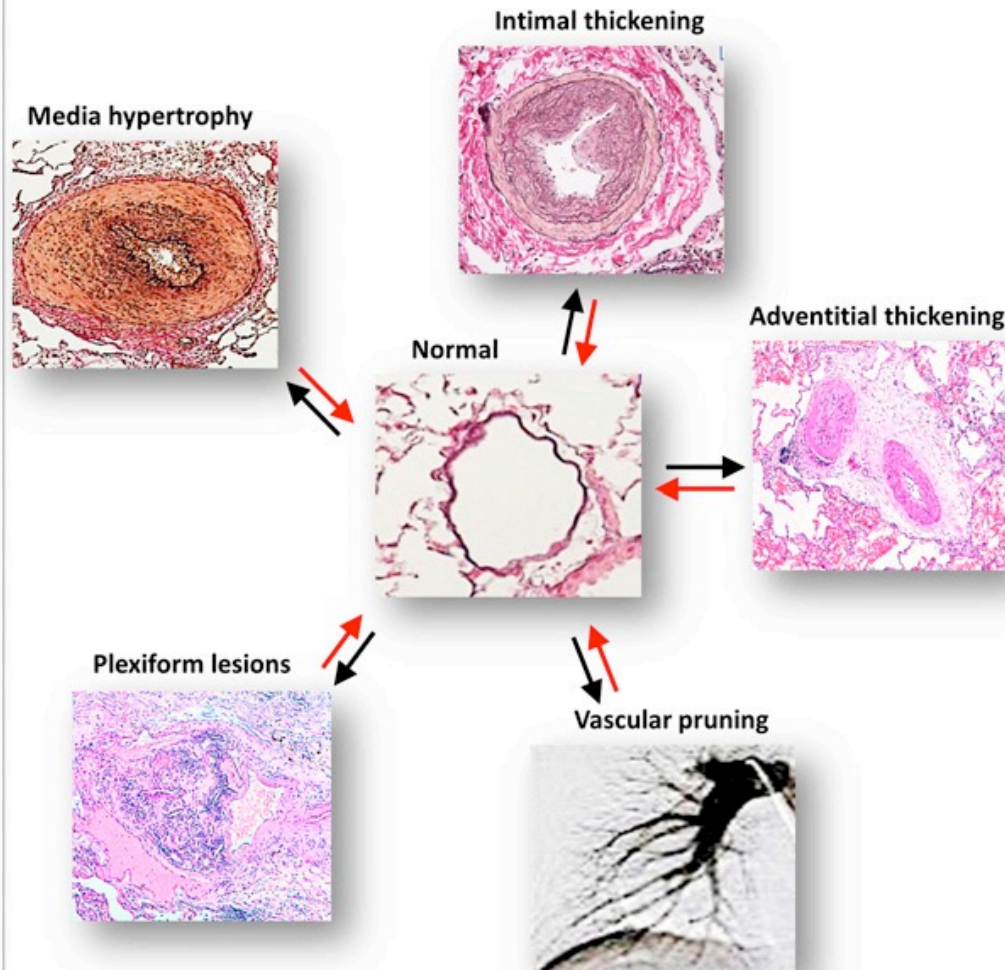
Redox nedenli uyarı hedefi



İyon kanallarındaki düzensizliğin hedeflenmesi



HEDEF-2



Reverse remodeling and regenerative strategies – Class I PH

Anti-proliferative strategies

- Tyrosine kinase inhibitors

Transcription factor based therapies

- NFATc inhibitor
- PPAR γ agonist
- Notch inhibitor

Anti – inflammatory strategies

- SDF1 blocker
- B cell antagonist

Epigenetic modulation based therapies

- microRNA mimics/ antagomirs
- HDAC inhibitors
- DNMT inhibitor

BMPR2 modulation strategies

Regenerative treatment strategies

- Genetically engineered EPCs
- Genetically engineered MSCs

Sonuç

- Spesifik güçlü hedefe yönelik tedaviler
- Hasta için kullanım kolayı olan ilaçlar
- Zamanında uygun tedaviye başlama
- Gerektiğinde Kombinasyon tedavisine geçme

Teşekkürler

