IPERTENSIONE POLMONARE NEL PAZIENTE ACHD

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Città della Salute e della Scienza di Torino

AGENDA

- INQUADRAMENTO PAH-ACHD
- CATH, TEST VASOREATTIVITA’
- S. EISENMENGER, FONTAN
- LINEE GUIDA ESC 2022: news..
- TERAPIA FARMACOLOGICA

DEFINIZIONE IPERTENSIONE POLMONARE

5 GRUPPI:

GRUPPO 1:PAH

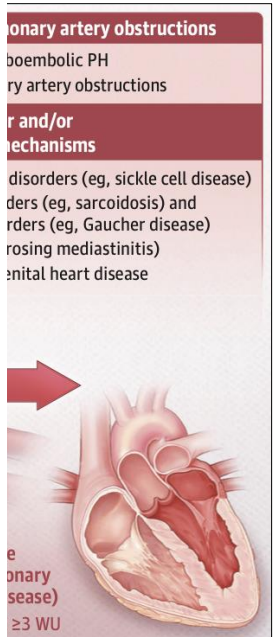
Dati emo:

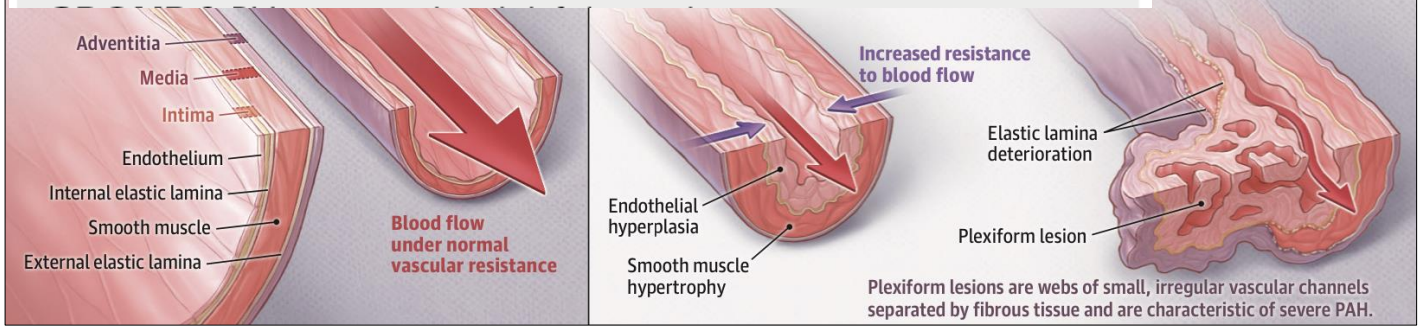
PAPm> 20mmHg
CWP ≤ 15mmHg
RVP > 2UW

VASOCOSTRIZIONE
INFIAMMAZIONE
REMODELING VASO
TROMBOSI IN SITU
AUMENTO TROMBOSSANO A2/ENDOTELINA1
RIDUZIONE NO/PROSTACICLINE

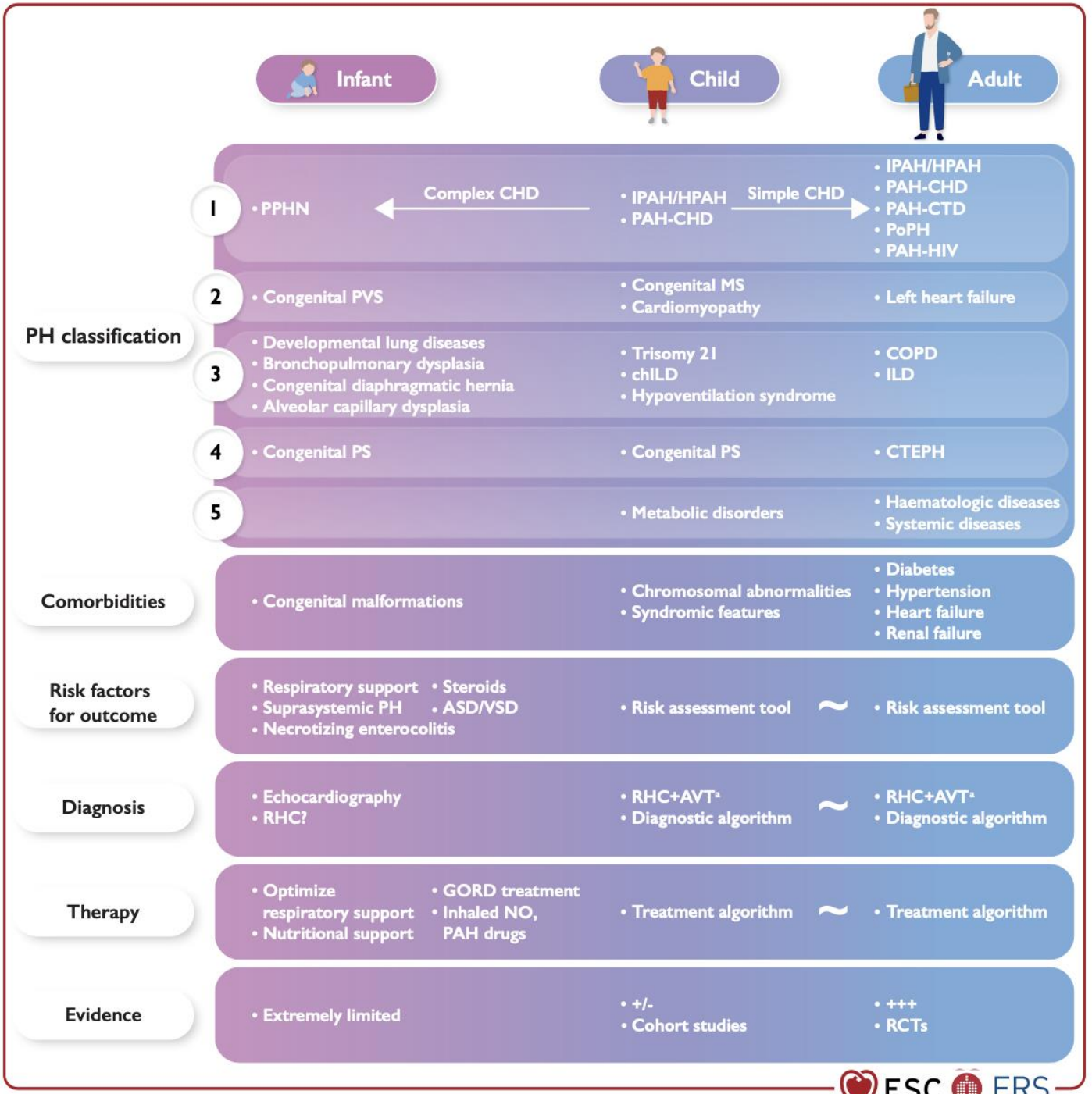
GROUP 1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable[a]
- 1.3 Associated with drugs and toxins[a]
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn





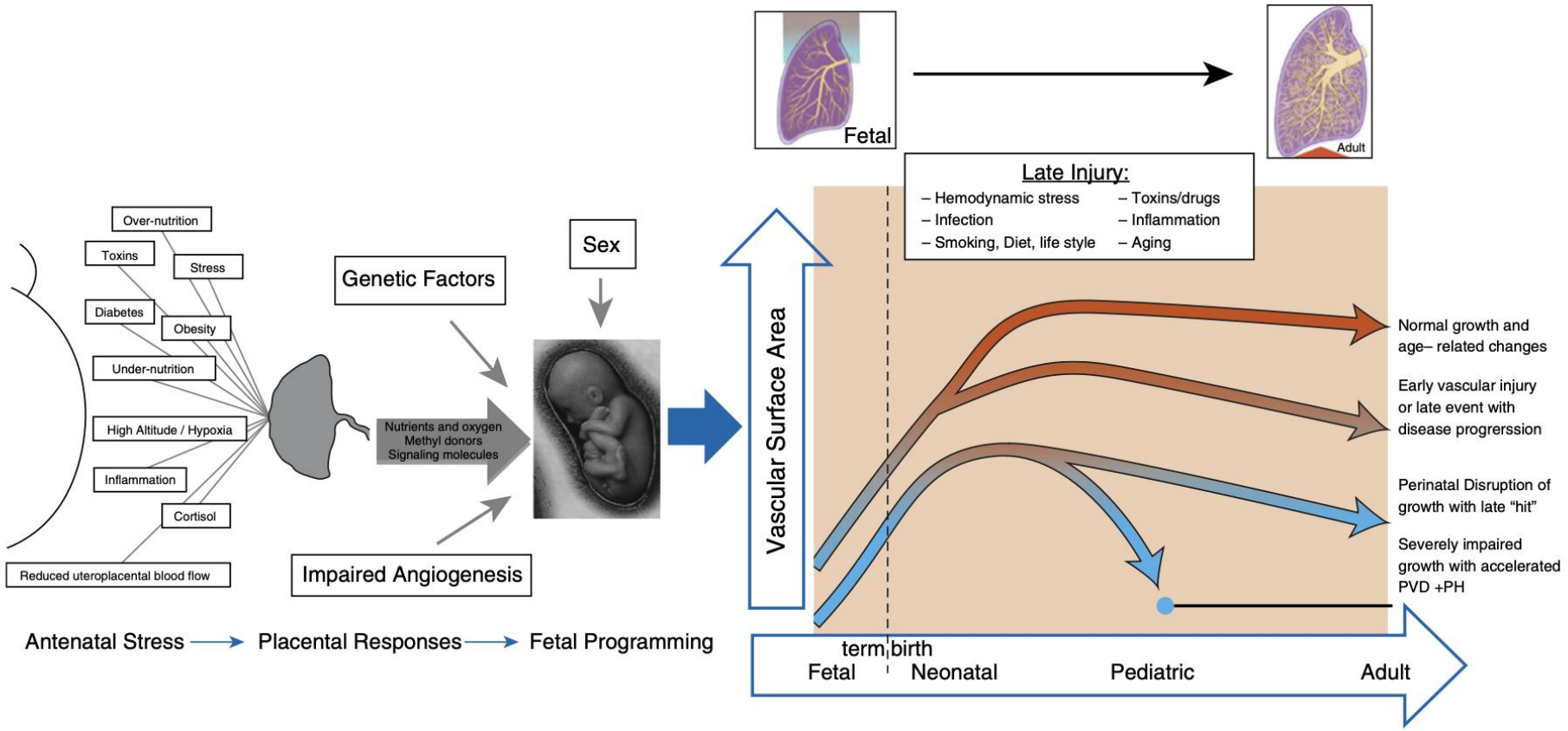
JAMA. 2022;327(14):1379-1391. ESC/ERS Guidelines 2022


Infant
Child
Adult
PH classification
1
• PPHN
Complex CHD
• IPAH/HPAH
• PAH-CHD
Simple CHD
• IPAH/HPAH
• PAH-CHD
• PAH-CTD
• PoPH
• PAH-HIV
2
• Congenital PVS
• Congenital MS
• Cardiomyopathy
• Left heart failure
3
• Developmental lung diseases
• Bronchopulmonary dysplasia
• Congenital diaphragmatic hernia
• Alveolar capillary dysplasia
• Trisomy 21
• chILD
• Hypoventilation syndrome
• COPD
• ILD
4
• Congenital PS
• Congenital PS
• CTEPH
5
• Metabolic disorders
• Haematologic diseases
• Systemic diseases
Comorbidities
• Congenital malformations
• Chromosomal abnormalities
• Syndromic features
• Diabetes
• Hypertension
• Heart failure
• Renal failure
Risk factors for outcome
• Respiratory support
• Suprasystemic PH
• Necrotizing enterocolitis
• Steroids
• ASD/VSD
• Risk assessment tool
~
• Risk assessment tool
Diagnosis
• Echocardiography
• RHC?
• RHC+AVT[a]
• Diagnostic algorithm
~
• RHC+AVT[a]
• Diagnostic algorithm
Therapy
• Optimize respiratory support
• Nutritional support
• GORD treatment
• Inhaled NO, PAH drugs
• Treatment algorithm
~
• Treatment algorithm
Evidence
• Extremely limited
• +/-
• Cohort studies
• +++
• RCTs
ESC ERS

ACHD PATIENTS

1. PAH with small/coincidental defects
2. PAH associated with predominant L-R shunts
3. PAH after defect correction (corrected CHD-PAH)
4. Eisenmenger's syndrome

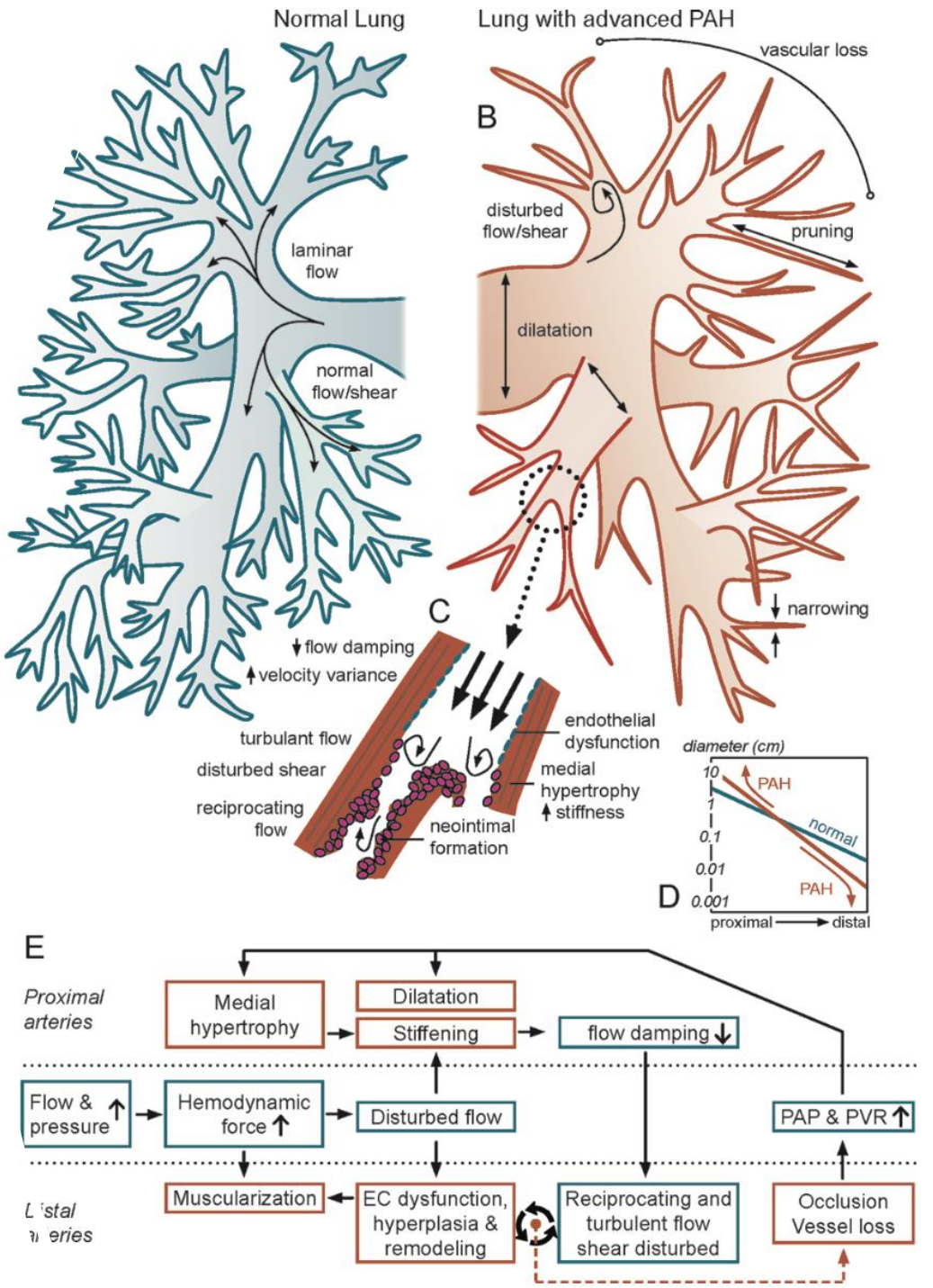
DISEASE INCEPTION



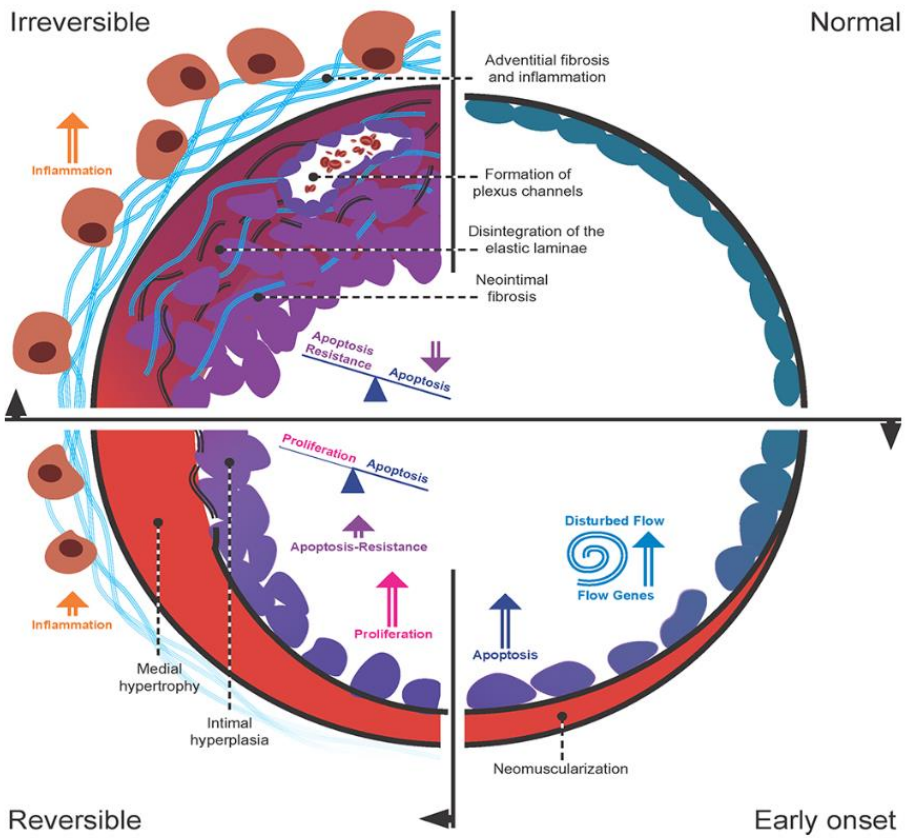
American Journal of Respiratory and Critical Care Medicine. 203; 12. 2021

PAH-CHD

- Assessment of reversibility in pulmonary arterial hypertension and congenital heart disease *Heart* 2019;105:276–282.



PAH-CHD



- Assessment of reversibility in pulmonary arterial hypertension and congenital heart disease *Heart* 2019;105:276–282.

PAH-CHD: FINESTRA DI REVERSIBILITÀ

- Arteriopatia polmonare **silente** per molti anni
- Forma PAH-CHD arteriopatia **triggerata** da aumentato flusso polmonare (L-R shunt)
- **Diagnosi precoce** PAH-CHD-> danno inizialmente reversibile
- Passato il "**punto di non ritorno**" PAH progredisce rapidamente e indipendentemente
- *Reversibilità* è sinonimo di *operabilità*?

Reversibility of plexogenic pulmonary arteriopathy following banding of the pulmonary artery. *J Thorac Cardiovasc Surg* 1984;87:876–86.

PAH-CHD: FINESTRA DI REVERSIBILITÀ

- Non c'è una valutazione strumentale "gold standard" per valutare reversibilità
- Reversibilità? Valutare: età, tipo shunt, cianosi da sforzo, genetica, LAB (Ht/Hb), cath
- AVT (acute vasodilator test): iNO o epoprostenolo-> PVR,PAP, SHUNT..
- Non esiste cut off affidabile nel predire reversibilità post operatoria !!
- Non usare criteri di Sitbon

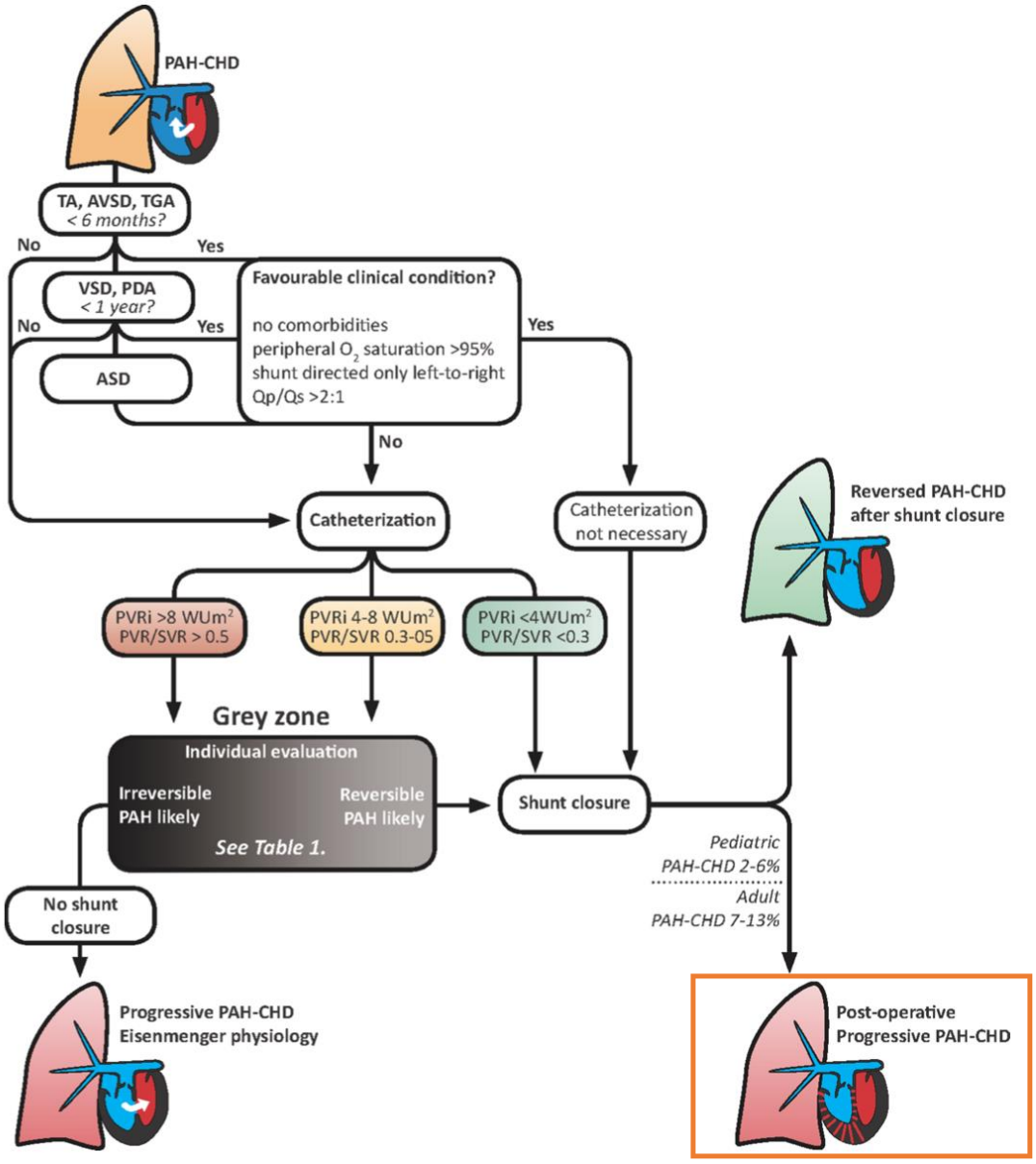
- **Linee guida:**

1) Operabile: L-R PVR <4UW/m2
2) Area grigia 4<PVR<8UW/m2
3) Sconsigliato PVR>8UW/m2
4) Controindicato R-L shunt

Reversibility of plexogenic pulmonary arteriopathy following banding of the pulmonary artery. *J Thorac Cardiovasc Surg* 1984;87:876–86.

PAH-CHD

- Assessment of reversibility in pulmonary arterial hypertension and congenital heart disease *Heart* 2019;105:276–282.



SINDROME DI EISENMENGER

- Descritta da Viktor Eisenmenger nel 1897
- Definita da Paul Wood nel 1958 come “Ipertensione polmonare, a livelli sistemici, causata da alte resistenze vascolari polmonari, con **shunt invertito/bidirezionale** a livello: AO-PO, V, A”
- Fenotipo emodinamico di ipertensione arteriosa polmonare più severo!!
- Si sviluppa in presenza di grandi difetti atriali / ventricolari /shunt, CHD complesse
- Prevalenza 1-5% centri terzo livello…frequente nei paesi in via di svilippo

Eisenmenger V. Die angeborenen Defecte der Kammerscheidewand des Herzens. Z Klin Med. 1897;32(Suppl):1–28
Wood P. The Eisenmenger syndrome or pul- monary hypertension with reversed central shunt. Br Med J. 1958;2:755–762.

SINDROME DI EISENMENGER

- Caratterizzata da **ipossia cronica**, interessamento multiorgano, eritrocitosi secondaria, rischio trombotico/emorragico, alto rischio aritmico, rischio infettivo, scompenso cardiaco progressivo
- Peggiore tolleranza allo sforzo di tutte le CHD!
- Alta prevalenza di insufficienza renale
- Qualità di vita pessima rispetto a CHD e ad altre forme di PAH!
- Età pediatrica: mortalità maggiore rispetto all'adulto!
- Trisomia 21 accelera sviluppo ES
- VD: sviluppa "**fenotipo fetale**".. Migliore prognosi rispetto a PAH idiopatica..

CARENZA DI FERRO

PERDITE GASTROINTESTINALI
ALTO CONSUMO
RIDOTTO ASSORBIMENTO INTESTINALE (GOTTA)

Hb ottimale attesa?
Calcolo sec. formula Broberg:

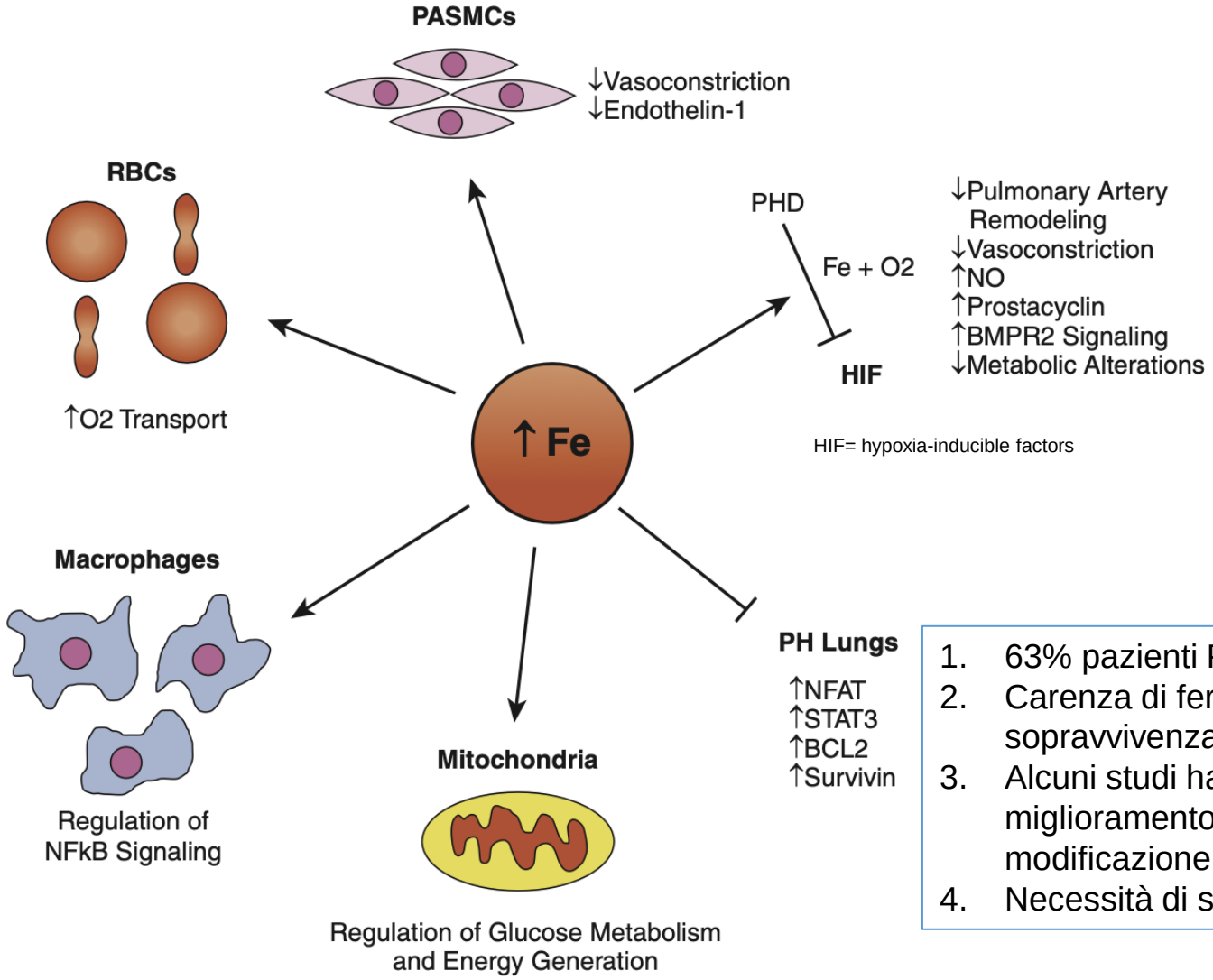
Hb predetta= $57.5-(0.444 \times SatO_2)$

…Se paziente satura 85% a riposo: Hb ottimale attesa è 19,76 g/dl

SUPPLEMENTAZIONE ORALE/EV FERRO!!
BILANCIO TRA ADEGUATA ERITROCITOSI / RISCHI DA IPERVISCOSITÀ / TROMBOCITOPENIA

Broberg CS, Jayaweera AR, Diller GP, et al. Seeking optimal relation between oxygen satura- tion and hemoglobin concentration in adults with cyanosis from congenital heart disease. Am J Cardiol. 2011;107:595–599.

FERRO: POTENZIALE TARGET TERAPEUTICO PAH?



1. 63% pazienti PAH ha carenza di ferro
2. Carenza di ferro associate a ridotta sopravvivenza
3. Alcuni studi hanno documentato miglioramento tolleranza all'esercizio. Non modificazione PVR
4. Necessità di studi ulteriori

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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Eisenmenger Syndrome

JACC State-of-the-Art Review

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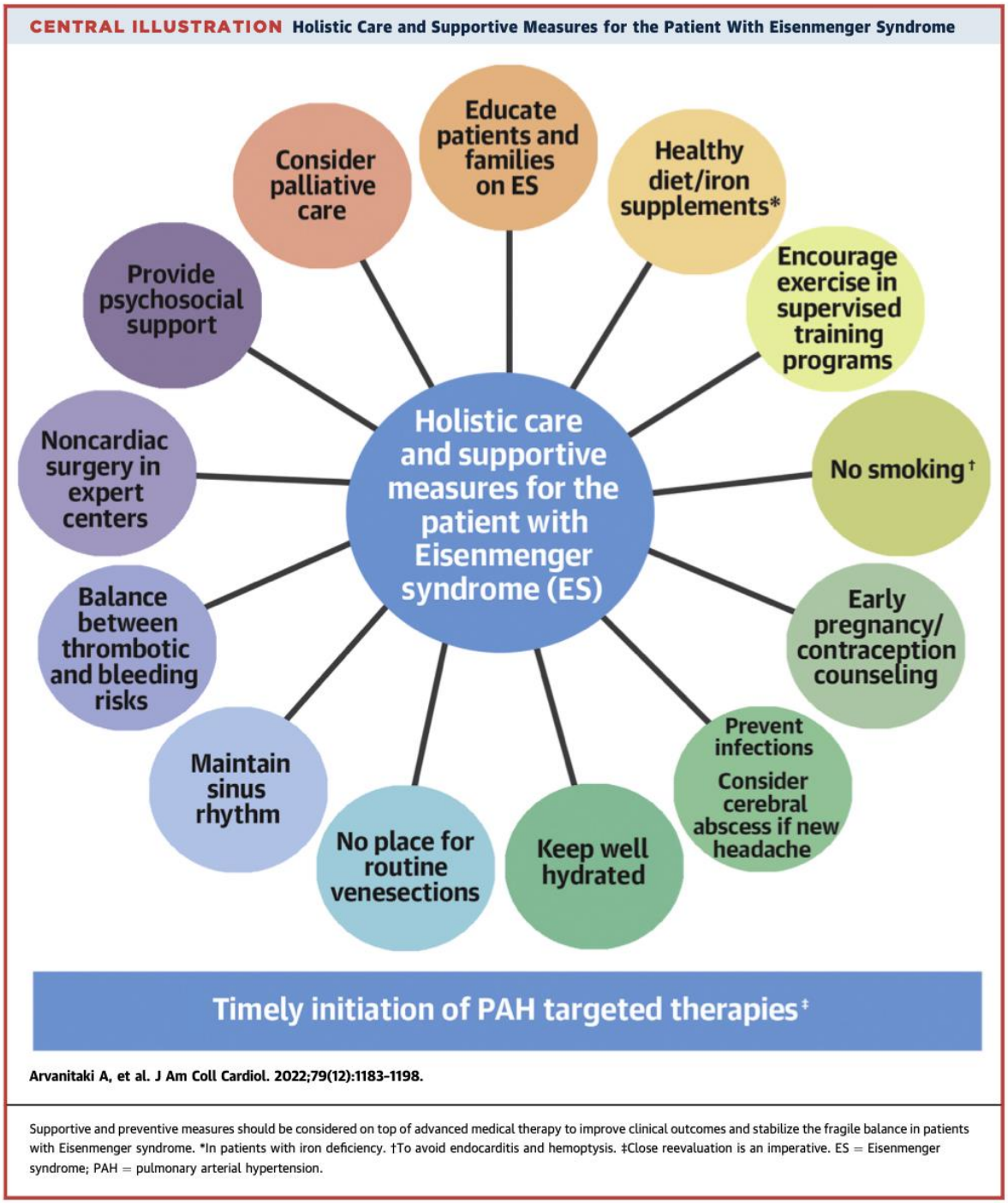
RACCOMANDAZIONI EISENMENGER S.

TABLE 1 Recommendations, Evidence Gaps, and Future Perspectives on Management of Patients With Eisenmenger Syndrome

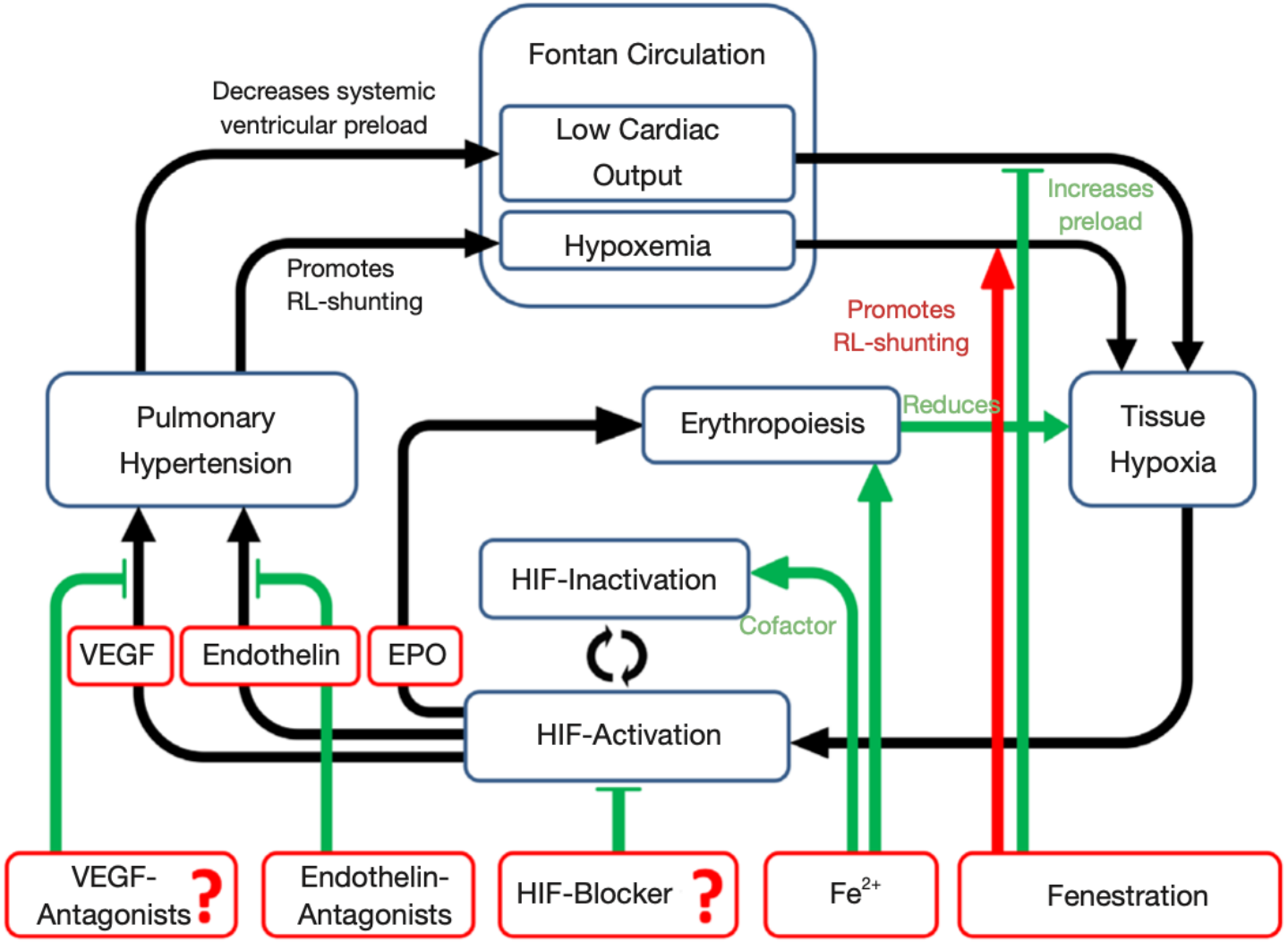
Issues	Suggestions/Recommendations	Gaps in Evidence/Future Perspectives
Secondary erythrocytosis	No place for routine venesections If a trial of venesection is considered • Only in expert centers • In patients with hemoglobin >22 g/dL and hematocrit >65% presenting with severe hyperviscosity symptoms in the absence of dehydration • At small volumes (250-500 mL) with simultaneous fluid replacement to avoid hemodynamic imbalance	Past clinical practice, not based on evidence, comprises oxygen caring capacity to the tissues
Iron deficiency	Check iron profile (transferrin saturation <20%, best marker of iron deficiency anemia) Oral iron supplementation • Consider gastrointestinal side-effects Intravenous supplementation • Administer at a slow rate • Take care to avoid air emboli Periodic blood tests (iron profile/full blood count)	Lack of trials comparing oral vs iron supplementation on safety and efficacy Unclear how long iron supplementation should continue
Thrombotic diathesis	Oral anticoagulation should be recommended in case of atrial arrythmia and in the presence of PA thrombus or emboli Vitamin K antagonists remain the oral anticoagulants of choice pending safety and efficacy data on direct oral anticoagulants	RCTs on safety and efficacy of oral anticoagulation for primary prevention in ES are lacking RCTs on the safety and efficacy of DOACs in ES are lacking RCTs comparing antiplatelets over anticoagulants for primary prevention in ES are lacking
Hemoptysis	Anticoagulation is not recommended in patients with active or recurrent hemoptysis Supportive treatment • Manage concomitant respiratory tract infections, suppress coughing, reduce physical activity, treat hypovolemia and (relative) anemia CTPA to determine the presence and location/origin of intrapulmonary hemorrhage Coil embolization of causative bronchial arteries in selected patients Inhaled tranexamic acid may be considered	RCTs on the safety and efficacy of fibrinolytic agents in ES are lacking
Arrhythmias	Prompt restoration and maintenance of sinus rhythm recommended Catheter ablation in specialized centers may be considered in patients with intractable arrhythmia Transvenous pacing requires anticoagulation. Alternative pacing strategies, including epicardial and leadless systems, may be considered and tailored according to individual patient risk assessment S-ICD may be considered for secondary prevention of sudden cardiac death and for high-risk patients (primary prevention, eg, severe ventricular dysfunction and syncope) S-ICD should be favored in suitable candidates with ICD indications not needing antibradycardia pacing.	Long-term safety data of leadless and epicardial pacing systems are lacking Long-term data on S-ICD for primary prevention are lacking A refined risk stratification score for primary prevention of SCD needs to be developed
Advanced PAH therapies	Risk stratification for all patients based on available predictors and risk scores (Figure 1) Consider starting with an ERA monotherapy in symptomatic (>I WHO FC) patients with reduced functional capacity followed by a combination therapy (with a PDE5 inhibitor) to optimize patient Consider escalating to triple combination therapy in selected high-risk patients	Debate on the need of targeted therapies in asymptomatic patients with an acceptable 6MWD (>450 m) No evidence for the use of up-front combination therapy Scarce evidence on the use of sequential combination therapy Lack of robust data on the use of riociguat, prostanoid analogues and IP receptor agonists
Mechanical support	Mechanical circulatory support can be employed as a rescue strategy for ES	The use of VA-ECMO or VAD has not been well documented
Transplantation	Patients at high risk and symptomatic despite optimal PAH therapy should be listed for transplantation Consider bilateral LTx with shunt repair for patients with an ASD Consider HLTx for patients with post-tricuspid shunts	Uncertainty on optimal timing and eligibility No validated risk score to guide the decision for transplantation Limited data on post Tx survival
Perioperative anesthesia	Perform noncardiac surgery only in expert centers by expert anesthesiologists Maintain a balance between pulmonary and systemic blood flow Prevent worsening of hypoxemia	No clear data to support general over regional anesthesia
Rehabilitation and exercise	Perform a preparticipation screening including ECG, TTE, 6MWD, and CPET to assess safety Develop and provide an individual-adjusted, supervised training program	Limited data on the benefits and risks of exercise in ES patients Further data is required on best training modality and setting

HOLISTIC CARE

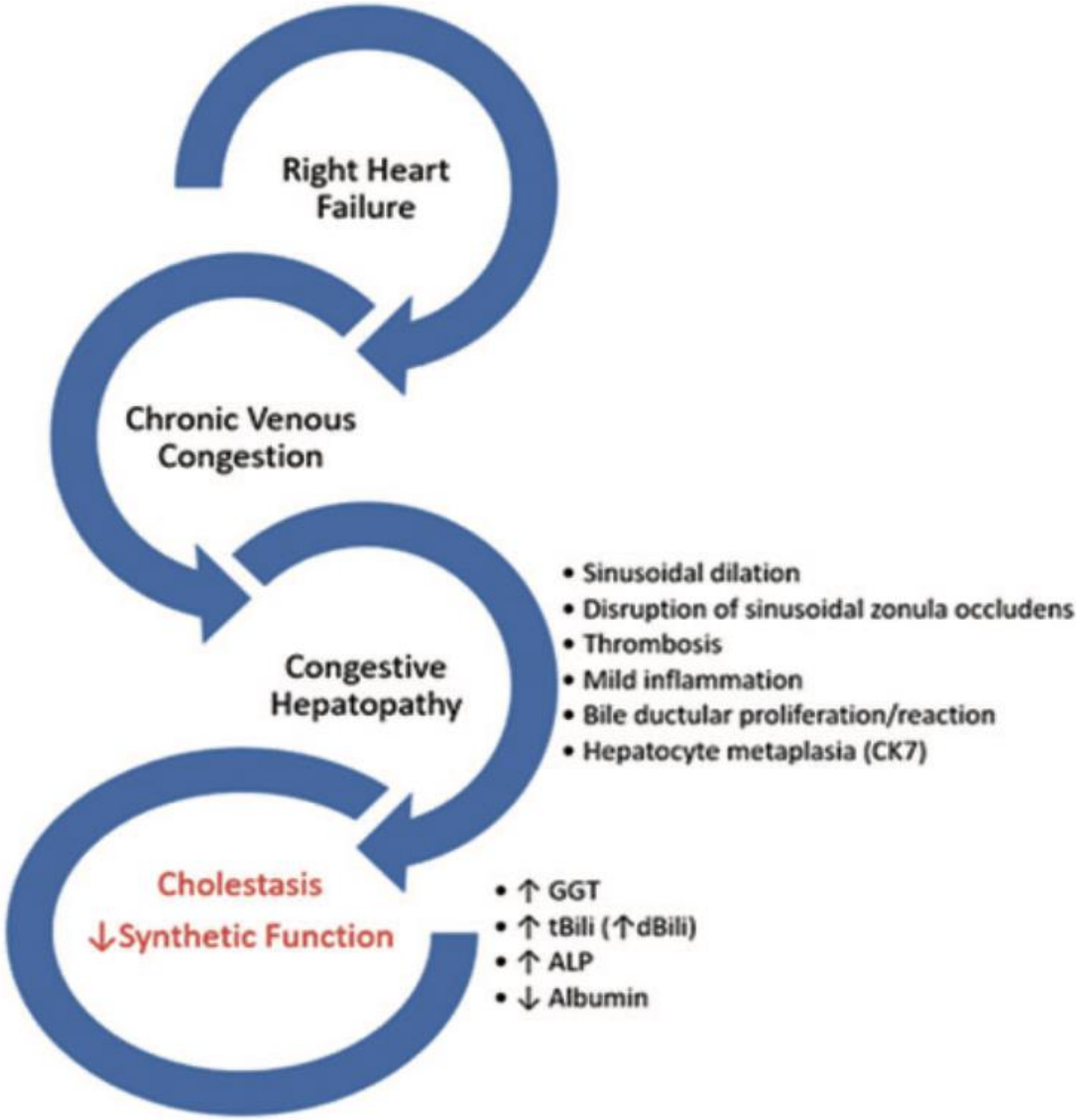


Pulmonary vascular disease in Fontan circulation—is there a rationale for pulmonary vasodilator therapies?

Kolja B



PAH MALATTIA MULTISISTEMICA: EPATOPATIA



Nils P. Nickel. Liver abnormalities in pulmonary arterial hypertension. Pulmonary Circulation 2021; 11(4) 1–12

CATETERISMO CARDIACO: gold standard diagnostico

- Pressione atriale destra-media: **mRAP**
- Cardiac Index: **CI**
- Resistenze vascolari polmonari indicizzate: **RVPI**
- Pumonary-to-systemic arterial pressure ratio: **mPAP/mSAP**
- Acute response to vasodilator testing: **AVT**
- RISCHIO PROCEDURALE: mortalità 0.6% / Complicanze maggiori 1-3% (soprattutto <1aa e >WHO-FC)

DEFINISCE PAH NEL MOMENTO DELLA DIAGNOSI

AVT POSITIVO CORRELA CON MIGLIORE PROGNOSI

DOCUMENTA PROGRESSIONE MALATTIA

DEFINISCE RISCHIO MORTALITÀ

OTTIMIZZARE TERAPIA E VALUTARNE EFFICACIA

Cardiovasc Diagn Ther 2021;11(4):1089-1101

ESC European Society of Cardiology
European Heart Journal (2022) **00**, 1–114
https://doi.org/10.1093/eurheartj/ehac237

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Nuova definizione emodinamica:

DEFINIZIONE	CARATTERISTICHE EMODINAMICHE
PH	PAPm > 20mmHg
PRE CAPILLARE	PAPm > 20mmHg CWP ≤ 15mmHg PVR > 2UW
ISOLATA POST CAPILLARE	PAPm > 20mmHg CWP > 15 mmHg PVR ≤ 2 UW
COMBINATA POST E PRE CAPILLARE	PAPm > 20mmHg CWP > 15 mmHg PVR > 2 UW

Recommendations	Class[a]	Level[b]
Right heart catheterization		
It is recommended that RHC is performed to confirm the diagnosis of PH (especially PAH or CTEPH) and to support treatment decisions[25,26]	I	B
In patients with suspected or known PH, it is recommended that RHC is performed in experienced centres[125]	I	C
It is recommended that RHC comprises a complete set of haemodynamics and is performed following standardized protocols[25,26,145]	I	C
Vasoreactivity testing		
Vasoreactivity testing is recommended in patients with I/H/DPAH to detect those who can be treated with high doses of a CCB[129,146]	I	B
It is recommended that vasoreactivity testing is performed at PH centres	I	C
It is recommended to consider a positive response to vasoreactivity testing by a reduction in mPAP ≥10 mmHg to reach an absolute value of mPAP ≤40 mmHg with an increased or unchanged CO[c][129]	I	C
Inhaled nitric oxide, inhaled iloprost, or i.v. epoprostenol are recommended for performing vasoreactivity testing[129–132]	I	C
Vasoreactivity testing, for identifying candidates for CCB therapy, is not recommended in patients with PAH other than I/H/DPAH, and in PH groups 2, 3, 4, and 5[124,129]	III	C

TEST DI VASOREATTIVITÀ (AVT)

- Nelle forme **idiopatiche/famigliari** (IPAH-HPAH)
- Predittore di Outcome e risposta ai Ca antagonisti
- Diversi farmaci utilizzati e poco standardizzato: iNO 10-80ppm, epoprostenolo, adenosina
- **CRITERI di SITBON:** Riduzione PAPm di almeno 10mmHg a un valore inferiore a 40mmHg, mantenendo uguale la portata cardiaca.
- **CRITERI di BARST:** Riduzione PAPm di almeno 20%, mantenendo uguale/aumentata la portata cardiaca e uguale o ridotto il rapporto PVR/SVR
- Se test pos: utilizzare Calcio antagonisti
- **ATTENZIONE** Circa il 50% dei soggetti trattati con Calcio antagonisti diventa resistente nel follow-up→ richiesto attento monitoraggio

TEST DI VASOREATTIVITÀ (AVT)

Nel pz ACHD con forme secondarie a cardiopatia congenita (**PAH-CHD**):

- **Mancano target di risposta specifici che definiscano la prognosi a lungo termine e il rischio chirurgico**

- Criteri di operabilità sono basati sul **Consenso di Esperti**

- Task Force definisce **operabilità con AVT nelle forme di CHD-PAH**

- **Out-come a lungo termine dopo la chiusura di un difetto** con PAH e IPVR aumentate è in realtà **poco definibile!!**

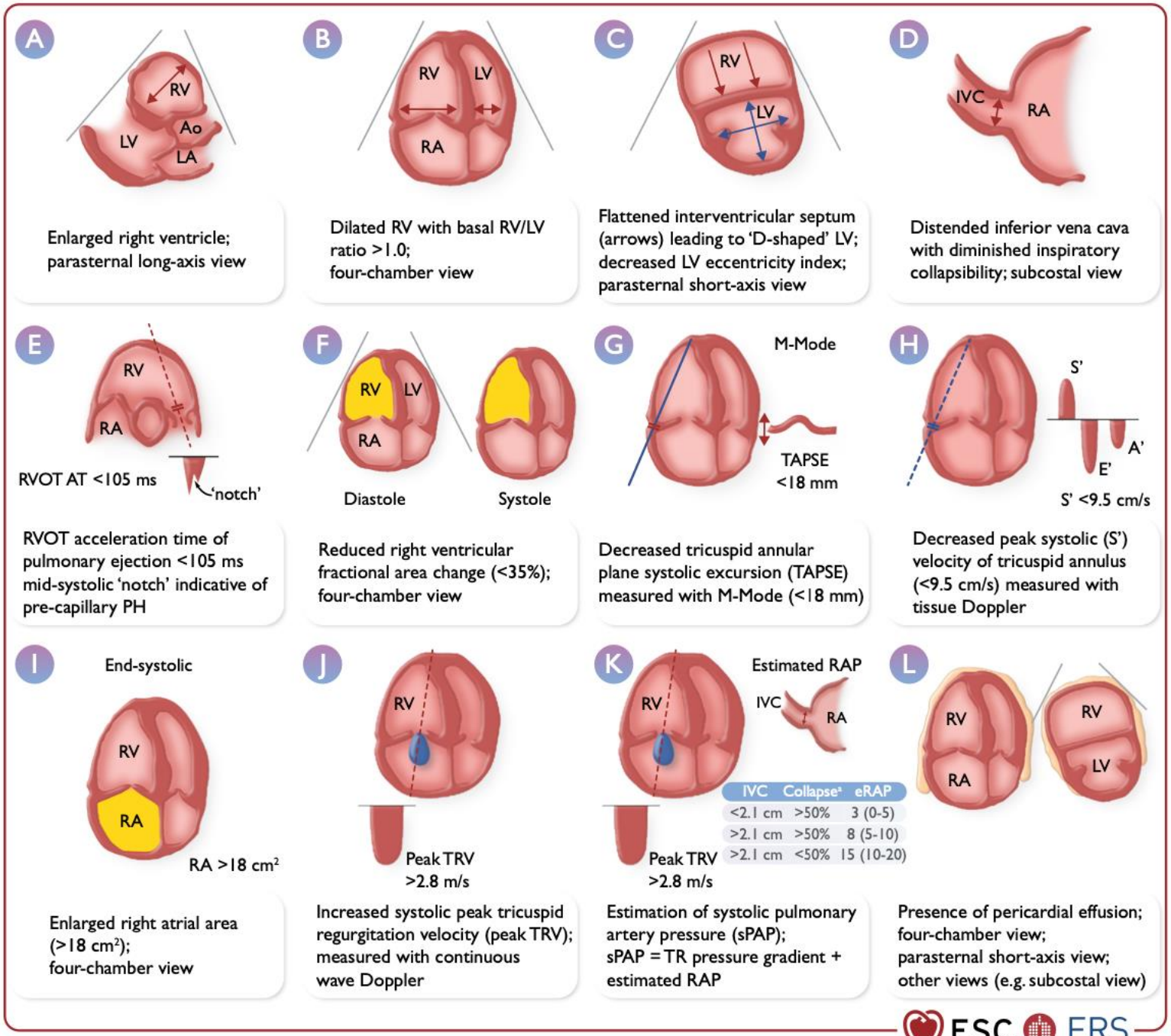
Pulmonary vascular resistance index WU·m^2	Pulmonary vascular resistance WU	Correctability/favourable long-term outcome
<4	<2.3	Yes
4–8	2.3–4.6	Individual patient evaluation in tertiary centres
>8	>4.6	No

ECO

ECO p

Cosa r

- TAP
- RV f
- Syst
- Pres
- RV r
- Res



RISONANZA MAGNETICA CARDIACA

- Definisce anatomia-morfologia cardiaca.. Fondamentale nel gruppo ACHD
- Definisce funzione bi-ventricolare
- Vantaggio: Maggiore accuratezza-riproducibilità
- RV dimensioni – volumi – massa- FE
- RA dimensioni
- LV stroke volume
- Rigurgito tricuspidale (FR%) o della valvola AV sottopolmonare
- Flusso sistemico/polmonare, dissincronia interventricolare, dinamica parete arteriosa polmonare ecc

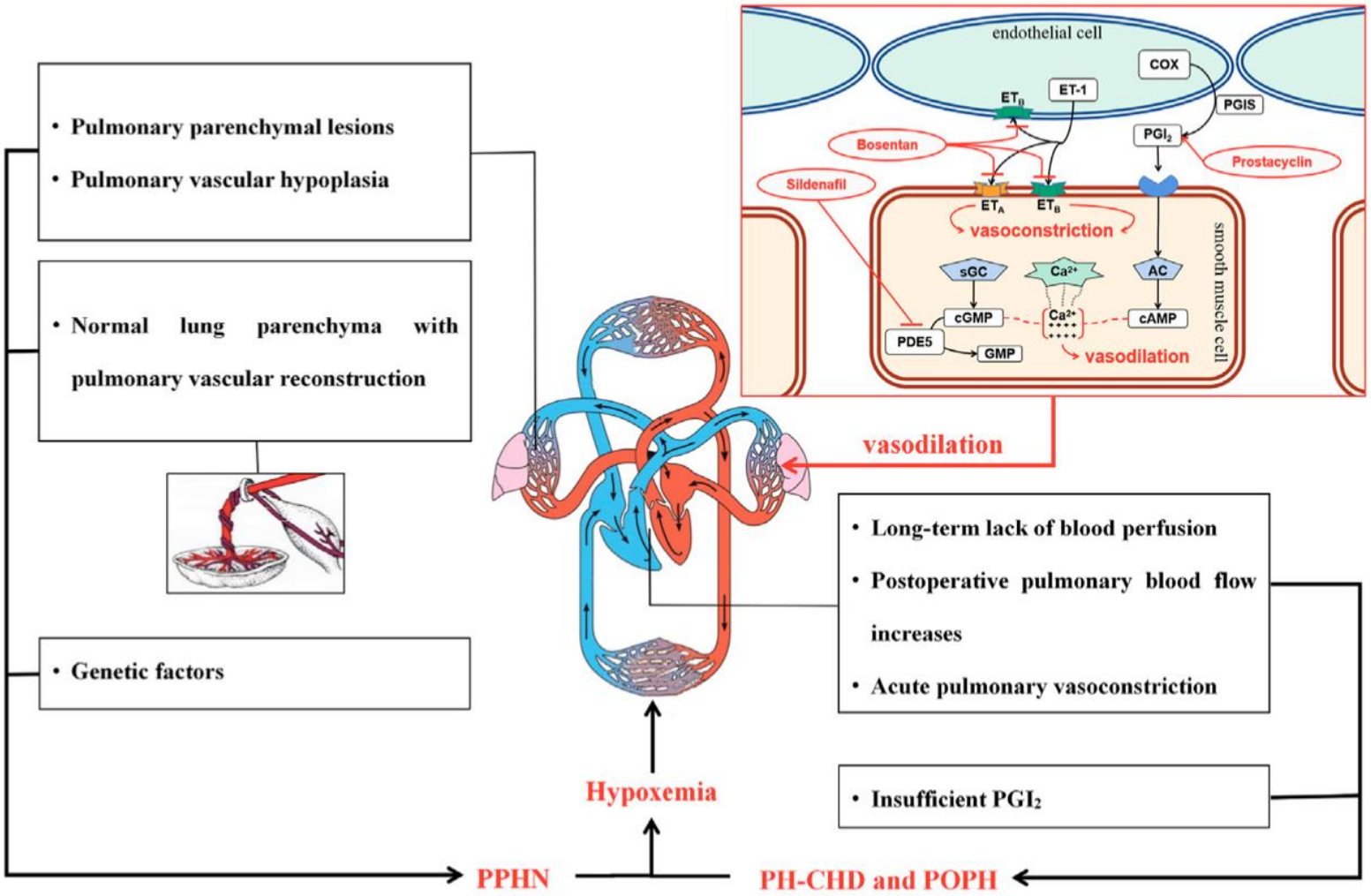
CORRELA CON PROGNOSI/MORTALITÀ

DOCUMENTA GRAVITÀ MALATTIA

VALUTA EFFICACIA TERAPEUTICA

Cardiovasc Diagn Ther 2021;11(4):1089-1101

TRE VIE FARMACOLOGICHE



The Efficacy and Safety of Pulmonary Vasodilators in Pediatric Pulmonary Hypertension (PH): A Systematic Review and Meta-analysis. Frontiers in Pharmacology. April 2021, 12, Article 668902

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Table 16 Comprehensive risk assessment in pulmonary arterial hypertension (three-strata model)

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid

Table 18 Variables used to calculate the simplified four-strata risk-assessment tool

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100
		TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI[e]		RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics		RAP <8 mmHg CI ≥2.5 L/min/m^2 SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 L/min/m^2 SVI <31 mL/m^2 SvO_2 <60%

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ESC European Society of Cardiology
European Heart Journal (2022) 00, 1–114
https://doi.org/10.1093/eurheartj/ehac237

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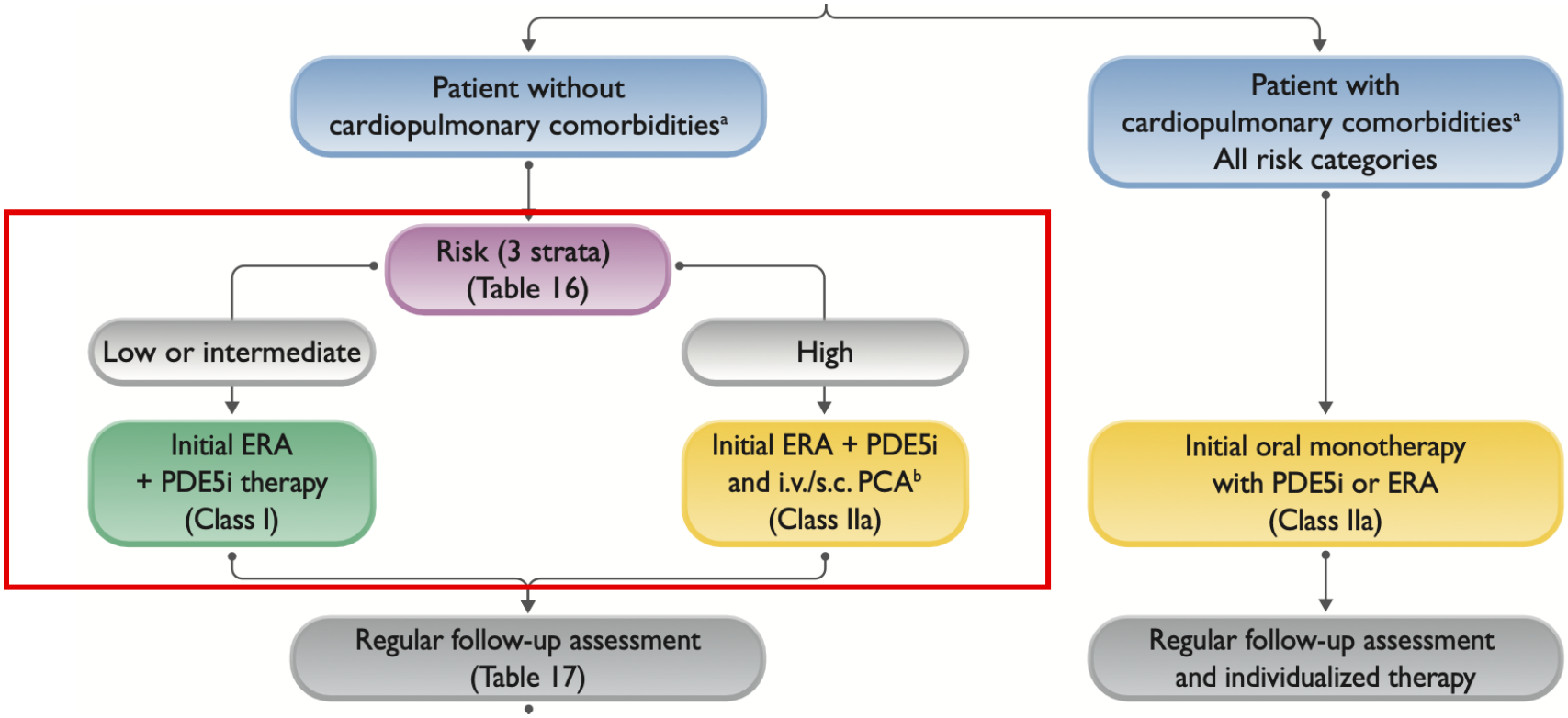

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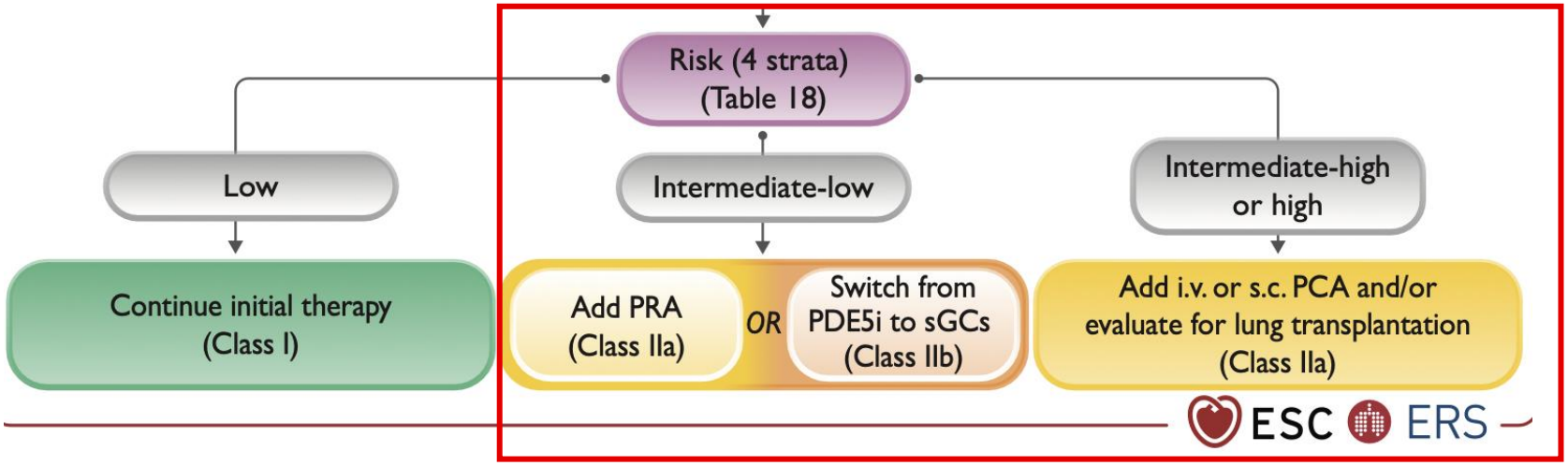


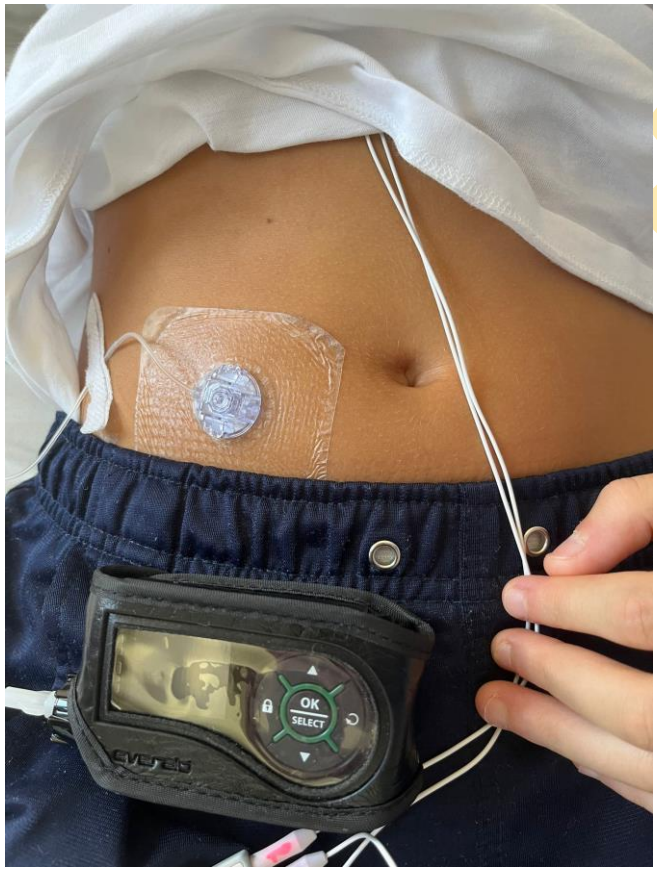
ANALOGHI DELLE PROSTACICLINE (PROSTANOIDI)

- Epoprostenolo e Treprostenil, Iloprost, (Beraprost)
- Range dose linee guida ped. (50-80 ng/kg/min)
- Dose aumentata nel tempo per **sviluppo tolleranza**
- **Dose eccessiva può impropriamente aumentare il CO**
- Dosi alte possono aumentare **rischio sanguinamento**
- **Effetti collaterali**: cefalea, nausea, vomito, diarrea, dolori articolari
- Riservati per pazienti con **insufficiente risposta a terapia orale o in classe III/IV**, disfunzione VD, PAPs>PA sistemica
- DOSE GOAL EPOPROSTENOLO: 75-100NG/KG/MIN
- DOSE GOAL TREPROSTENIL: 125-150NG/KG/MIN

Prostanoids in pediatric pulmonary hypertension: clinical response, time-to-effect, and dose–response. Pulmonary Circulation 2020; 10(4) 1–10

ANALOGHI DELLE PROSTACICLINE (PROSTANOIDI)

- **TREPROSTENIL:** possibile somministrazione e.v./inalatoria/orale/**sottocute**
- Somministrazione sottocutanea riduce effetti collaterali
- Indicato per classe WHO II-IV
- **Ottima alternativa a prostacicline ev**
- Evita effetti collaterali della sommonistrazione e.v. (batteriemie/sepsi)
- Effetti collaterali locali minori (**dolore ≃85%** ; infezioni localizzate al sito di infusione)
- Trattamento **efficace e sicuro**
- Dose media 40 ng/kg/min
- Dose ottimale varia tra individui tra 20 and 80 ng/kg/min
- Inizio 1.25 ng/kg/min, aumentare lentamente !



Safety, efficacy and Management of subcutaneous treprostinil infusions in the treatment of severe pediatric pulmonary hypertension. Int J Cardiol 2018; 264: 153-157.
Use of subcutaneous treprostinil in pediatric pulmonary arterial hypertension-Bridge-to-transplant or long-term treatment?. Pediatr Transplant 2018; 22: 13106.
Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002;165:800–804.

ANALOGHI DELLE PROSTACICLINE (PROSTANOIDI)

- **EPOPROSTENOLO** (Flolan) (PGI2) **PRIMA SCELTA nei pazienti in classe WHO IV**.
- Necessità di **infusione continua in via centrale** (emivita di pochi minuti)
- **Effetti collaterali**: Emorragia polmonare, scompenso cardiaco, emottisi, bradicardia, ipotensione trombocitopenia, infezioni
- **Migliora la sopravvivenza nell'adulto**

- **ILOPROST**: analogo delle prostacicline
- Non riduce la Pas
- Può essere assunto per **via inalatoria**
- Effetto simile a iNO nel postoperatorio
- Può essere usato per test di vasoreattività
- Per trattamento crisi PAH 10μg/dose per 10-15min ogni 2 ore (8volte/die)
- **Effetti collaterali**: broncospasmo, cefalea, rash attorno alla bocca, nausea, vomito, diarrea
- Usare in associazione non in monoterapia

Short- and long- term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol 2008; 51: 161-169.
Combined treatment of silde- nafil and inhaled iloprost in pediatric patients with severe pulmonary arterial hypertension. Arch Cardiol Mex 2015; 85: 80-84.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

- **GRIPHON trial**: long-term, event-driven, randomised, placebo-controlled, phase III STUDY
- Evaluated the selective IP prostacyclin receptor agonist Selexipag in **1156 patient** (IPAH, HPAH, PAH-CHD, HIV-rel, connective d. ecc)
- Enrolled **110** patients with corrected **CHD-PAH** (ASD 55,VSD 36, PDA 14)
- In the overall population, Selexipag reduced the risk of the primary composite outcome of morbidity/mortality by 40% ($P < 0.001$) compared with placebo
- The treatment effect was consistent in the corrected CHD-PAH subgroup

ESC European Society of Cardiology

European Journal of Heart Failure (2019) **21**, 352–359
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RESEARCH ARTICLE

Selexipag treatment for pulmonary arterial hypertension associated with congenital heart disease after defect correction: insights from the randomised controlled GRIPHON study

Table 2 Events related to pulmonary arterial hypertension and death for patients with pulmonary arterial hypertension associated with congenital heart disease after defect correction

	Placebo ($n = 50$)	Selexipag ($n = 60$)	Overall ($n = 110$)
Primary composite endpoint of morbidity/mortality up to the end of treatment			
All events, *n* (%)	13 (26.0)	9 (15.0)	22 (20.0)
Hospitalisation for worsening of PAH	7 (14.0)	8 (13.3)	15 (13.6)
Disease progression	4 (8.0)	1 (1.7)	5 (4.5)
Death from any cause	2 (4.0)	–	2 (1.8)
Initiation of parenteral prostanoid therapy or long-term O_2 therapy for worsening PAH	–	–	–
Need for lung transplantation or balloon atrial septostomy for worsening of PAH	–	–	–
Secondary endpoint of all-cause death up to the end of the study			
Death from any cause, *n* (%)	5 (10.0)	2 (3.3)	7 (6.4)

Differences between corrected CHD-PAH patients and the non-CHD population: Patients with corrected CHD-PAH were **younger**, more likely to be in **WHO FC I/II** and **less likely to be on background therapy**

Selexipag may **delay disease progression** and is **well tolerated** in patients with corrected CHD-PAH

ANTAGONISTI RECETTORE ENDOTELINA-1

Bosentan, Macitentan, Ambrisentan

Endothelin receptor antagonists (ERA) have been recognised as **effective therapy for pulmonary arterial hypertension in congenital heart disease (CHD-PH**), and **Eisenmenger syndrome (ES)** since **The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (Breathe 5) study.**

SERAPHIN enrolled **742 patients** of WHO FC II to IV with IPAH, FPAH, PAH associated with connective tissue disease, **PAH associated with simple congenital systemic-to-pulmonary shunts at least one year post-surgical repair**, or PAH associated with either HIV infection or drug and toxin use.
Eligible patients were **men or women ≥ 12 years of age** with a baseline six-minute walk distance (6MWD) ≥ 50 m; mean pulmonary arterial pressure (mPAP) > 25 mm Hg; pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure ≤ 15 mm Hg; or pulmonary vascular resistance (PVR) at rest ≥ 320 dyn × sec/cm^5.
A total of 250 patients were randomly assigned to placebo, 250 to the 3-mg macitentan dose, and 242 to the 10-mg macitentan dose. The **primary end point occurred in 46.4%, 38.0%, and 31.4%** of the patients in these groups, respectively.

EFFICACIA E SICUREZZA DI TADALAFIL

- È un potente e selettivo inibitore delle fosfodiesterasi-5 (PDE-5)
- Tadalafil è un **farmaco sicuro nella popolazione pediatrica**
- **Dose 40/mg** in singola somministrazione per soggetti **>40kg**
- **Dose 20/mg** in singola somministrazione per soggetti **<40kg ma > 2 aa**.
- Migliora 6MWT a 24 settimane di terapia rispetto a placebo (limite numerosità dello studio per problema di arruolamento)

Galie N. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009; 119: 2894–2903.
Takatsuki S. Initial experience with tadalafil in pediatric pulmonary arterial hypertension. Pediatr Cardiol 2012; 33: 683–688.
Yamazaki H. Safety and effectiveness of tadalafil in pediatric patients with pulmonary
Dunbar Ivy . Efficacy and safety of tadalafil in a pediatric population with pulmonary arterial hypertension: phase 3 randomized, double-blind placebo-controlled study. Pulmonary Circulation 2021; 11(3) 1–8

Recommendations	Class[a]	Level[b]
General measures		
Supervised exercise training is recommended in patients with PAH under medical therapy[314,315,317]	I	A
Psychosocial support is recommended in patients with PAH	I	C
Immunization of patients with PAH against SARS-CoV-2, influenza, and *Streptococcus pneumoniae* is recommended	I	C
Diuretic treatment is recommended in patients with PAH with signs of RV failure and fluid retention	I	C
Long-term oxygen therapy is recommended in patients with PAH whose arterial blood oxygen pressure is <8 kPa (60 mmHg)[c]	I	C
In the presence of iron-deficiency anaemia, correction of iron status is recommended in patients with PAH	I	C
In the absence of anaemia, iron repletion may be considered in patients with PAH with iron deficiency	IIb	C
Anticoagulation is not generally recommended in patients with PAH but may be considered on an individual basis	IIb	C
The use of ACEis, ARBs, ARNIs, SGLT-2is, beta-blockers, or ivabradine is not recommended in patients with PAH unless required by comorbidities (i.e. high blood pressure, coronary artery disease, left HF, or arrhythmias)	III	C

ESC European Society of Cardiology
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ESC/ERS GUIDELINES

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

RACCOMANDAZIONI GENERALI

CONCLUSIONI

PAH-CHD **MALATTIA SILENTE**

SEGUIRE PAZIENTE ANCHE DOPO CORREZIONE

RAGGIUNGERE UN **BASSO RISCHIO** CON LA TERAPIA

EMODINAMICA INDISPENSABILE

CENTRI III LIVELLO

POPOLAZIONI PARTICOLARI (FONTAN, S EISENMENGER)