医学信息速递

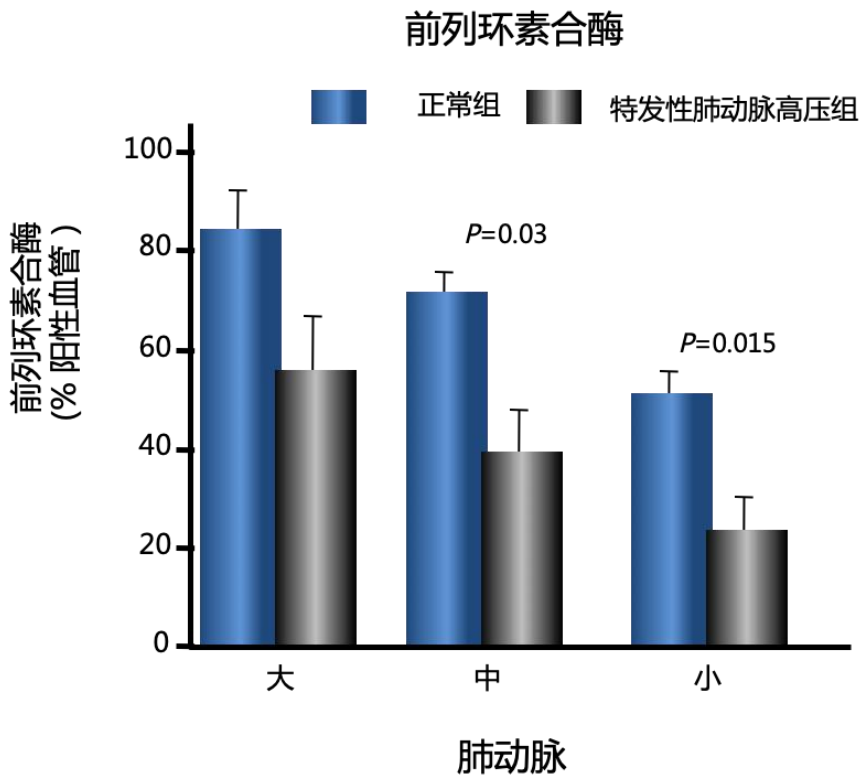
Medical Information Express

医学及信息部　　陈骁康

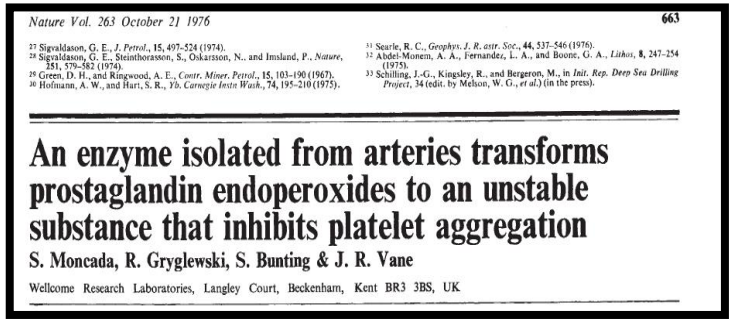
2019/9/9

前列环素“前世今生”

前列环素的诞生



IPAH患者体内前列环素合酶表达减少，前列环素生成减少



Nature Vol. 263 October 21 1976 663

An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation

S. Moncada, R. Gryglewski, S. Bunting & J. R. Vane

Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK

Sr. John R. Vane

1976年发表文章，指出血管能生成一种不稳定的短链脂质介质（PG-X），即前列环素。体外实验证实PG-X具有抑制血小板聚集、扩血管作用。

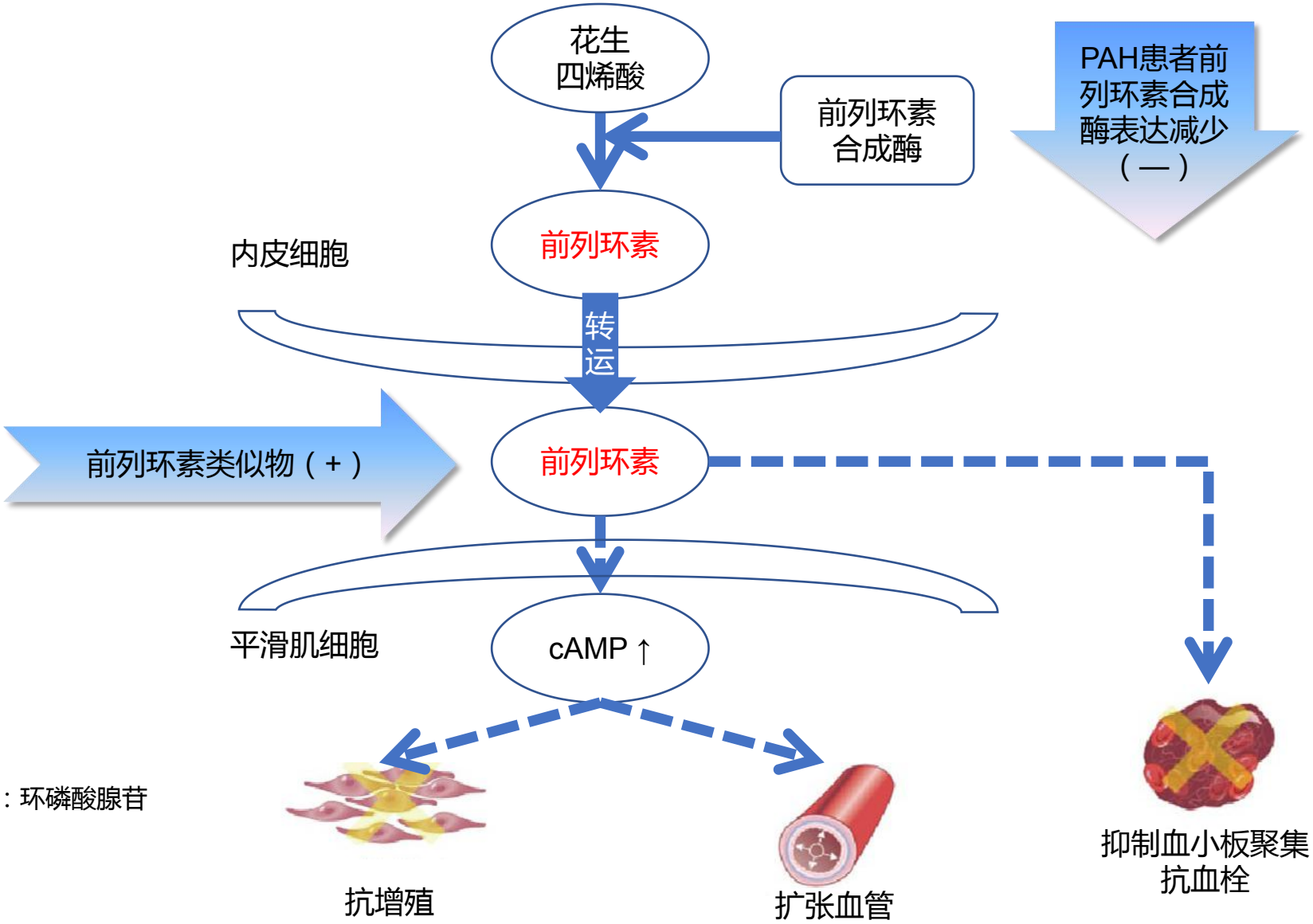
因发现前列腺素及相关生物活性物质。1982年被授予“诺贝尔生理学或医学奖“

先后在实验室合成依前列醇&曲前列尼尔。外源性补充前列环素，抗衡体内缩血管物质，靶向性扩张肺血管。

Tuder et al. Am J Respir Crit Care Med. 1999;159:1925-1932.

https://www.nobelprize.org/prizes/medicine/1982/vane/facts/

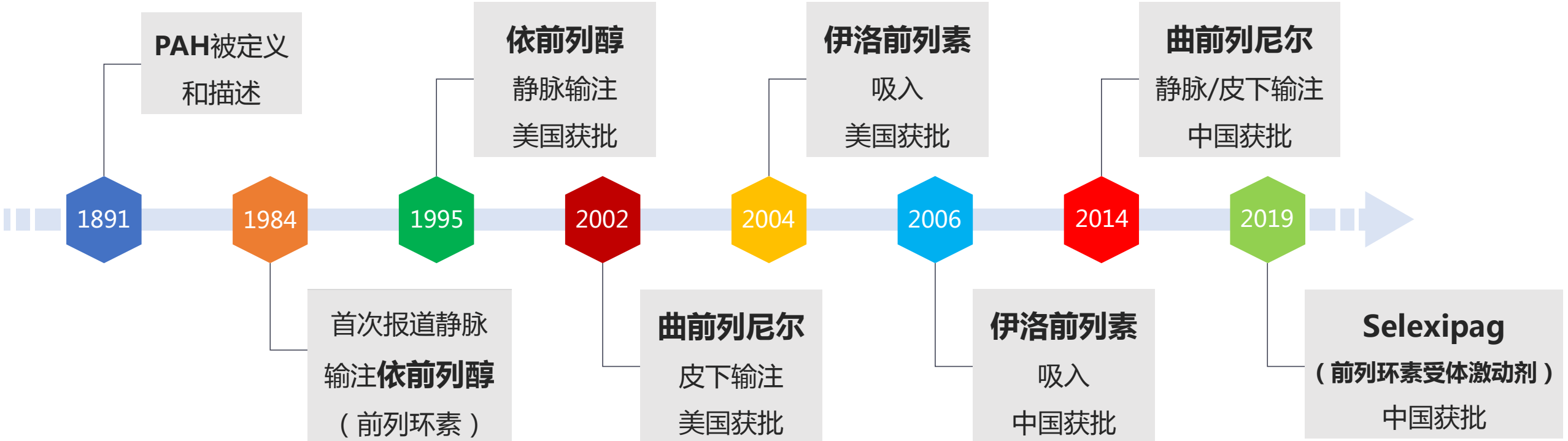
前列环素作用机制



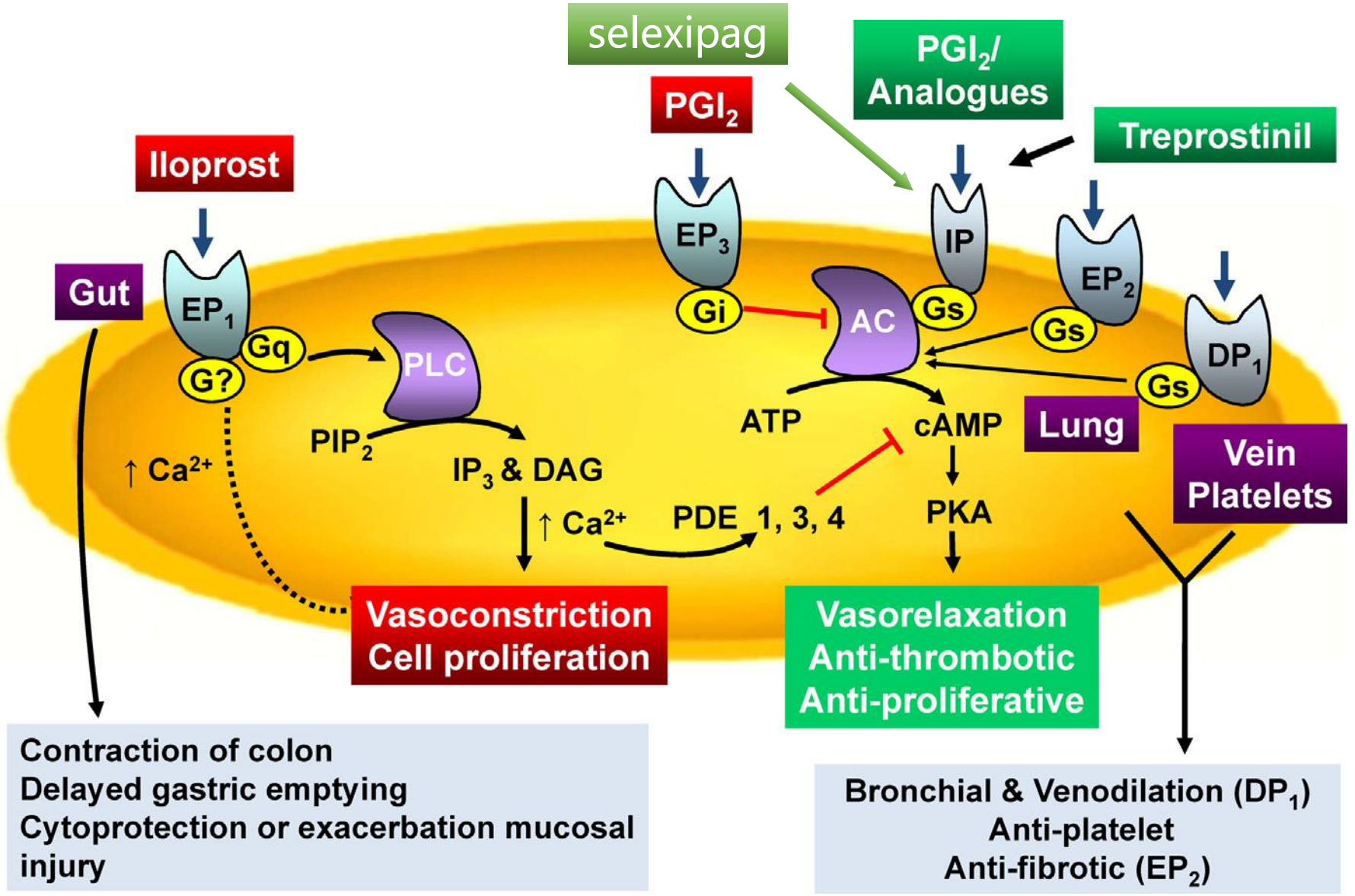
cAMP：环磷酸腺苷

Humbert M et al. N Engl J Med. 2004;351:1425-1436.

前列环素的发展


1891
PAH被定义
和描述
1984
首次报道静脉
输注**依前列醇**
（前列环素）
治疗**PAH**
1995
依前列醇
静脉输注
美国获批
2002
曲前列尼尔
皮下输注
美国获批
2004
伊洛前列素
吸入
美国获批
2006
伊洛前列素
吸入
中国获批
2014
曲前列尼尔
静脉/皮下输注
中国获批
2019
Selexipag
（前列环素受体激动剂）
中国获批

前列环素及其类似物受体作用机制

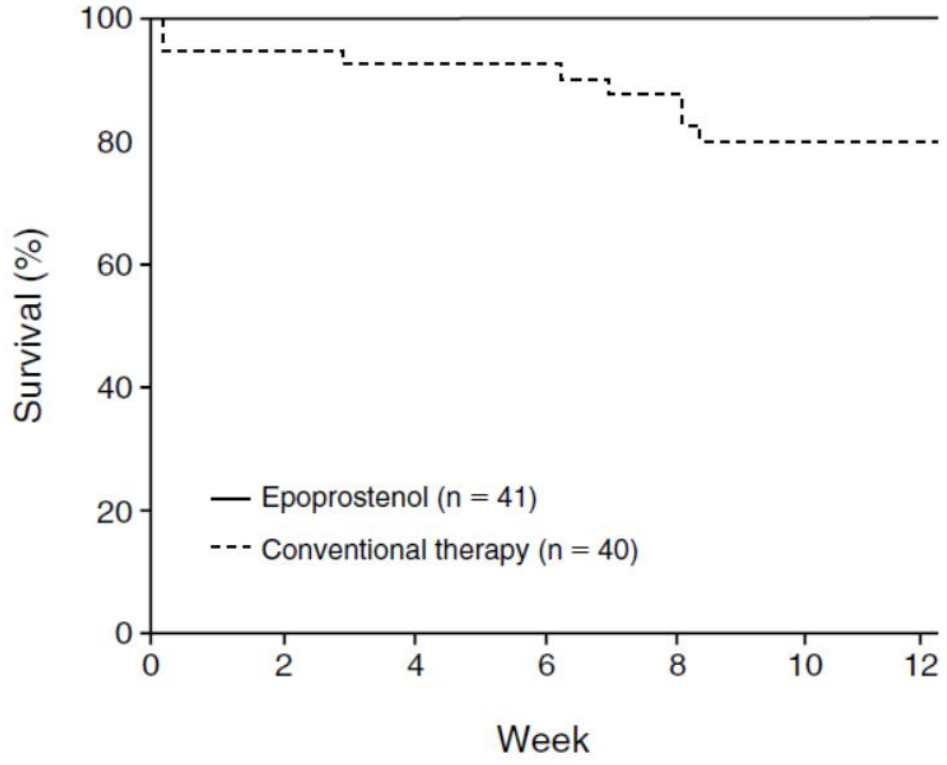


Lucie H. Clapp, et al. Prostaglandins and Other Lipid Mediatiors. 2015,120: 56-71.

依前列醇—首个用于治疗PAH的前列环素

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

ROBYN J. BARST, M.D., LEWIS J. RUBIN, M.D., WALKER A. LONG, M.D., MICHAEL D. MCGOON, M.D., STUART RICH, M.D., DAVID B. BADESCH, M.D., BERTRON M. GROVES, M.D., VICTOR F. TAPSON, M.D., ROBERT C. BOURGE, M.D., BRUCE H. BRUNDAGE, M.D., SPENCER K. KOERNER, M.D., DAVID LANGLEBEN, M.D., CESAR A. KELLER, M.D., SRINIVAS MURALI, M.D., BARRY F. URETSKY, M.D., LINDA M. CLAYTON, PHARM.D., MARIA M. JÖBSIS, B.A., SHELMER D. BLACKBURN, JR., B.A., DENISE SHORTINO, M.S., JAMES W. CROW, PH.D., FOR THE PRIMARY PULMONARY HYPERTENSION STUDY GROUP*



- 前瞻性、随机、开放、对照试验。
- 81例NYHA III-IV级PAH患者。
- 12周后静脉依前列醇组的6MWD明显增加，肺动脉平均压及肺血管阻力降低。
- 常规治疗组8人在试验期间死亡，依前列醇组无死亡病例。

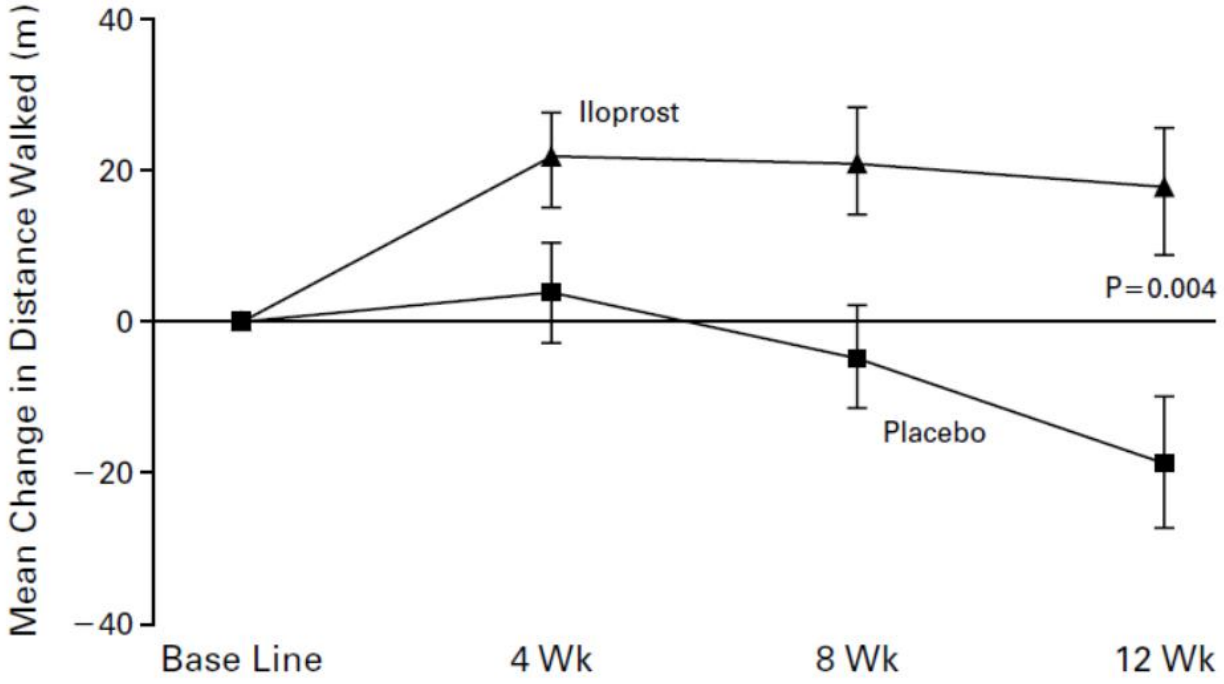
Barst, RJ et al. N Engl J Med.1996 Feb 01 ;334(5):296-301.

伊洛前列素—吸入治疗PAH

LEE'S PHARM. 李氏大藥廠 Department of medicine and information 医学及信息部

INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION

HORST OLSCHEWSKI, 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*



- 多中心随机双盲对照研究。
- 203例NYHA III-IV级PAH患者。
- 至少心功能改善及6MWD提高10%为主要有效性观察终点。
- 吸入伊洛前列素组的有效率为16.8%，对照组仅为4.9%。

Olschewski, H et al. N Engl J Med.2002 Aug 01 ;347(5):322-9.

曲前列尼尔—治疗肺动脉高压

LEE'S PHARM. 李氏大藥廠 Department of medicine and information 医学及信息部

Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension

A Double-blind, Randomized, Placebo-controlled Trial

GERALD SIMONNEAU, ROBYN J. BARST, NAZZARENO GALIE, ROBERT NAEIJE, STUART RICH, ROBERT C. BOURGE, ANNE KEOGH, RONALD OUDIZ, ADAANI FROST, SHELMER D. BLACKBURN, JAMES W. CROW, and LEWIS J. RUBIN, for the Treprostinil Study Group

- 一项随机、双盲、安慰剂对照试验。
- 1998年12月-1999年10月，40个中心，470名患者。
- NYHA FC III-IV级：416/469（88.7%）
- 曲前列尼尔显著改善6MWD、血流动力学、呼吸困难指数、肺动脉高压症状和体征。

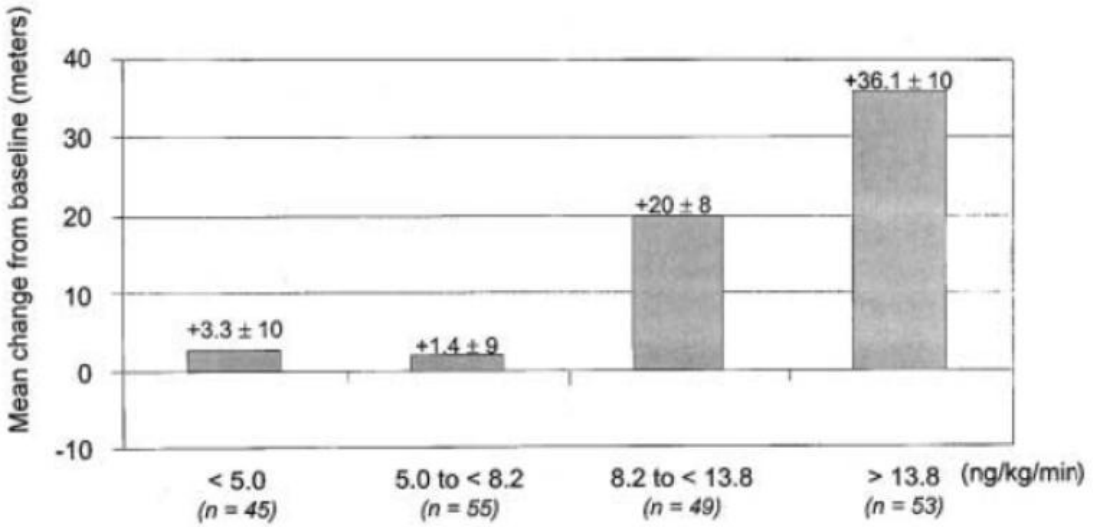


Figure 1. Mean change in the six-minute walk distance from baseline to Week 12 versus Week 12 trepostinil dose quartile.

TABLE 4. CARDIOPULMONARY HEMODYNAMICS: CHANGE FROM BASELINE TO WEEK 12

	Treprostinil	Placebo	p Value
Heart rate, beats/min	−0.5 ± 0.8	−0.8 ± 0.7	ns
Mean right atrial pressure, mm Hg	−0.5 ± 0.4	+1.4 ± 0.3	0.0002
Mean pulmonary artery pressure, mm Hg	−2.3 ± 0.5	+0.7 ± 0.6	0.0003
Cardiac index, L/min/m^2	+0.12 ± 0.04	−0.06 ± 0.04	0.0001
Pulmonary vascular resistance index, units/m^2	−3.5 ± 0.6	+1.2 ± 0.6	0.0001
Mean systemic artery pressure, mm Hg	−1.7 ± 0.9	−1.0 ± 0.9	ns
Systemic vascular resistance index, units/m^2	−3.5 ± 0.9	−0.8 ± 0.8	0.0012
Mixed venous oxygen saturation, %	+2.0 ± 0.8	−1.4 ± 0.7	0.0001

Simonneau, G et al. Am J Respir Crit Care Med.2002 Mar 15 ;165(6):800-4.

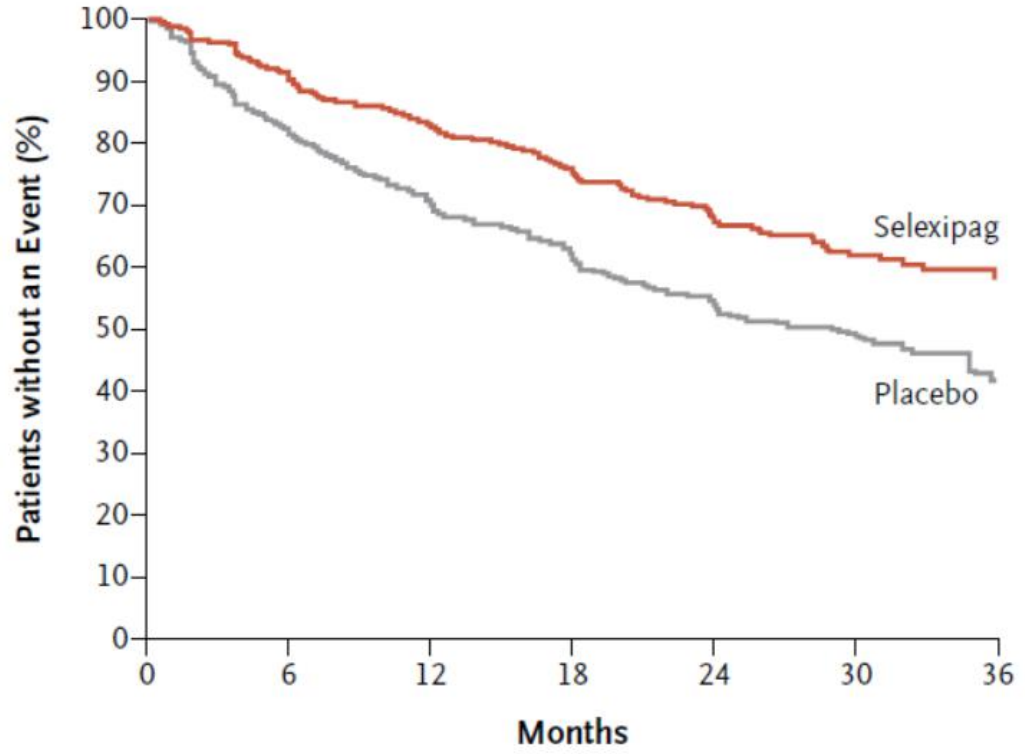
Selexipag—前列环素受体激动剂

The NEW ENGLAND JOURNAL of MEDICINE

Selexipag for the Treatment of Pulmonary Arterial Hypertension

Olivier Sitbon, M.D., Richard Channick, M.D., Kelly M. Chin, M.D., Aline Frey, Pharm.D., Sean Gaine, M.D., Nazzareno Galiè, M.D., Hossein-Ardeschir Ghofrani, M.D., Marius M. Hoeper, M.D., Irene M. Lang, M.D., Ralph Preiss, M.D., Lewis J. Rubin, M.D., Lilla Di Scala, Ph.D., Victor Tapson, M.D., Igor Adzerikho, M.D., Jinming Liu, M.D., Olga Moiseeva, M.D., Xiaofeng Zeng, M.D., Gérald Simonneau, M.D., and Vallerie V. McLaughlin, M.D., for the GRIPHON Investigators*

- 随机，双盲，安慰剂对照试验。
- 1156名肺动脉高压患者。
- 397例主要终点事件-安慰剂组41.6% vs selexipag组27.0%。
- 由于不良事件过早终止既定方案-安慰剂组7.1% vs selexipag组14.3%。



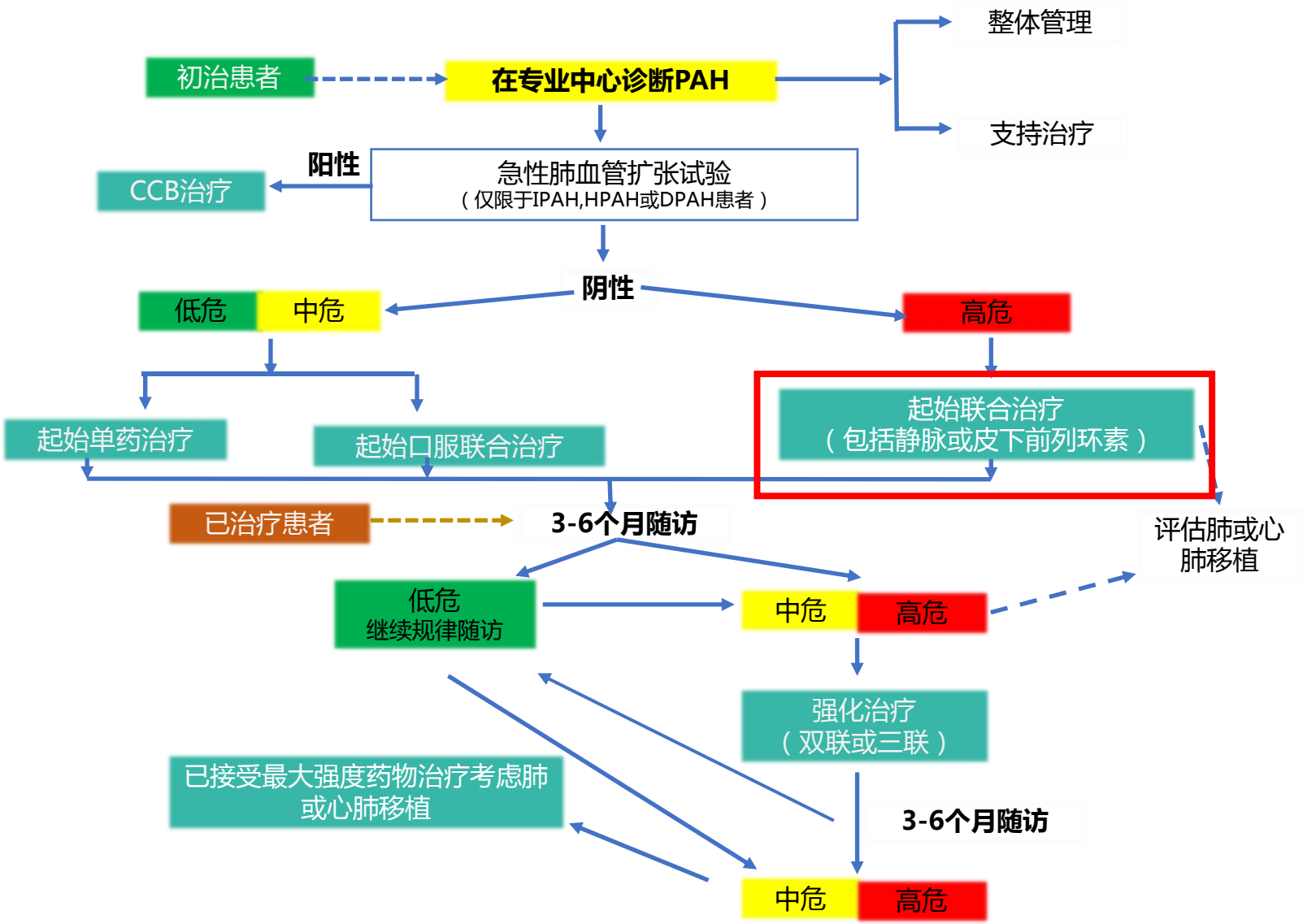
No. at Risk							
Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

Sitbon, O et al. N Engl J Med.2015 Dec 24 ;373(26):2522-33.

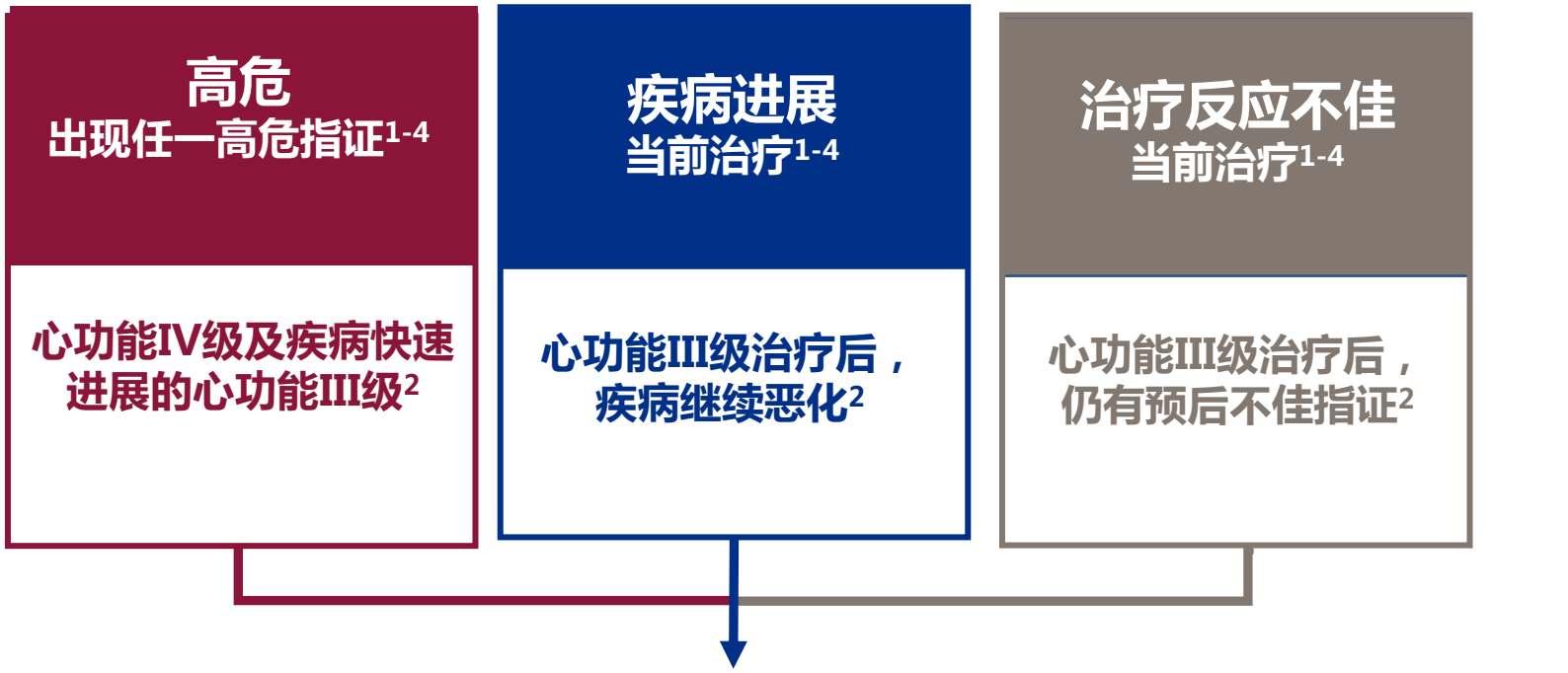
肺动脉高压患者危险分层（2018中国指南）

指标	低风险	中等风险	高风险
WHO心功能分级	Ⅰ级、Ⅱ级	Ⅲ级	Ⅳ级
6min步行距离（m）	>440	165~440	<165
NT- proBNP（ng/L）	<300	300~1400	>1400
RAP（mmHg）	<8	8~14	>14
CI（$L \cdot min^{-1} \cdot m^{-2}$）	≥2.5	2.1~2.4	≤2.0
SvO_2（%）	>65	60~65	<60
危险分层标准	至少3种低风险指标且无高风险指标	介于低风险和高风险之间	至少2个高风险指标，其中必须包括CI和SvO_2

肺动脉高压患者治疗（2018中国指南）



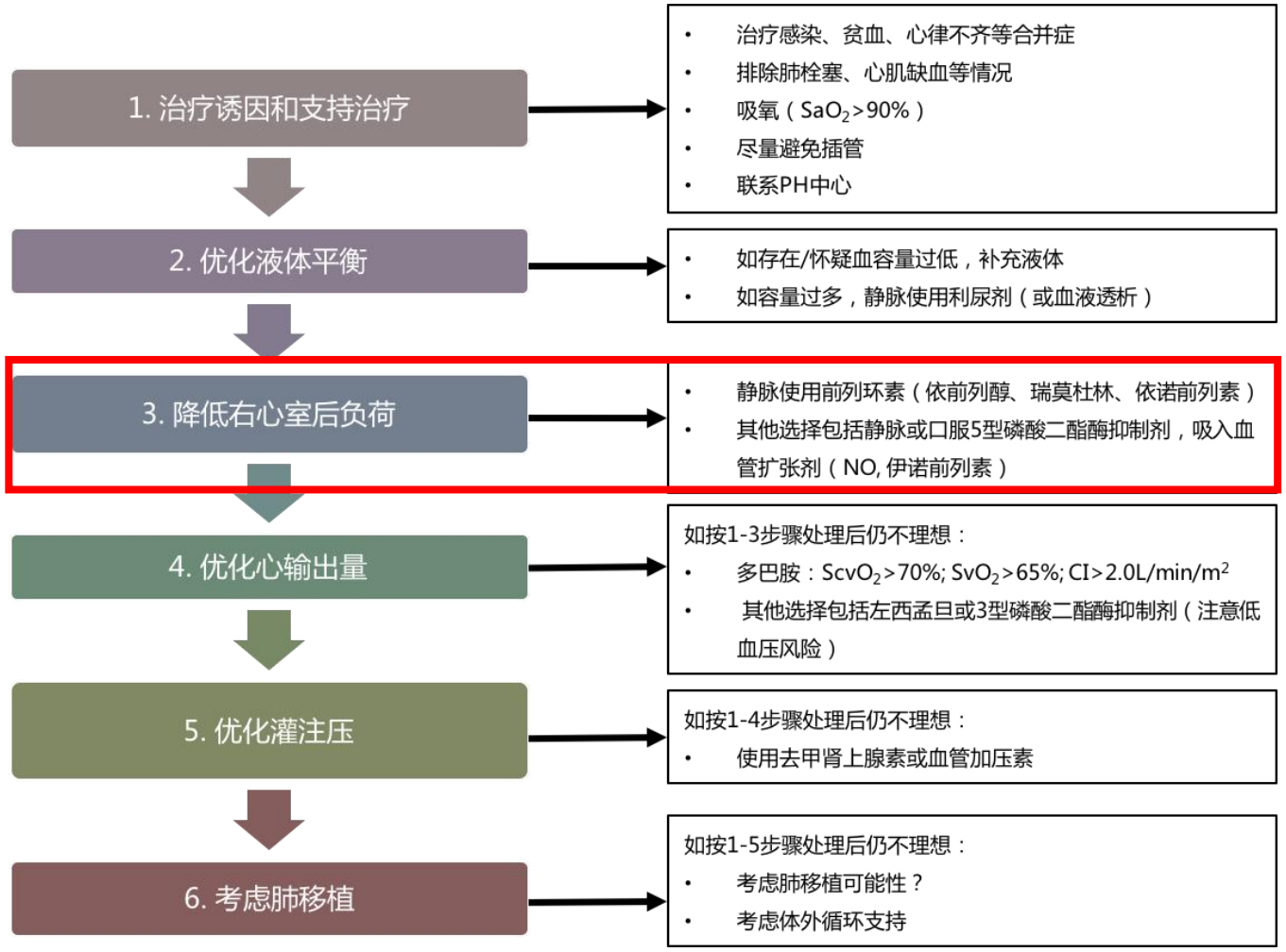
前列环素治疗优势-指南推荐治疗



ACCF=American College of Cardiology Foundation; AHA=American Heart Association; ERS=European Respiratory Society; ESC=European Society of Cardiology; FC=Functional Class.

References: 1. McLaughlin et al. J Am Coll Cardiol. 2009;53(17):1573-1619. **2.** Taichman et al. Chest. 2014;146(2):449-475. **3.** Galiè et al. Eur Heart J. 2016;37(1):67-119. **4.** Galiè et al. J Am Coll Cardiol. 2013;62(25 suppl):D60-72.

围术期急性右心衰竭管理



Hoeper MM. Am J Respir Crit Care Med. 2011; 1114–1124.

Table 8 Peri-operative haemodynamic goals.

Systolic blood pressure ≥ 90 mmHg and/or 40 mmHg above sPAP
MAP ≥ 65 and/or 20 mmHg above mPAP
mPAP < 35 mmHg or 25 mmHg lower than MAP
PVR/SVR ratio < 0.5 or aim for pre-operative PVR/SVR ratio
RAP the lowest possible that maintains MAP > 65 mmHg
Cardiac index ≥ 2.2 $l.min^{-1}.m^2$

sPAP, systolic pulmonary artery pressure; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PVR/SVR ratio, pulmonary vascular resistance/systemic vascular resistance ratio; RAP, right atrial pressure.

围术期血流动力学目标：

- 平均体循环压>=65 和（或）超过平均肺动脉压 20 mmHg以上；
- 平均肺动脉压<35 mmHg 或 至少 低于平均体循环压 25mmHg；
- PVR/SVR<0.5
- 右房压越低越好

Pilkington SA, et al. Anaesthesia 2015, 70, 56–70

围术期PH静脉用药

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Table 3. Intravenous Therapy for the Perioperative Management of PH

	Dose	Mechanism of Action	Comments
Vasodilators			
Epoprostenol	2 mg/kg/min, titrate up	↑ cAMP via G protein-coupled receptor	Inhibition of platelet aggregation; systemic hypotension; rebound PH after discontinuation (epoprostenol > iloprost > treprostinil)
Iloprost	1 ng/kg/min, titrate up		
Treprostinil	2 ng/kg/min, titrate up		
Sildenafil	10 mg 3 times daily (equivalent to 20 mg PO 3 times daily)	PDE-5 inhibitor; ↑ cGMP	Approved for use in patients unable to continue PO form
Nesiritide	2 μg/kg followed by 0.01-0.03 μg/kg/min	↑ cGMP via G protein-coupled receptor	Natriuresis and diuresis; ↑ capillary permeability
Nitroprusside	0.2-2 μg/kg/min	Releases NO that activates guanylyl cyclase and ↑ cGMP	Systemic hypotension; risk of cyanide toxicity; tachyphylaxis
Nitroglycerin	0.5-2.5 μg/kg/min	Converted to NO by aldehyde dehydrogenase	Systemic hypotension
Nicardipine	5-20 mg/h	CCB; ↓ intracellular Ca	Systemic hypotension

停药后反跳（依前列醇>伊洛前列素>曲前列尼尔）

Christopher A. Journal of Cardiothoracic and Vascular Anesthesia, Vol 27, No 3 (June), 2013: pp 551-572.

围术期PH用药

Perioperative Anesthesiological Management of Patients with Pulmonary Hypertension

Jochen Gille,[1] Hans-Jürgen Seyfarth,[2] Stefan Gerlach,[1] Michael Malcharek,[1] Elke Czeslick,[3] and Armin Sablotzki[1]

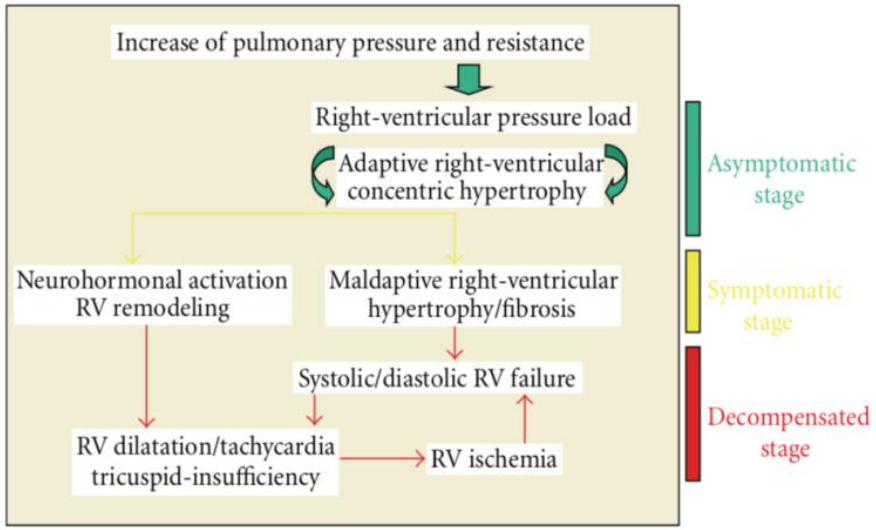


Figure 1: Development of right-ventricular failure in patients with pulmonary hypertension.

Table 4: Therapy of pulmonary hypertension: approved drugs (mod. [8]).

Drug		Dosage	Side effect
Bosentan	Endothelin receptor antagonist	2 × 62,5–125 mg/d po	Increase of liver enzymes edema
Ambrisentan	Selective endothelin-A Receptor-antagonist	1 × 5–10 mg/d po	Increase of liver enzymes edema
Sildenafil	PDE-5 inhibitor	3 × 20 mg/d po	Reflux esophagitis
Tadalafil	PDE-5 inhibitor	1 × 40 mg/d po	Headache and pain in the limbs
Iloprost	Prostacyclin-analog	6–9 × 2,5/5 μg inhalative	Hypotension and flush
Treprostinil	Prostacyclin-analog	1,25–22,5 ng/kg/min s.c.	Local pain

Gille, J et al. Anesthesiol Res Pract.2012 ;2012:356982.

肠外前列环素 VS 口服药物

Influence of various therapeutic strategies on right ventricular morphology, function and hemodynamics in pulmonary arterial hypertension

Roberto Badagliacca, MD, PhD[a,*], Amresh Raina, MD[b], Stefano Ghio, MD[c], Michele D'Alto, MD[d], Marco Confalonieri, MD[e], Michele Correale, MD[f], Marco Corda, MD[g], Giuseppe Paciocco, MD[h], Carlo Lombardi, MD[i], Massimiliano Mulè, MD[j], Roberto Poscia, MD[a], Laura Scelsi, MD[c], Paola Argiento, MD[d], Susanna Sciomer, MD[a], Raymond L. Benza, MD[b], Carmine Dario Vizza, MD[a]

患者人群：10个中心的69名连续治疗的初治IPAH患者

治疗时间：155 +/- 65天（3-7个月）

考察终点：PVR；心超参数；达“低危”人数比例

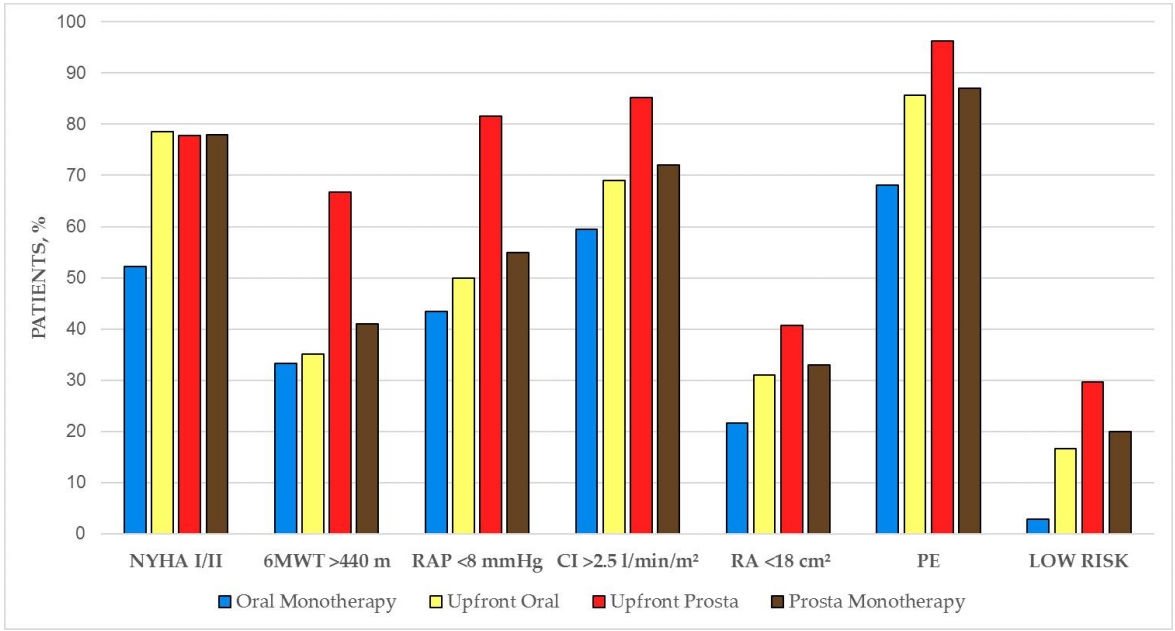
各治疗组达“低危标准”比例：

起始联合组：PGI_2+ERA或PDE5i：29.6%

单药组PGI_2：22.2%

口服起始联合组：ERA+PDE5i：16.7%

口服单药组ERA或PDE5i：2.8%



前列环素为基础的治疗

优于口服药物联合治疗

Badagliacca, R et al. J Heart Lung Transplant.2018 Mar ;37(3):365-375.

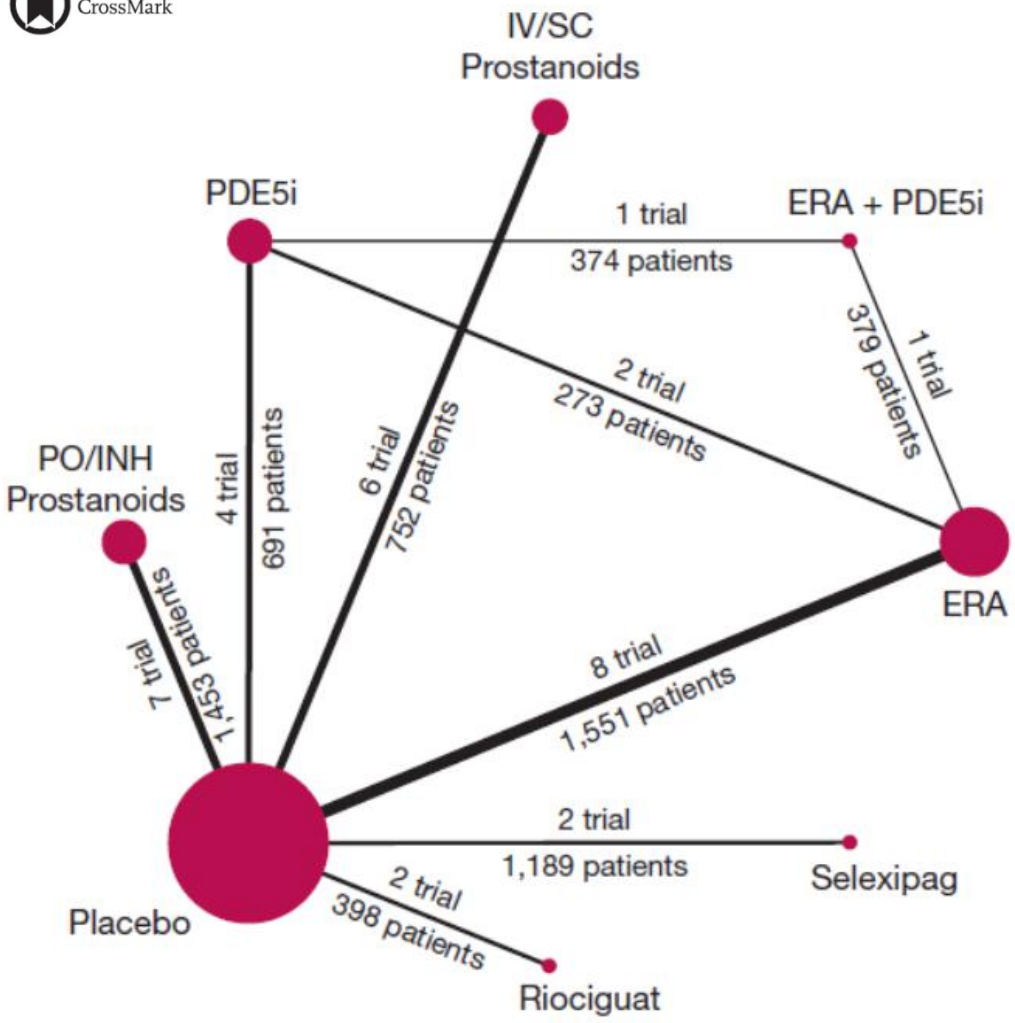
肠外前列环素 VS 口服药物

LEE'S PHARM. 李氏大藥廠 Department of medicine and information 医学及信息部

Comparative Effectiveness of Pharmacologic Interventions for Pulmonary Arterial Hypertension

A Systematic Review and Network Meta-Analysis

Snigdha Jain, MD; Rohan Khera, MD; Saket Girotra, MD, SM; David Badesch, MD; Zhen Wang, PhD; Mohammad Hassan Murad, MD; Amy Blevins, MALS; Gregory A. Schmidt, MD; Siddharth Singh, MD; and Alicia K. Gerke, MD



31个随机对照试验

共6,565名患者

Jain, S et al. Chest.2017 Jan ;151(1):90-105.

肠外前列环素 VS 口服药物

NYHA/WHO FC至少改善1级，81.8% IV/SC前列环素组（RR 5.06; 95% CI 2.32-11.04），28.3% ERA+PDE5i（RR 1.75; 95% CI 1.05-2.92），16.2% 安慰剂组。

Efficacy in reducing clinical worsening as risk ratio (95% CI)	Efficacy in improving functional status as risk ratio (95% CI)							
	ERA	1.02 (0.70-1.50)	0.89 (0.48-1.65)	**0.31 (0.14-0.70)**	1.10 (0.56-2.17)	0.89 (0.55-1.45)	1.01 (0.56-1.82)	**1.56 (1.22-2.00)**
	1.37 (0.86-2.18)	**PDE5i**	0.87 (0.45-1.68)	**0.30 (0.13-0.71)**	1.08 (0.52-2.24)	0.87 (0.53-1.42)	0.98 (0.51-1.88)	**1.53 (1.06-2.19)**
	0.71 (0.39-1.29)	**0.52 (0.27-1.00)**	**PO/ INH Prostanoid**	**0.35 (0.13-0.89)**	1.24 (0.52-2.94)	1.01 (0.47-2.15)	1.13 (0.52-2.50)	1.76 (0.99-3.13)
	–	–	–	**IV/ SC Prostanoid**	**3.57 (1.31-9.77)**	**2.89 (1.14-7.32)**	**3.26 (1.27-8.41)**	**5.06 (2.32-11.04)**
	2.85 (0.66-12.31)	2.09 (0.47-9.20)	4.02 (0.91-17.68)	–	**Riociguat**	0.81 (0.36-1.83)	0.91 (0.40-2.09)	1.42 (0.75-2.66)
	1.98 (1.10-3.59)	1.45 (0.79-2.66)	**2.79 (1.26-6.20)**	–	0.70 (0.15-3.29)	**ERA + PDE5i**	1.13 (0.54-2.37)	**1.75 (1.05-2.92)**
	0.82 (0.42-1.60)	0.60 (0.29-1.22)	1.15 (0.56-2.35)	–	0.29 (0.06-1.30)	**0.41 (0.18-0.97)**	**Selexipag**	1.55 (0.91-2.66)
	0.53 (0.36-0.78)	**0.39 (0.24-0.62)**	0.75 (0.47-1.19)	–	**0.19 (0.05-0.76)**	**0.27 (0.14-0.52)**	0.65 (0.38-1.12)	**Placebo**

Columns in pink/red represent improvement in FC. Risk ratio >1 with higher improvement.
Bold numbers with darker backgrounds are statistically significant.

Jain, S et al. Chest.2017 Jan ;151(1):90-105.

谢谢关注！

thanks for your attention.