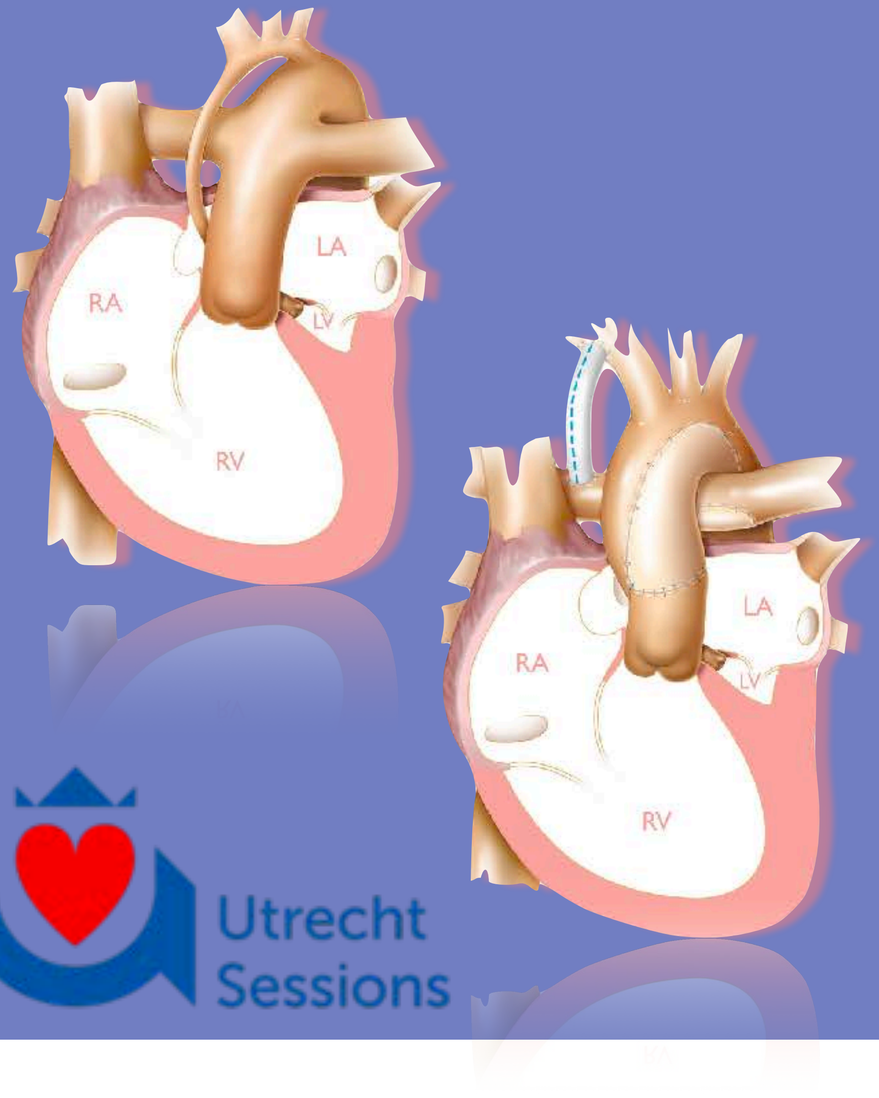


The good and the bad: strategical considerations before stage I

Damien Bonnet
Service de Cardiologie Congénitale et Pédiatrique
Hôpital Universitaire Necker Enfants malades – APHP
Université de Paris Cité
INSERM-U781 - Institut Hospitalo-Universitaire IMAGINE

Centre de Référence Maladies Rares
Malformations Cardiaques Congénitales Complexes-M3C
Centre de Référence Maladies Rares
Maladies Cardiaques Héréditaires- CARDIOGEN

Utrecht Sessions

M3C

ARCFA
Association pour la Recherche en Cardiologie du Fœtus à l'Adulte

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
NECKER-ENFANTS MALADES

FONDATION imagine
INSTITUT DES MALADIES GÉNÉTIQUES

Necker ENFANTS MALADES HÔPITAL UNIVERSITAIRE

UNIVERSITÉ PARIS DESCARTES

Université de Paris

Inserm
Institut national de la santé et de la recherche médicale

cardiogen
Filière nationale de santé maladies cardiaques héréditaires

Centre de Référence des Maladies Cardiaques Héréditaires

European Reference Network
for rare or low prevalence complex diseases
Network Respiratory Diseases (ERN-LUNG)

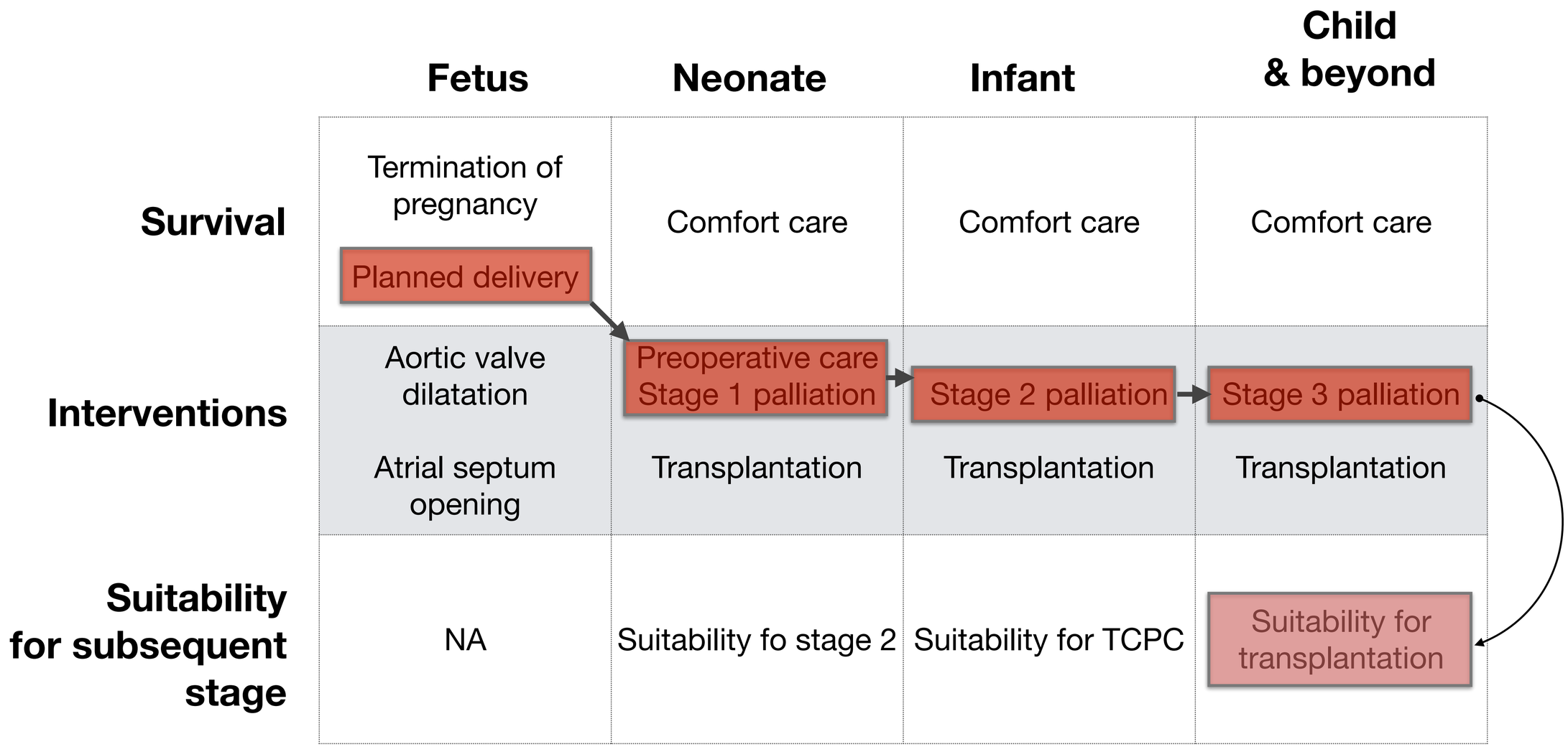
European Reference Network
for rare or low prevalence complex diseases
Network Heart Diseases (ERN GUARD-HEART)

Definition of a strategy:
« a plan of action designed to achieve a long-term aim »

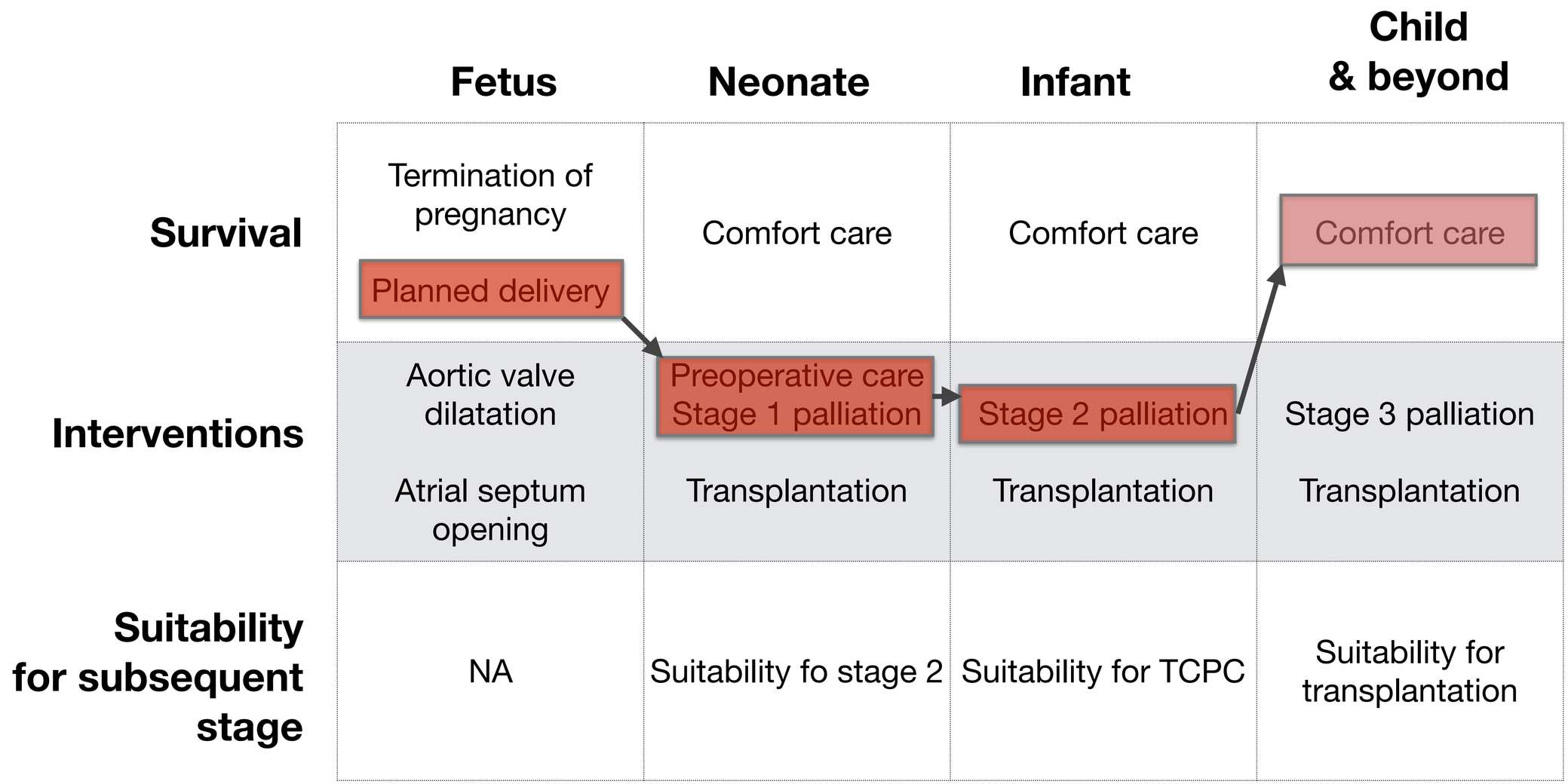
The plan of action may change at different time points

	Fetus	Neonate	Infant	Child & beyond
Survival	Termination of pregnancy Planned delivery	Comfort care	Comfort care	Comfort care
Interventions	Aortic valve dilatation Atrial septum opening	Preoperative care Stage 1 palliation Transplantation	Stage 2 palliation Transplantation	Stage 3 palliation Transplantation
Suitability for subsequent stage	NA	Suitability fo stage 2	Suitability for TCPC	Suitability for transplantation

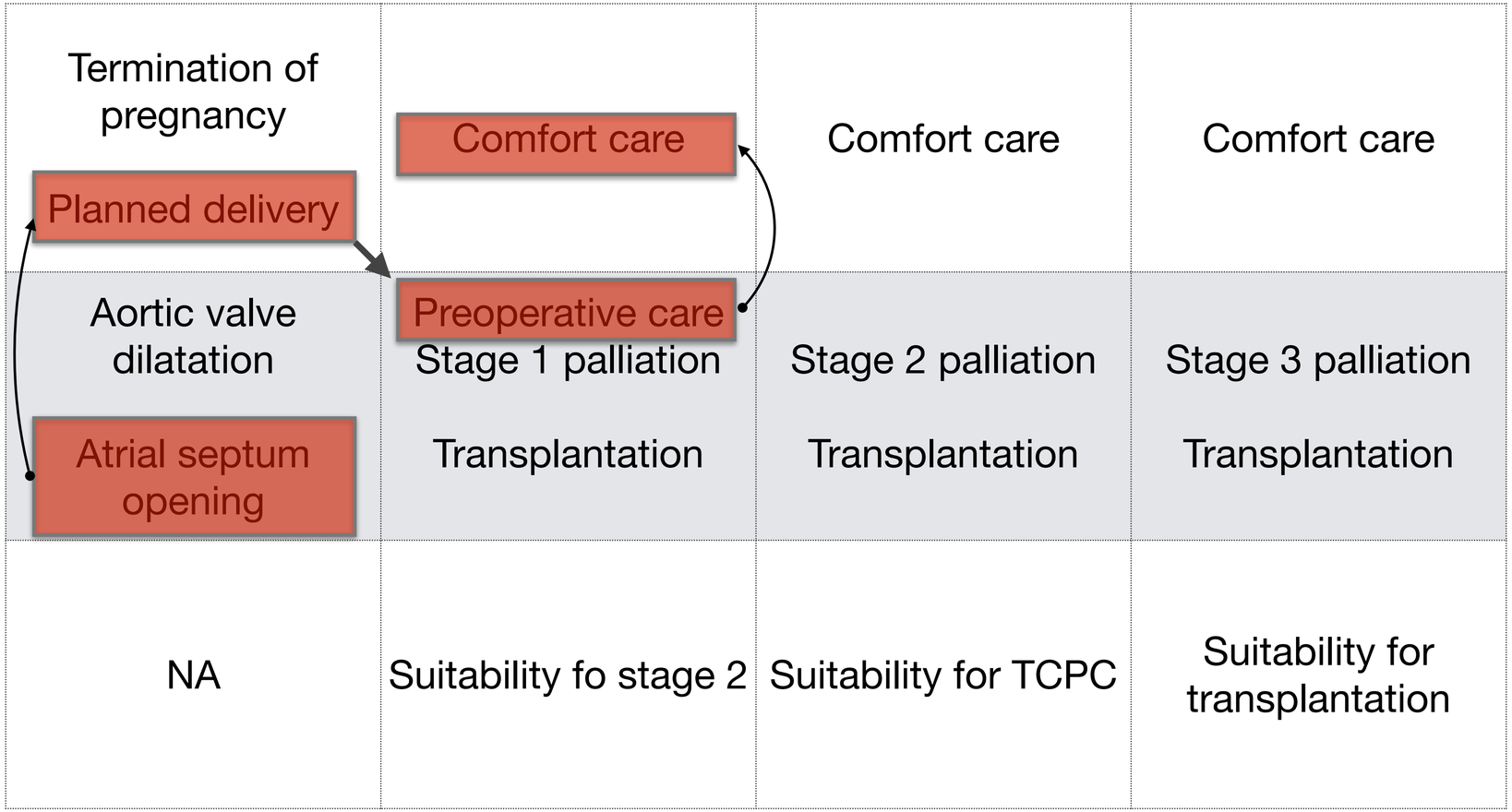
The plan of action may change at different time points



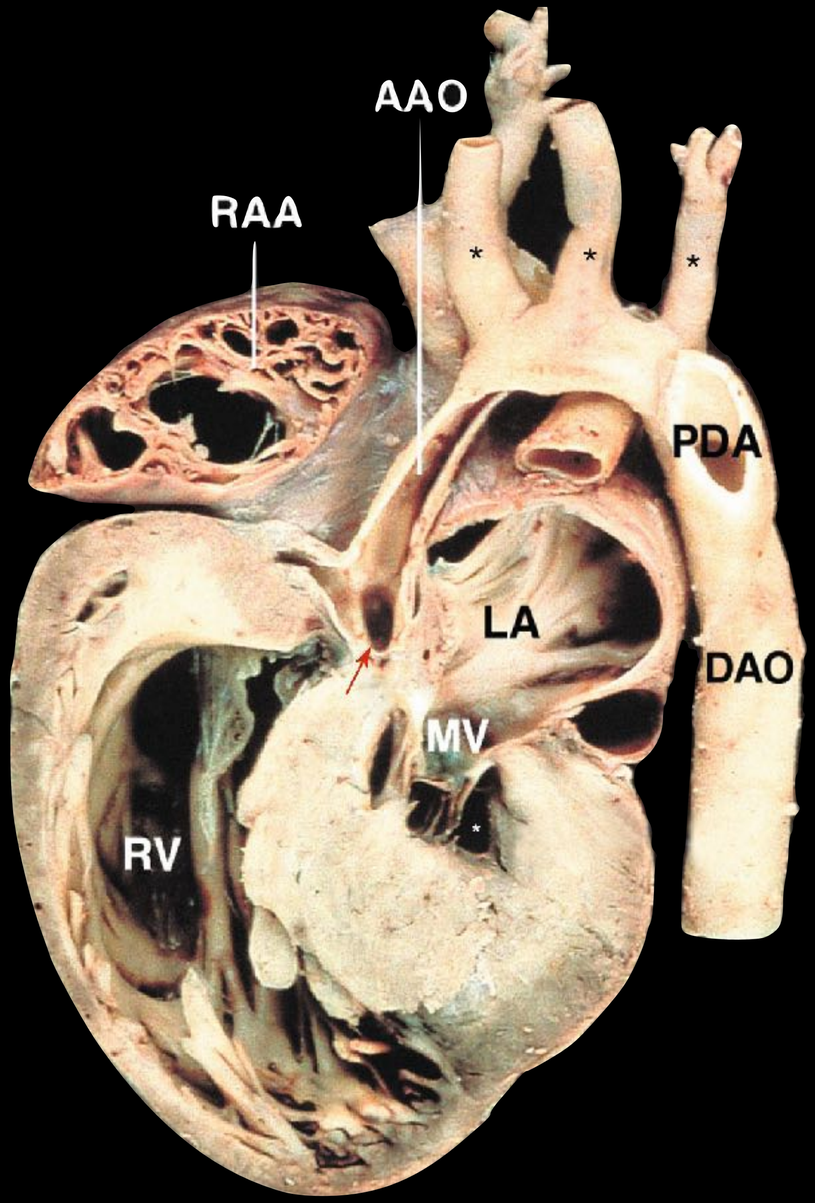
The plan of action may change at different time points



The plan of action may change at different time points



Hypoplastic left heart syndrome/HLH complex



Is it possible stratify risk in HLHS before stage 1 ?

- **The current goal of HLHS management before stage 1 is to identify the factors associated with the achievement initial objectives of stage 1 palliation that are:**

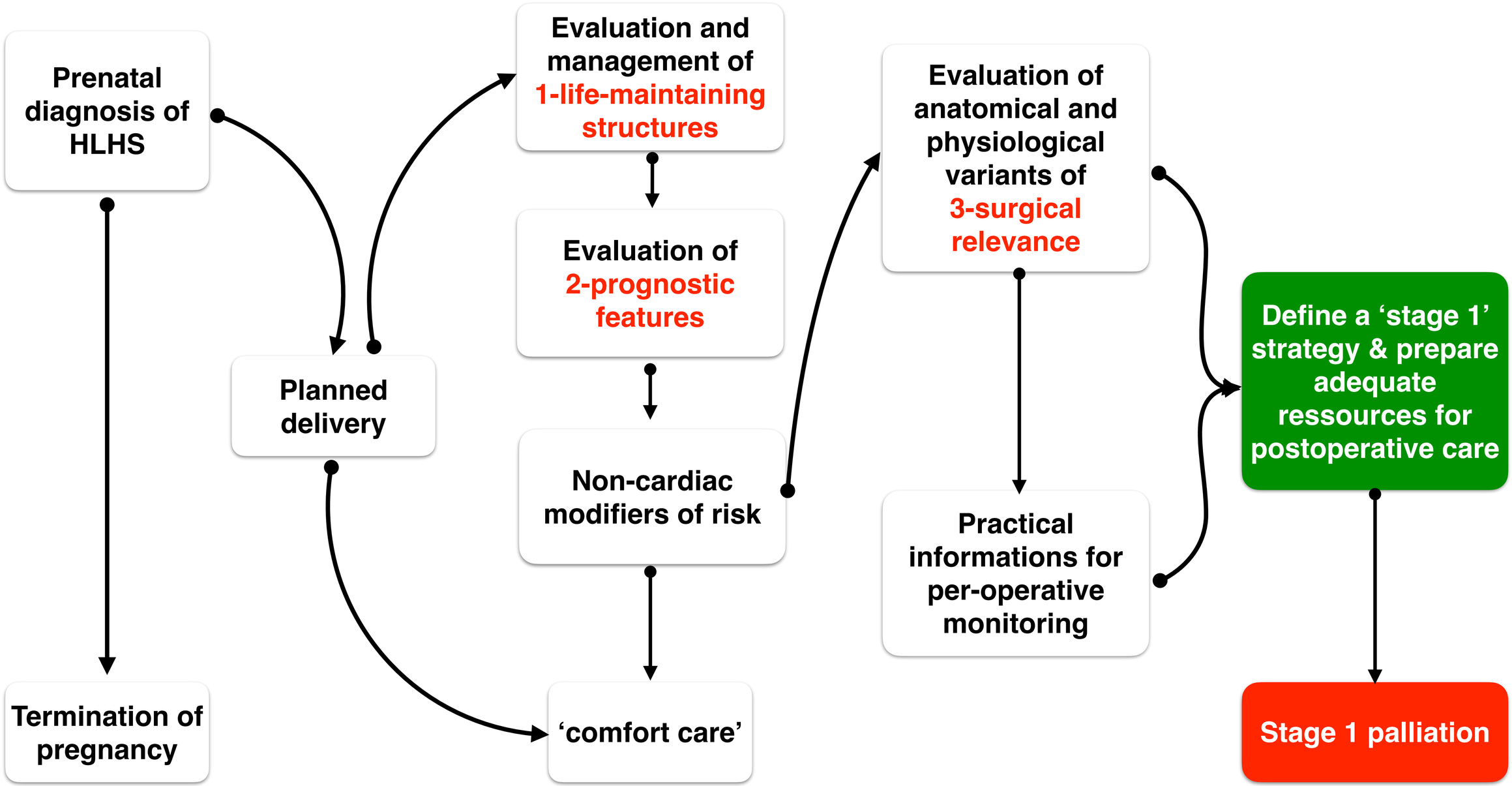
  1. Provide unobstructed systemic cardiac output;
  2. Provide a controlled source of pulmonary blood flow;
  3. Provide a reliable source of coronary blood flow;
  4. Provide unobstructed egress of blood from the pulmonary veins.

- **To achieve a low-mortality/adverse events-risk status** during postoperative course and during interstage period.

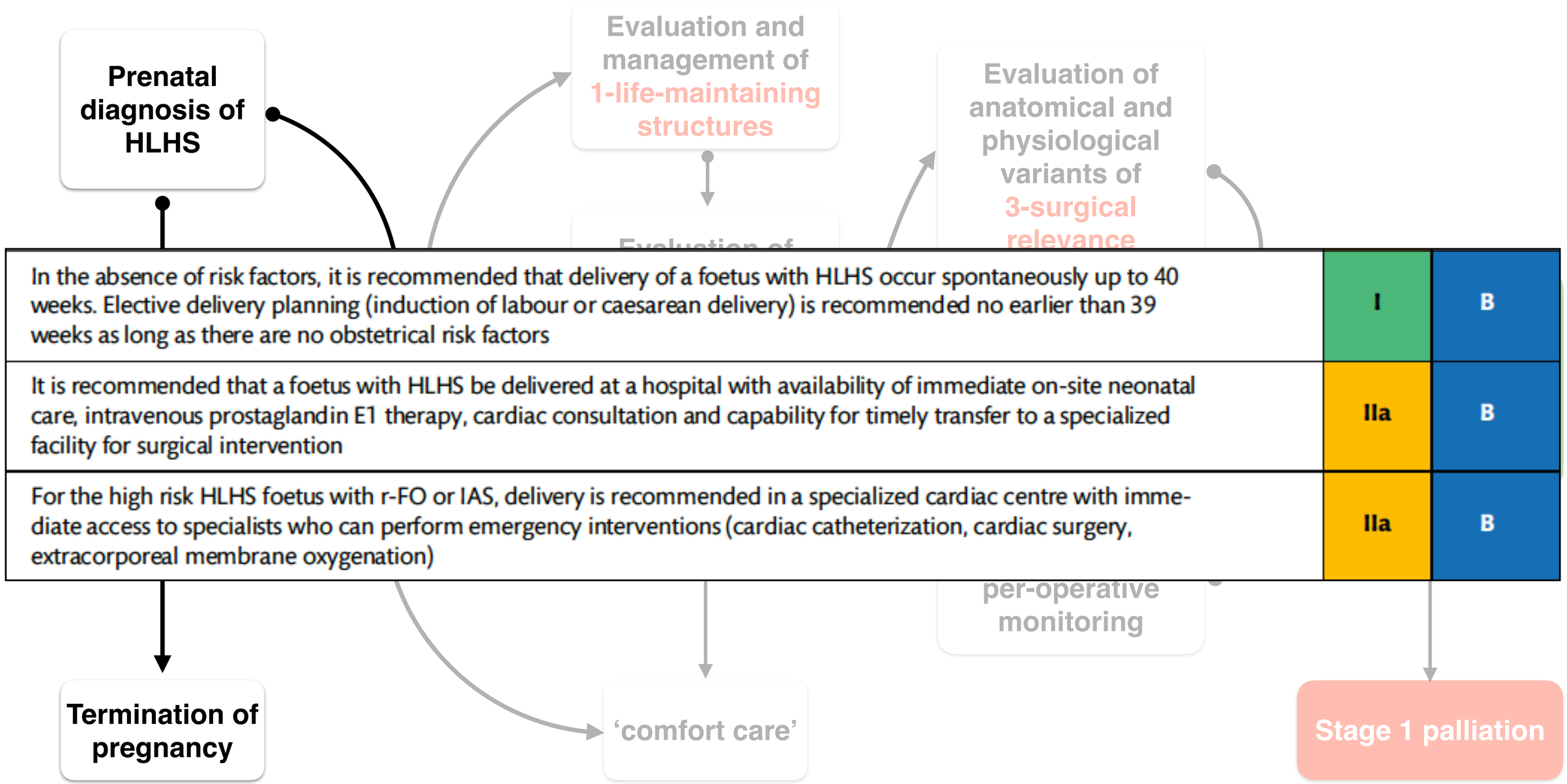
- To enable this outcome, **assessments of mortality/adverse events risk factors** should be made **at diagnosis and during pre-Stage 1palliation period** with appropriate tools.

- **The results of these assessments should be used to guide preoperative medical management and surgical strategy.**

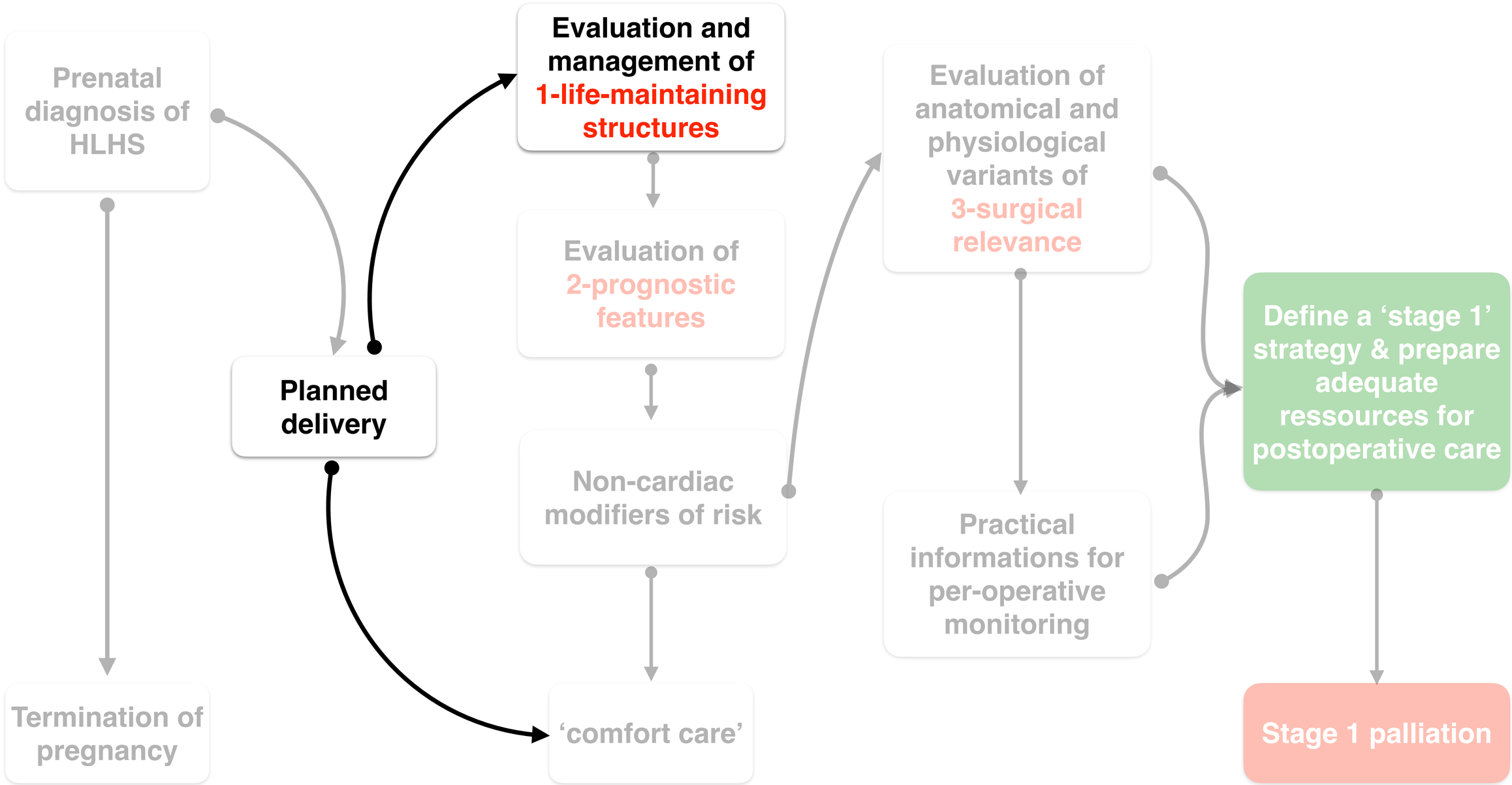
- Finally, these assessments should lead to a proactive change in therapy according to risk status.



Guidelines for the management of neonates and infants with hypoplastic left heart syndrome. European Journal of Cardio-Thoracic Surgery 2020;58:416–499

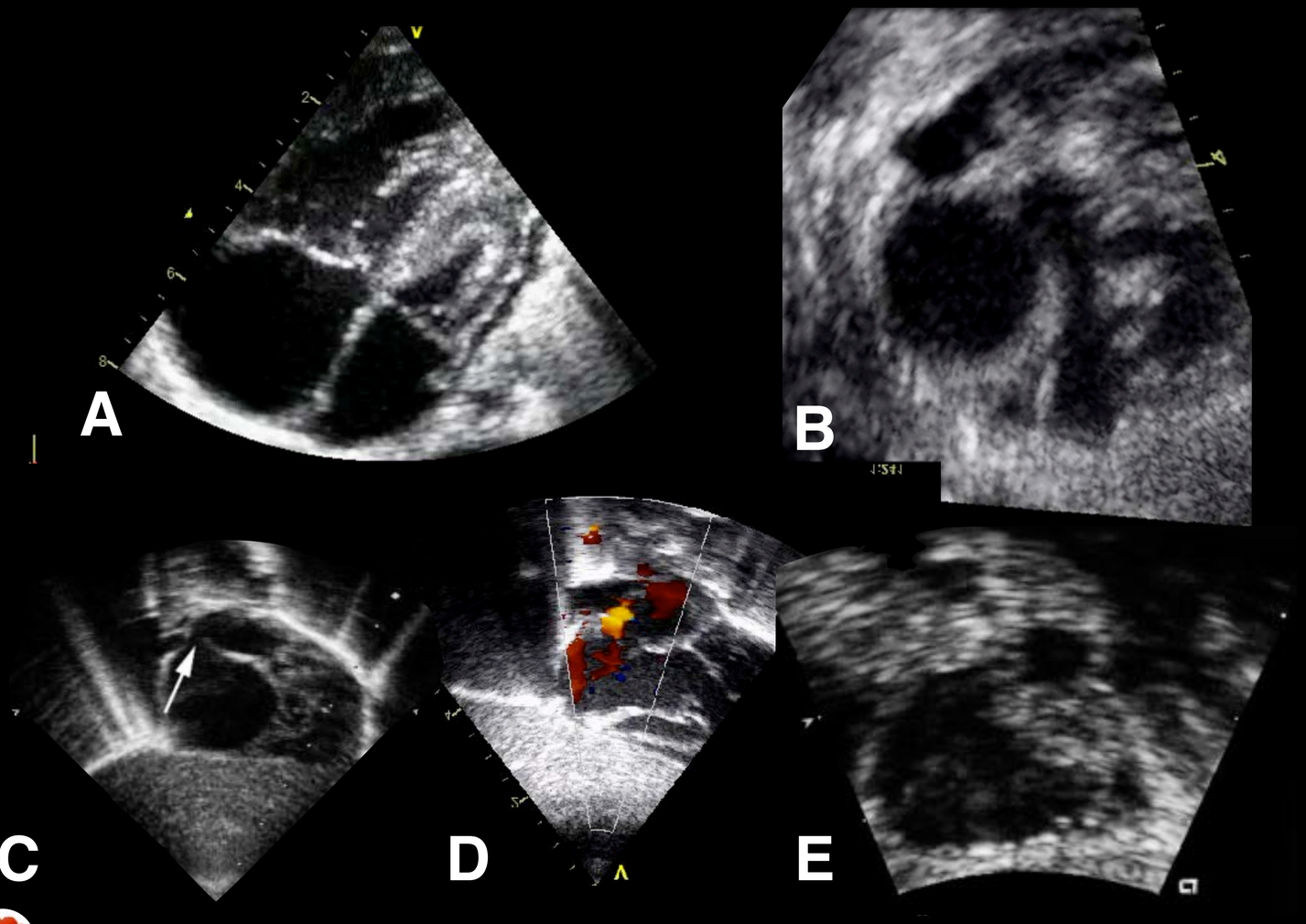


In the absence of risk factors, it is recommended that delivery of a foetus with HLHS occur spontaneously up to 40 weeks. Elective delivery planning (induction of labour or caesarean delivery) is recommended no earlier than 39 weeks as long as there are no obstetrical risk factors	I	B
It is recommended that a foetus with HLHS be delivered at a hospital with availability of immediate on-site neonatal care, intravenous prostaglandin E1 therapy, cardiac consultation and capability for timely transfer to a specialized facility for surgical intervention	IIa	B
For the high risk HLHS foetus with r-FO or IAS, delivery is recommended in a specialized cardiac centre with immediate access to specialists who can perform emergency interventions (cardiac catheterization, cardiac surgery, extracorporeal membrane oxygenation)	IIa	B


Prenatal diagnosis of HLHS
Evaluation and management of 1-life-maintaining structures
Evaluation of 2-prognostic features
Non-cardiac modifiers of risk
Evaluation of anatomical and physiological variants of 3-surgical relevance
Practical informations for per-operative monitoring
Define a ‘stage 1’ strategy & prepare adequate ressources for postoperative care
Stage 1 palliation
Planned delivery
‘comfort care’
Termination of pregnancy

Evaluation and management of life-maintaining structures

Atrial septum



1. **Type A atrial morphology**. A relatively large left atrium with a thick septum secundum and a thin septum primum adherent to each other. Frequent leftward and posteriorly deviated septum primum attached to the roof of the left atrium.

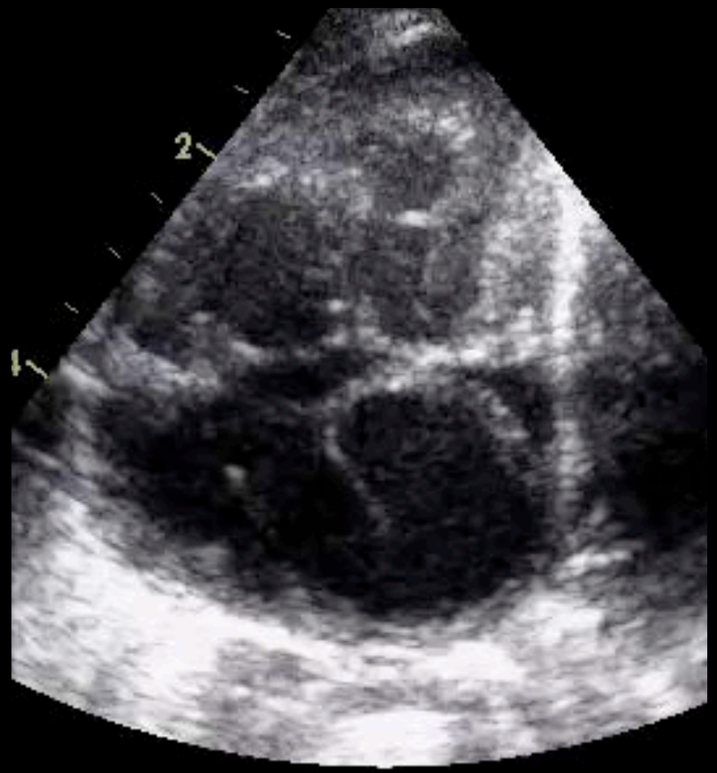
2. **Type B atrial morphology**. A small, muscular left atrium with circumferential thickening of the atrial walls and a thick “spongy” muscular atrial septum without ostensible distinction between septum primum and septum secundum.

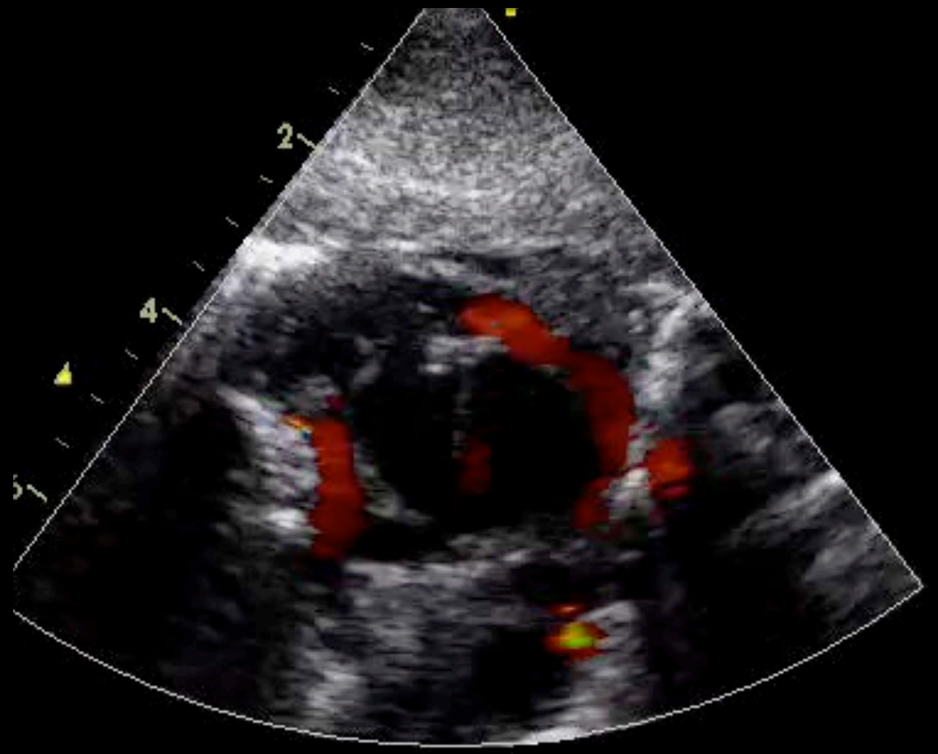
3. ***Type C atrial morphology***. *A giant left atrium with a thin, rightward bulging, septum primum and secundum, this in the setting of severe mitral regurgitation*

Rychick J et al. J Am Coll Cardiol 1999;34:554–60

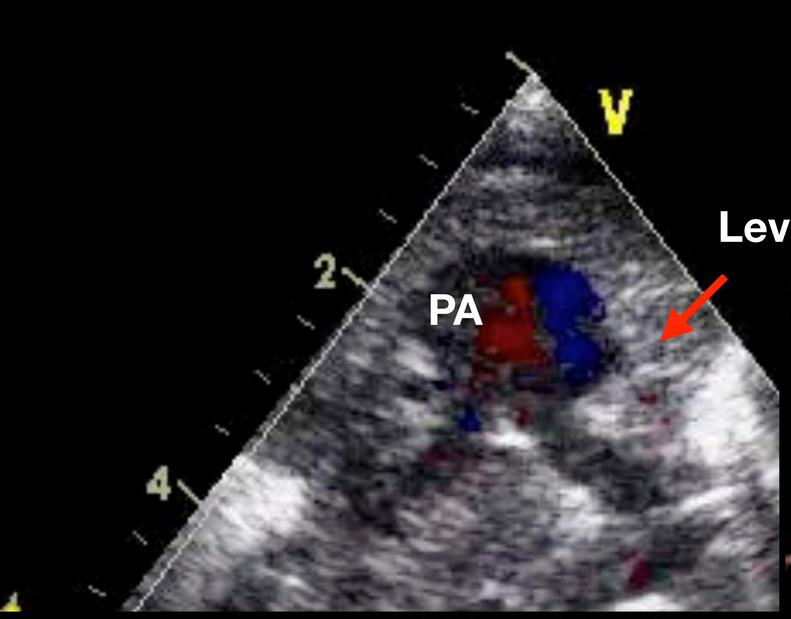
Evaluation and management of life-maintaining structures

Atrial septum with decompression pathway

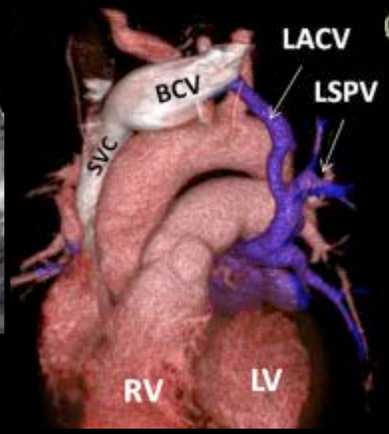




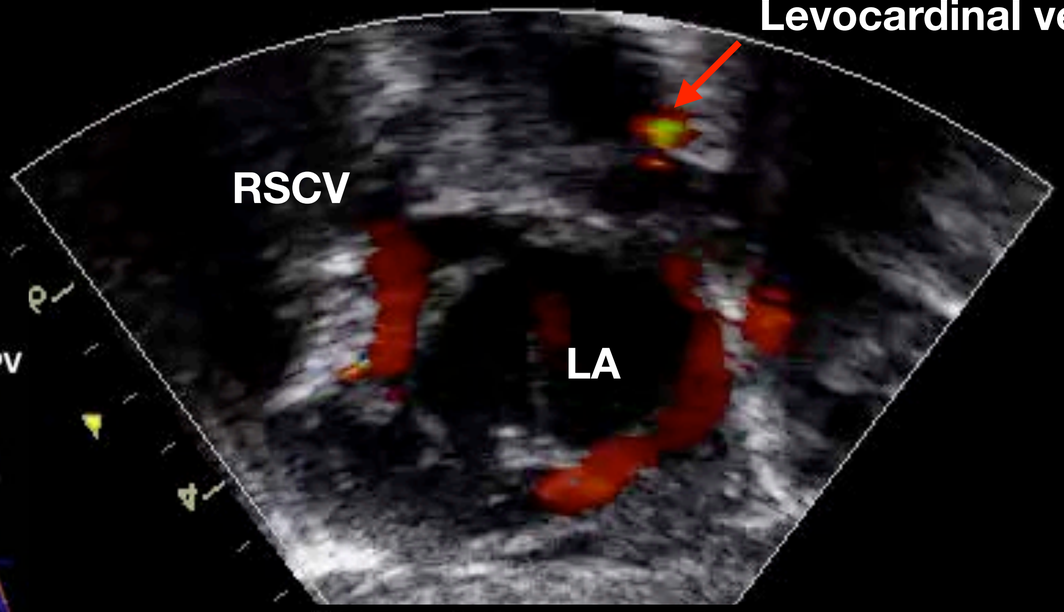
Levo-cardio-atrial vein (Levocardinal vein)

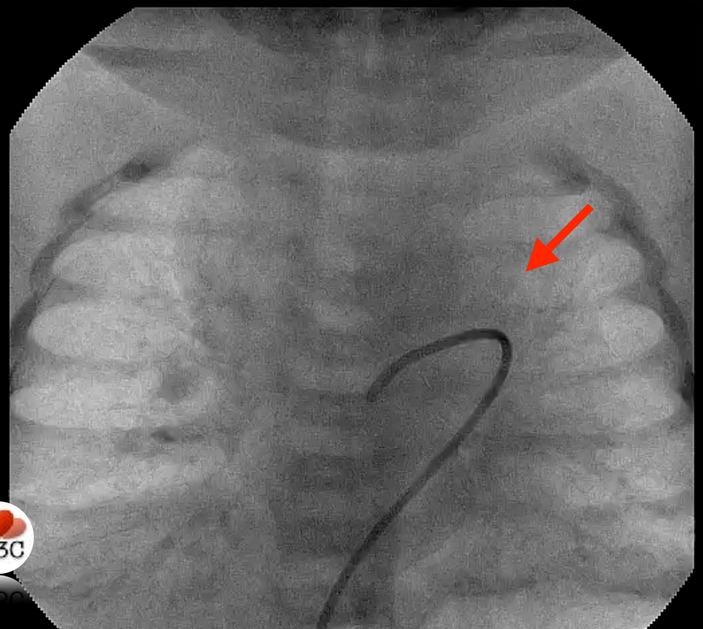


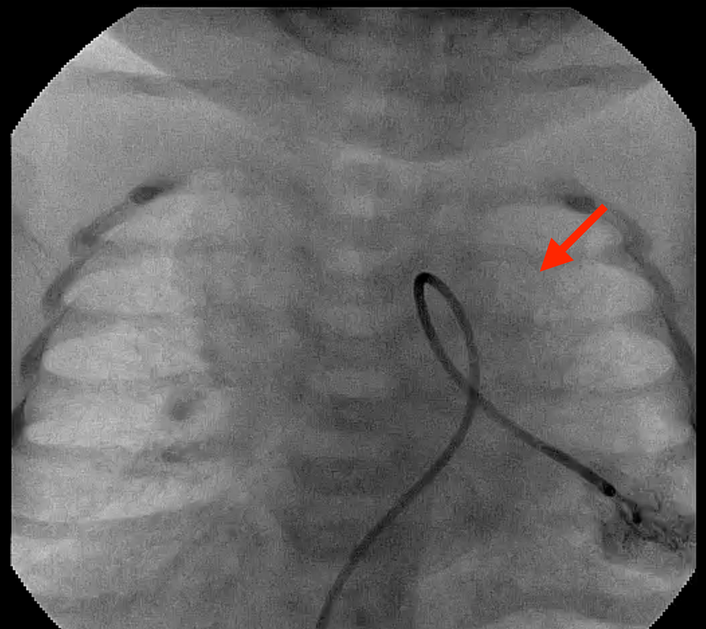
Levocardinal vein

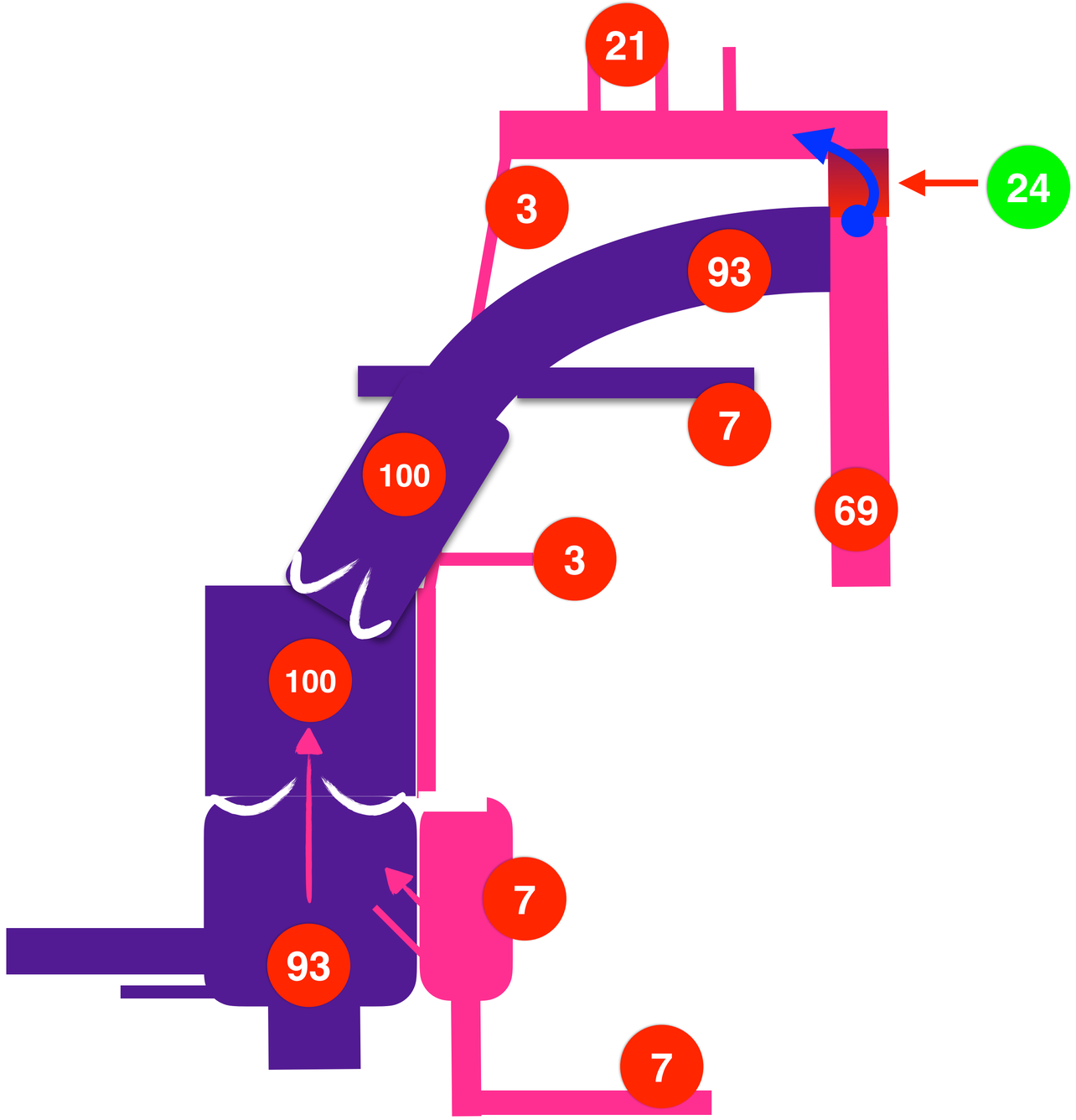


Levocardinal vein

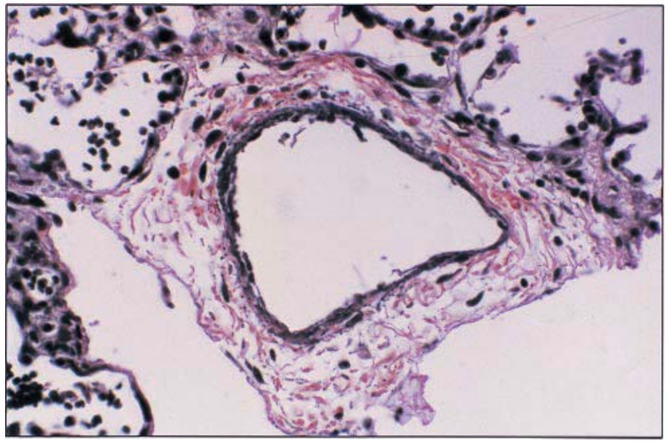




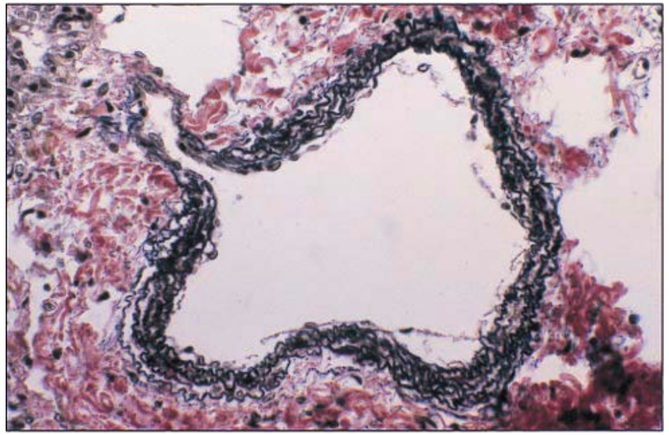




Patent Foramen ovale



Intact-restrictive Foramen ovale



Rychick J et al. J Am Coll Cardiol 1999;34:554–60

Atrial septal characteristics distinguishing Standard atrial septal anatomy (group A) from Complex atrial septal anatomy (group B)

Standard atrial septal anatomy, group A (Fig. 2)	Complex atrial septal anatomy, group B (Fig. 3)

• Typical central ASD location
• Mean gradient <15 mm Hg
	• Intact atrial septum (Fig. 3C and E)
	• Severely restrictive intraatrial septum (mean Doppler gradient ≥15 mm Hg)
	• Nontypical ASD location:
	  ○ Superior (close to the pulmonary veins) (Fig. 3A)
	  ○ Inferior (close to AV node) (Fig. 3D)
	  ○ Other unusual ASD location
	• Combination of atrial septal aneurysm and tunnel-type PFO (Fig. 3B)
	• Very thick intra-atrial septum (Fig. 3F)

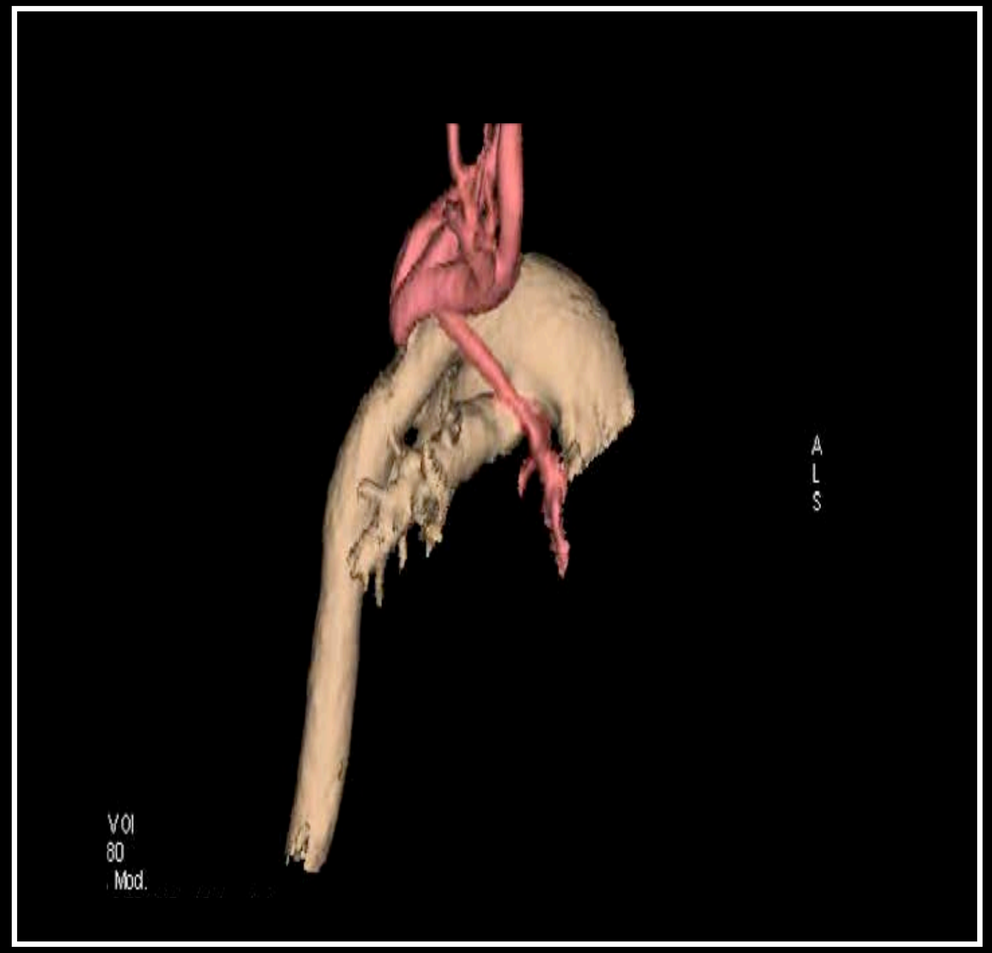
Atrial septal interventions performed	Procedures n (%)
Balloon atrial septostomy	52/67 (77.6%)
Static balloon septoplasty	18/67 (26.9%)
Cutting balloon septoplasty	12/67 (17.9%)
RF perforation of intra-atrial septum	08/67 (11.9%)
Stenting of intra-atrial septum	04/67 (5.9%)

10% of patients had restrictive or intact atrial septum
9% serious adverse events
25% of minor adverse events
50% of adverse events in group B
Reintervention on atrial septum in 20%
Stage 2 palliation 73% in group A and 57% in group B

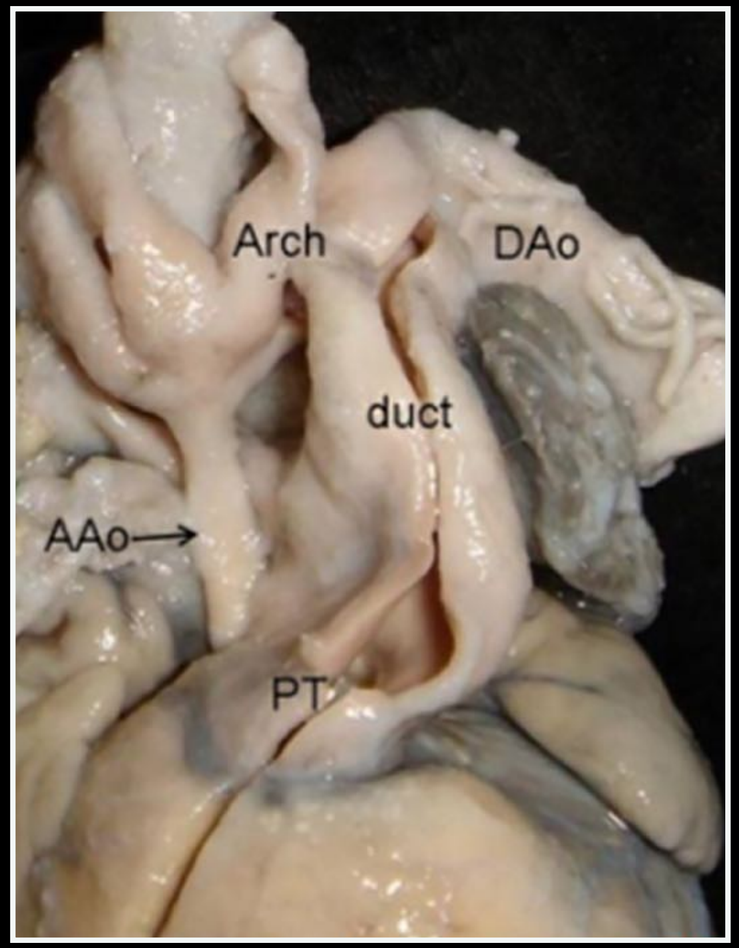
Holzer RJ et al. CCI 2008;72:696-704

Evaluation and management of life-maintaining structures

Arterial duct

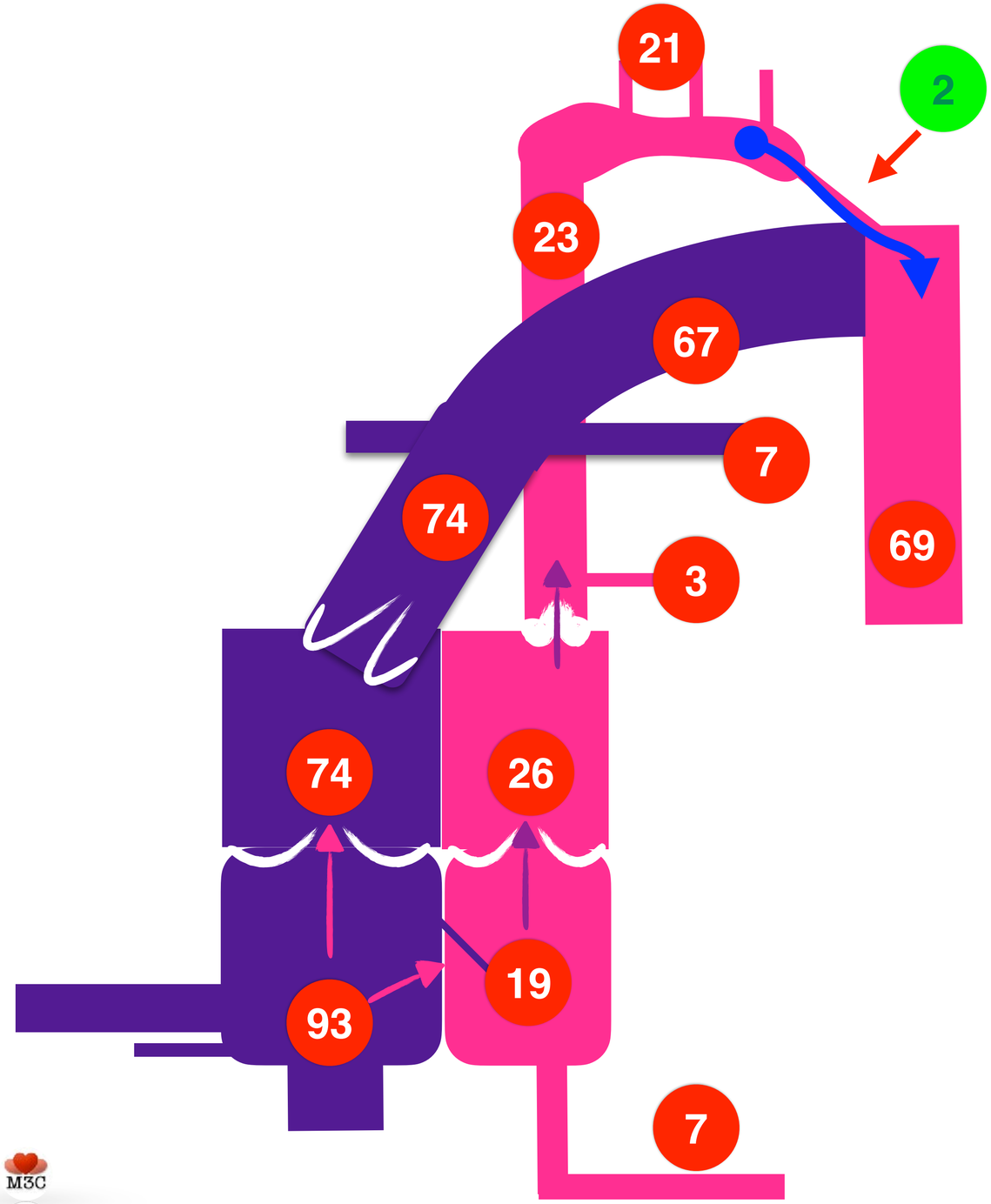


Hypoplastic left heart syndrome
Aortic atresia

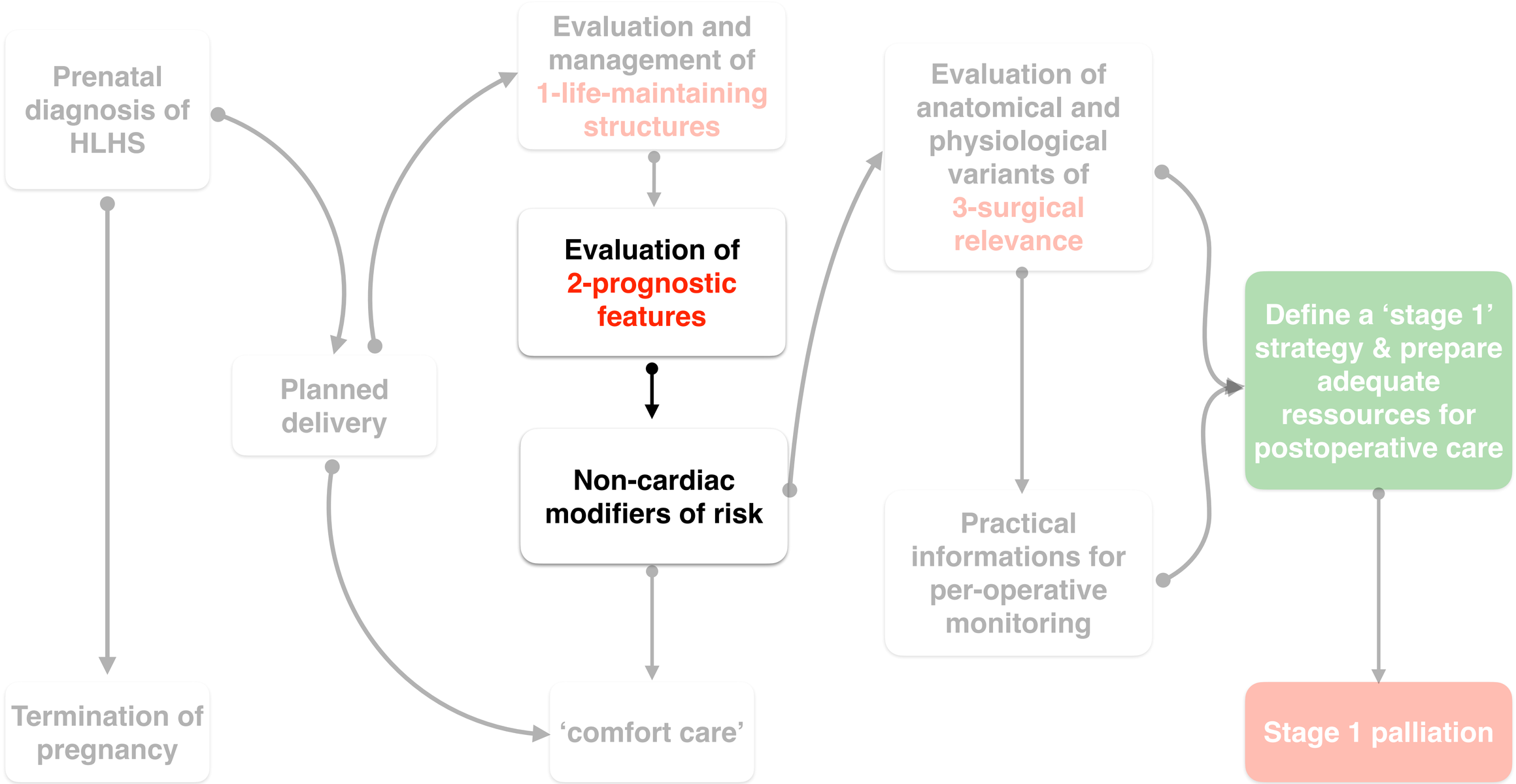


Large in HLHS with aortic atresia

Images Paediatr Cardiol. 2008 Jan-Mar; 10(1): 27–38.


21
2
23
67
7
74
69
3
74
26
19
93
7


S 16
HOPITAL NECKER ENFANT
L
P
I 85


Prenatal diagnosis of HLHS
Evaluation and management of 1-life-maintaining structures
Evaluation of 2-prognostic features
Evaluation of anatomical and physiological variants of 3-surgical relevance
Planned delivery
Non-cardiac modifiers of risk
Practical informations for per-operative monitoring
Define a ‘stage 1’ strategy & prepare adequate ressources for postoperative care
Termination of pregnancy
‘comfort care’
Stage 1 palliation

Prognostic features in hypoplastic left heart syndrome

Anatomical & functional factors

1. Right ventricular function
2. Tricuspid valve function
3. Pulmonary valve function
4. Branch pulmonary arteries
5. Ascending aorta
6. Coronary arteries

7. Associated cardiac malformations

Non-cardiac modifiers of risk

1. Birth weight
2. Extracardiac anomalies
3. Maternal-fetal environment

Anatomical and functional factors associated with outcomes

1. **Right ventricular function** needs to be repeatedly evaluated after birth (increased SVR and systemic pressure).
2. **Tricuspid valve function** may worsen after birth if present in fetus (higher SVR and systemic pressure).
3. **Ascending aorta**
4. **Coronary arteries**
5. ***Pulmonary valve function***
6. ***Branch pulmonary arteries***

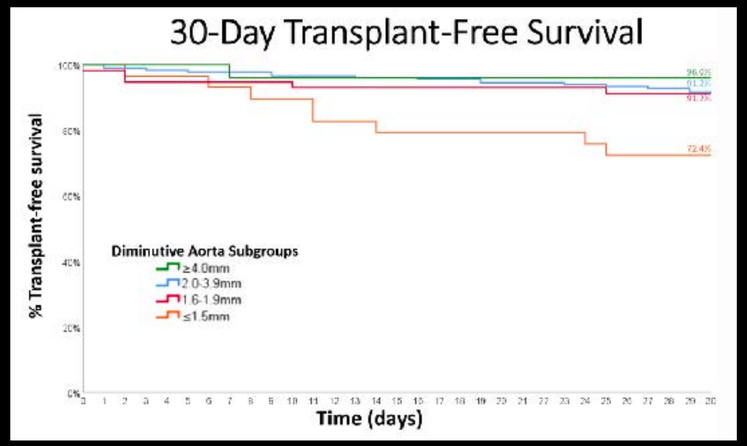
7. *Associated cardiac malformations*

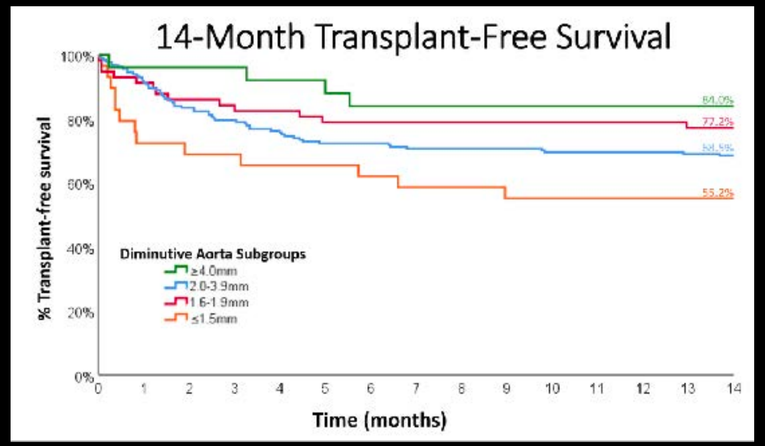
Anatomical and functional factors associated with outcomes

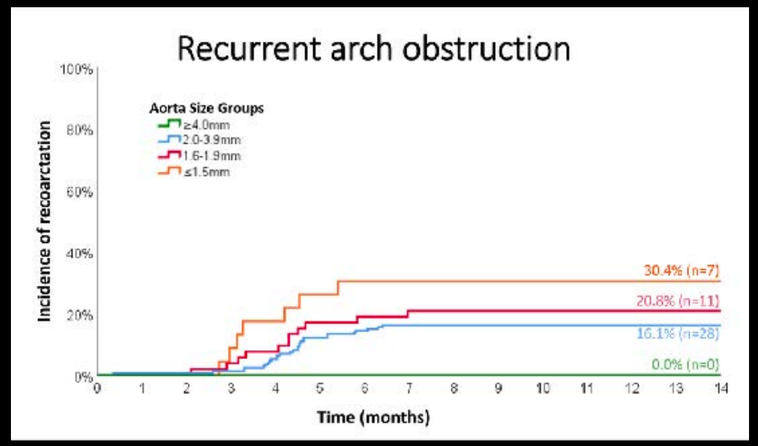
1. **Right ventricular function** needs to be repeatedly evaluated after birth (increased SVR and systemic pressure).
2. **Tricuspid valve function** may worsen after birth if present in fetus (higher SVR and systemic pressure).
3. **Ascending aorta**
4. **Coronary arteries**
5. ***Pulmonary valve function***
6. ***Branch pulmonary arteries***

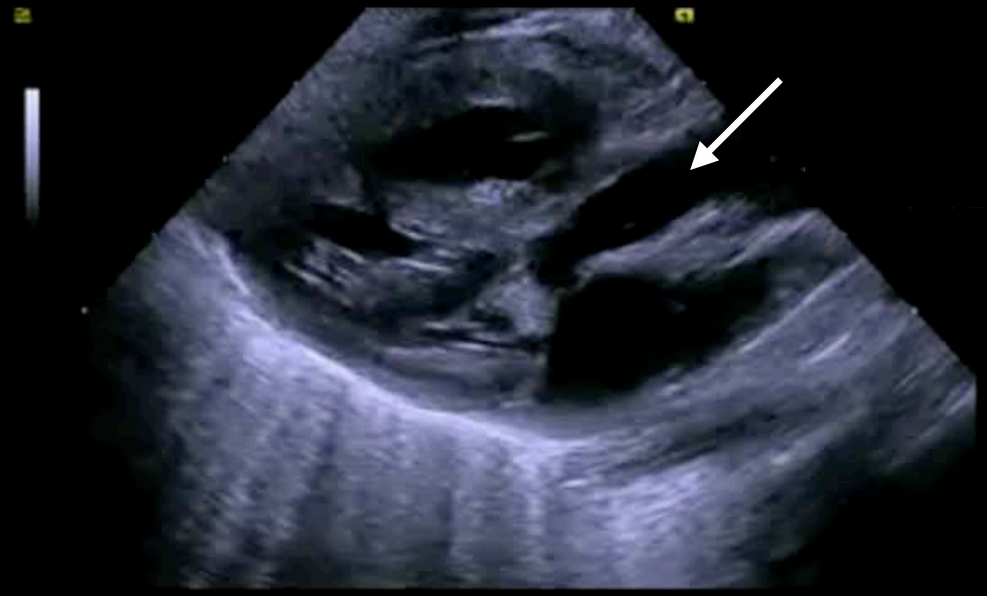
7. Associated cardiac malformations

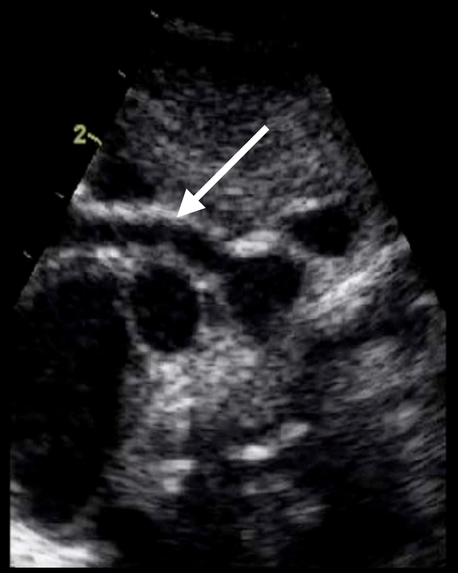
Ascending aorta size and outcomes

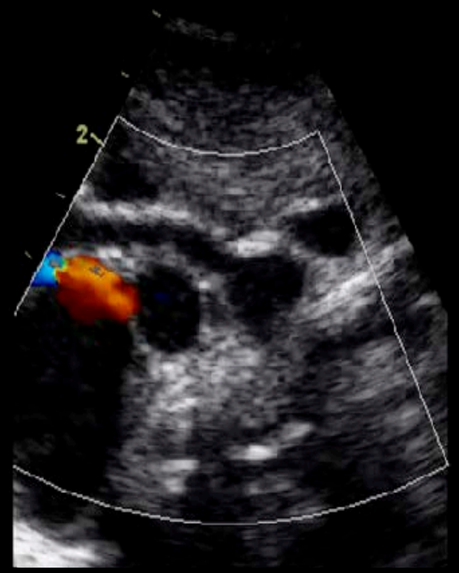












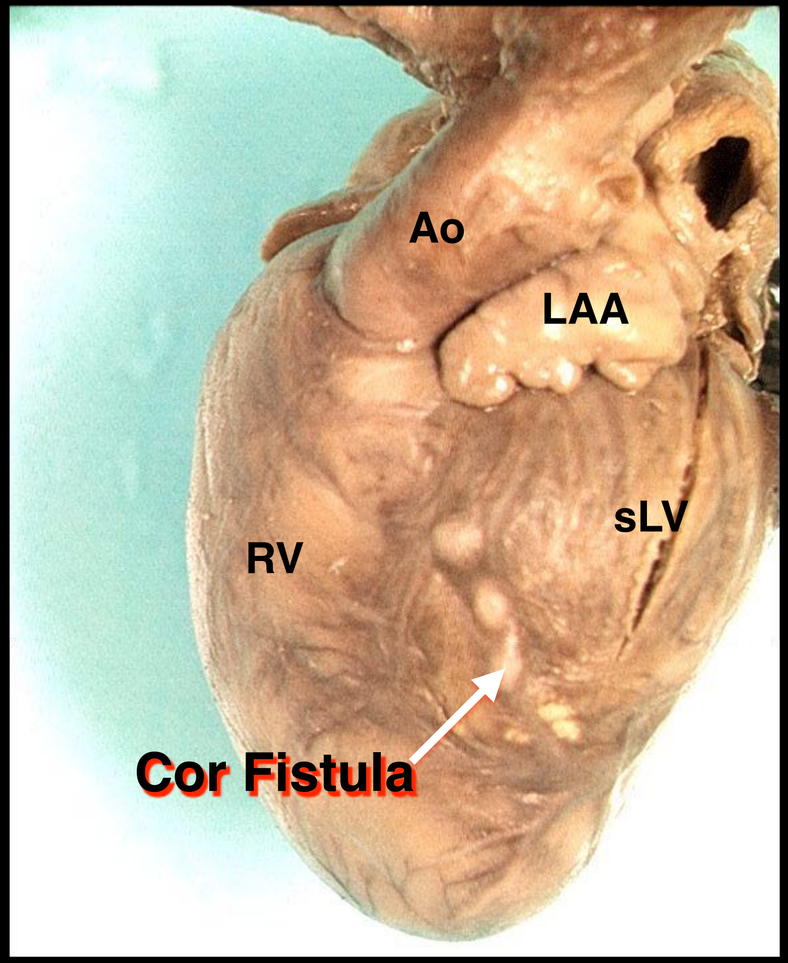
Carvajal HG, et al. Does Ascending Aorta Size Affect Norwood Outcomes in Hypoplastic Left Heart With Aortic Atresia? Ann Thorac Surg. 2020;110:1651-1658.

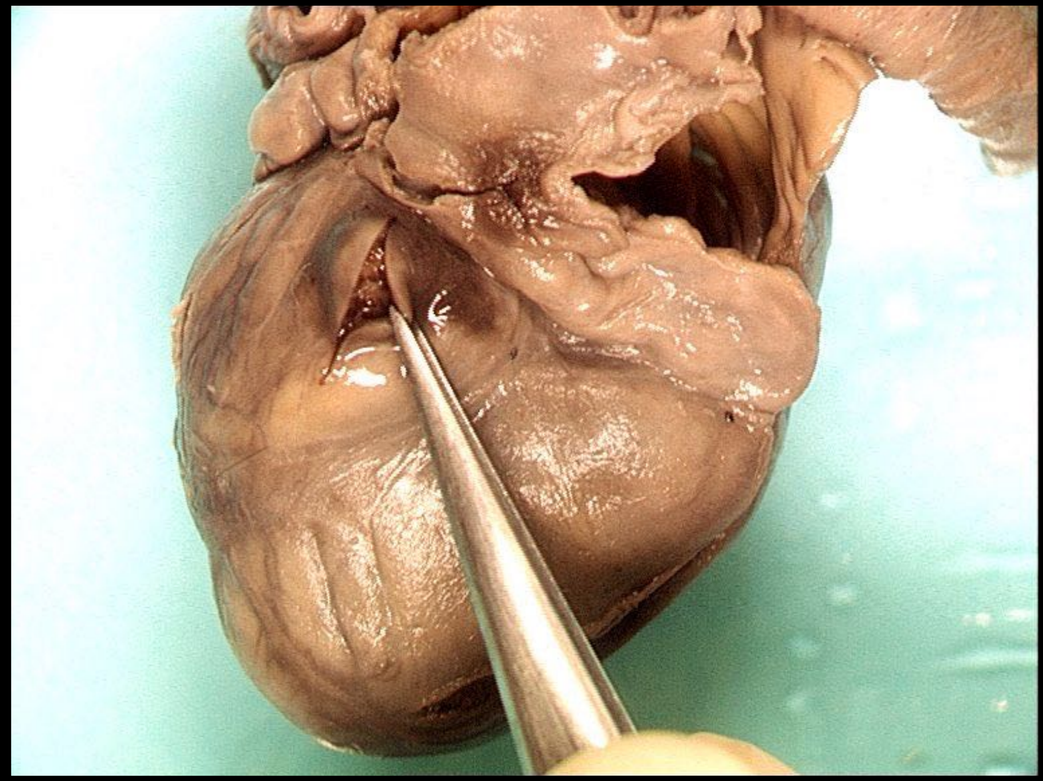
Anatomical and functional factors associated with outcomes

1. **Right ventricular function** needs to be repeatedly evaluated after birth (increased SVR and systemic pressure).
2. **Tricuspid valve function** may worsen after birth if present in fetus (higher SBR and systemic pressure).
3. **Ascending aorta**
4. **Coronary arteries**
5. ***Pulmonary valve function***
6. ***Branch pulmonary arteries***

7. Associated cardiac malformations

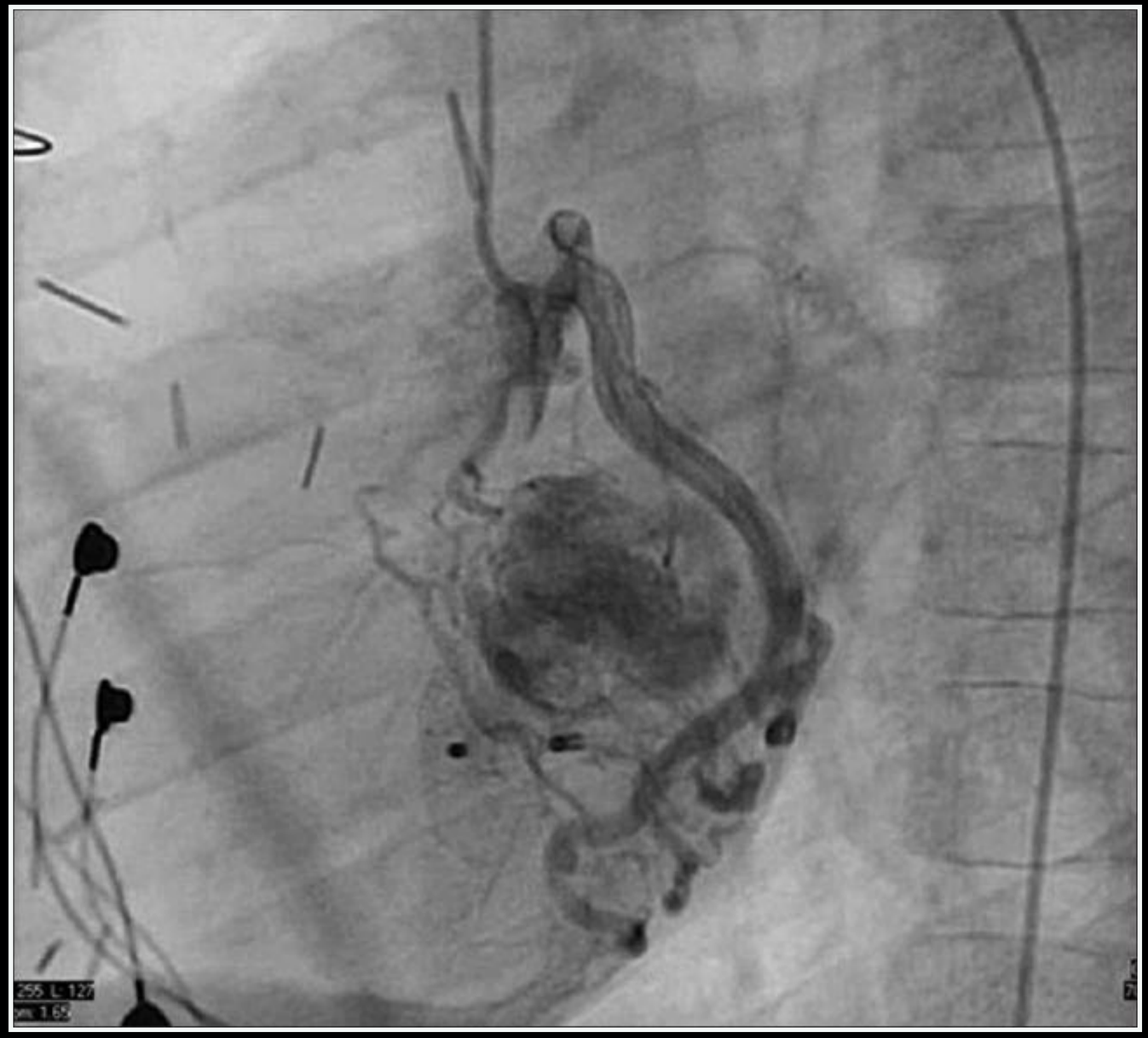
Coronary fistula in HLHS



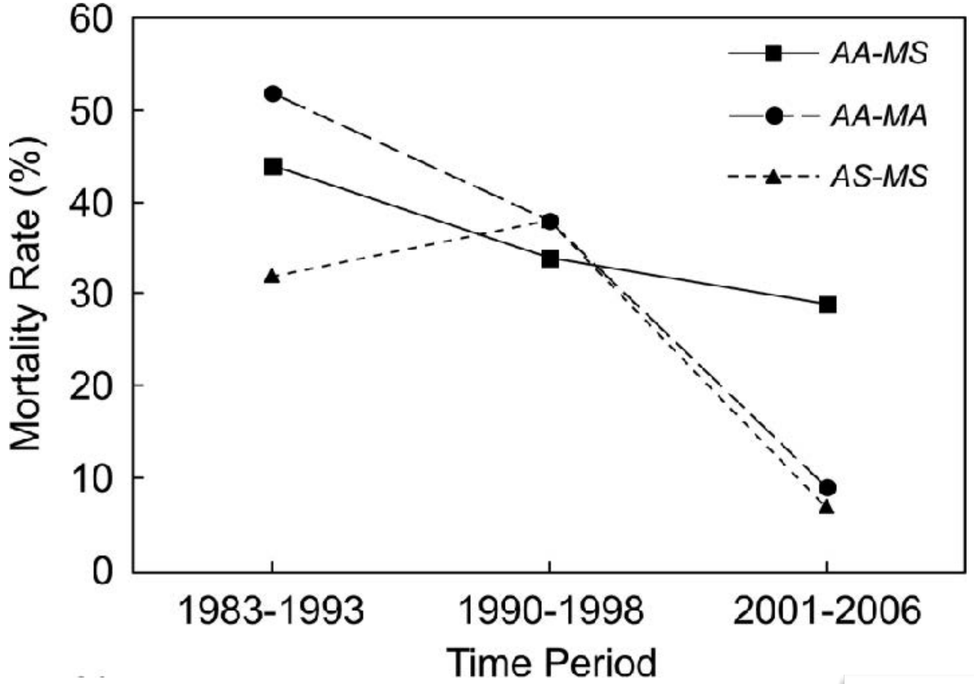


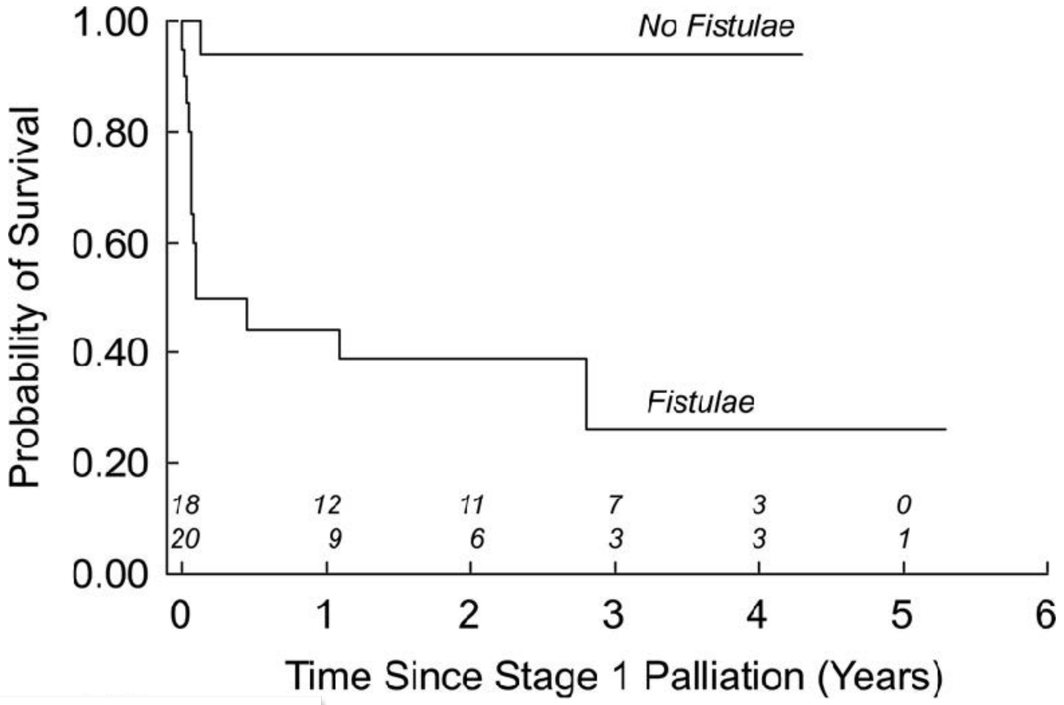
Courtesy Pr Lucile Houyel M3C museum

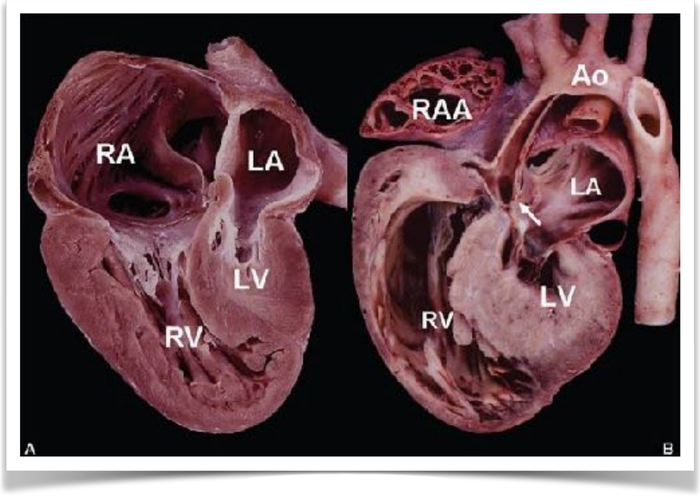
Coronary fistula in HLHS



Anatomic subtype and mortality







Vida VL, et al. J Thorac Cardiovasc Surg. 2008;135:339-46.

Anatomical and functional factors associated with outcomes

1. **Right ventricular function** needs to be repeatedly evaluated after birth (increased SVR and systemic pressure).
2. **Tricuspid valve function** may worsen after birth if present in fetus (higher SBR and systemic pressure).
3. **Ascending aorta**
4. **Coronary arteries**
5. ***Pulmonary valve function***
6. ***Branch pulmonary arteries***

7.Associated cardiac malformations : totally anomalous pulmonary venous drainage

Non cardiac modifiers of risk in HLHS

Preoperative mortality associated with :
Gestational age < 36 weeks
Low birth weight < 2500 g
Major extracardiac congenital abnormality

Increased mortality after stage 1 palliation
Impaired maternal fetal environment (maternal gestational hypertension, preeclampsia, gestational diabetes, and/or smoking during pregnancy)

Atz AM, et al; Pediatric Heart Network Investigators. Prenatal diagnosis and risk factors for preoperative death in neonates with single right ventricle and systemic outflow obstruction: screening data from the Pediatric Heart Network Single Ventricle Reconstruction Trial(*). J Thorac Cardiovasc Surg. 2010;140(6):1245-50.
Savla JJ, et al. Impact of Maternal-Fetal Environment on Mortality in Children With Single Ventricle Heart Disease. J Am Heart Assoc. 2022;11(2):e020299.

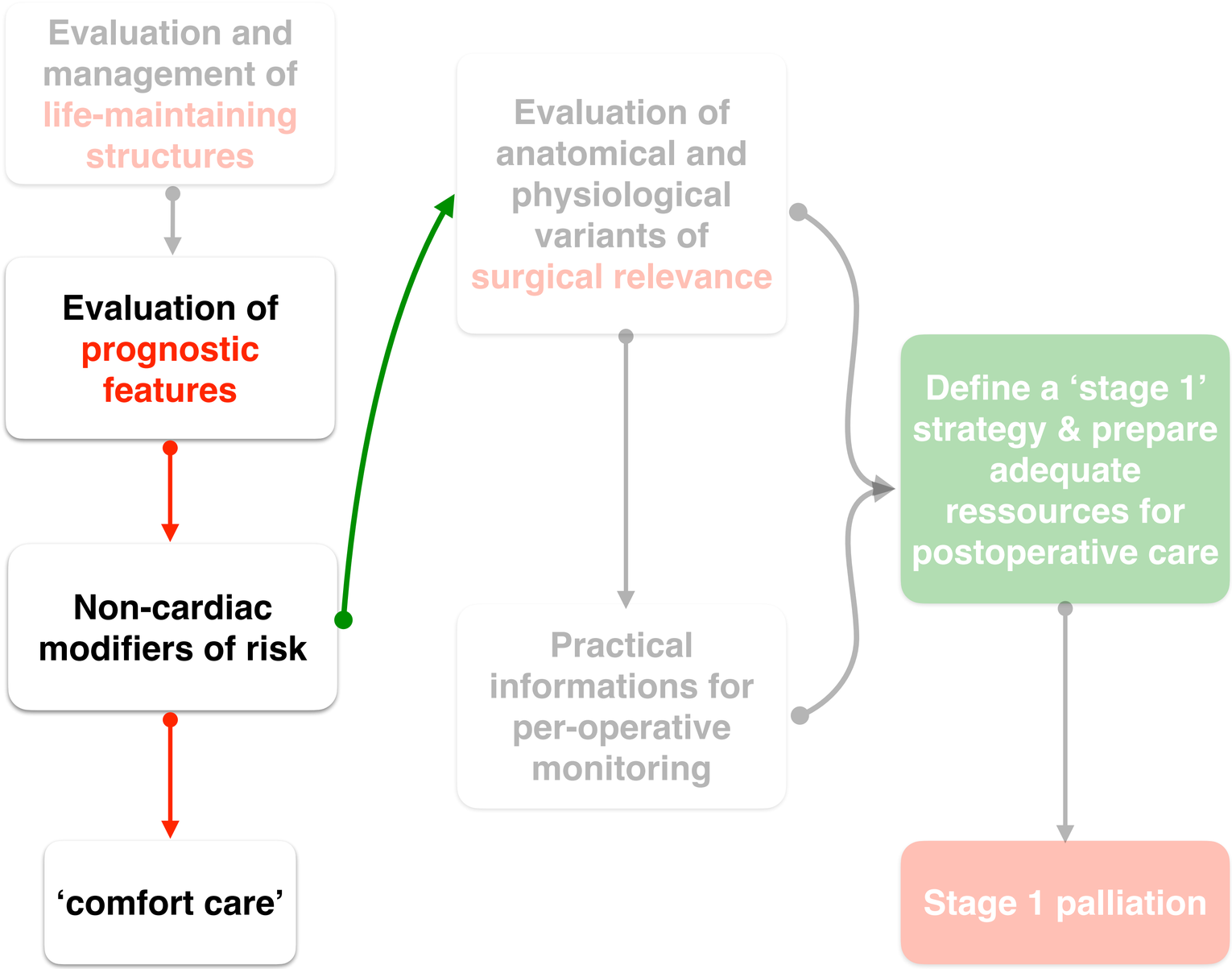
Hazard ratios of independent risk factors

1- For early death

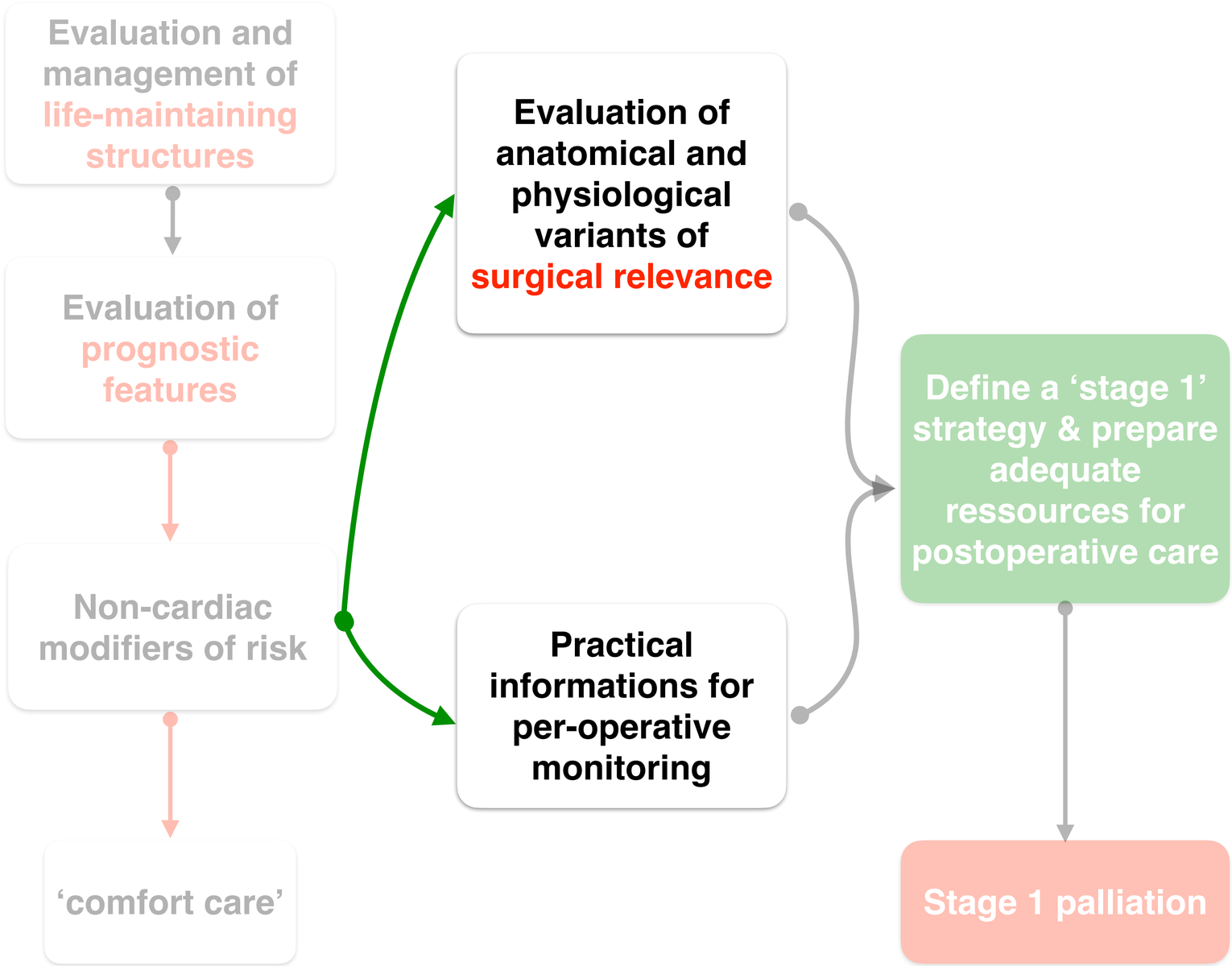
- obstructed pulmonary venous return 4.75
- smaller ascending aorta, per mm 1.23
- anatomic subtype AA/MA vs. AA/MS 0.84
- lower socioeconomic status 1.28

2- For constant phase

- Lower gestational age 1.56
- Genetic syndrome present 9.34



Tweddell JS et al. J Thorac Cardiovasc Surg 2012;144:152-9.



Tweddell JS et al. J Thorac Cardiovasc Surg 2012;144:152-9.

Evaluation of anatomical and physiological variants of surgical relevance
&
Practical informations for per-operative monitoring

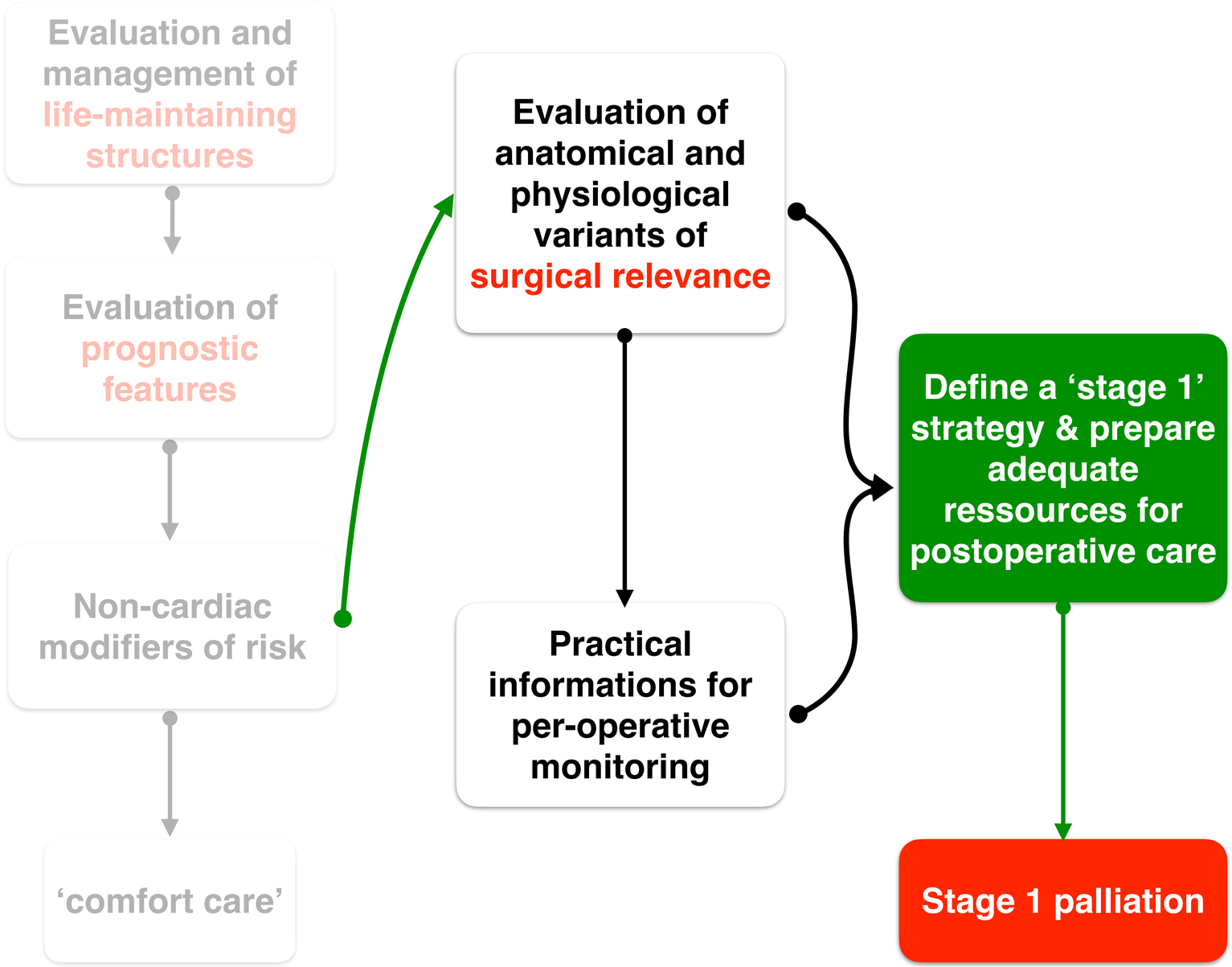
1.Aortic arch position and branching
- a.Surgical reconstruction
- b.BT shunt placement
- c.Monitoring

2.Aortic valve patency and aortic arch size
- a.Reconstruction of the aortic arch (patch augmentation, DKK)
- b.Retrograde coarctation (for hybrid procedures)
- c.Coronary perfusion issues

3.Systemic venous anatomy

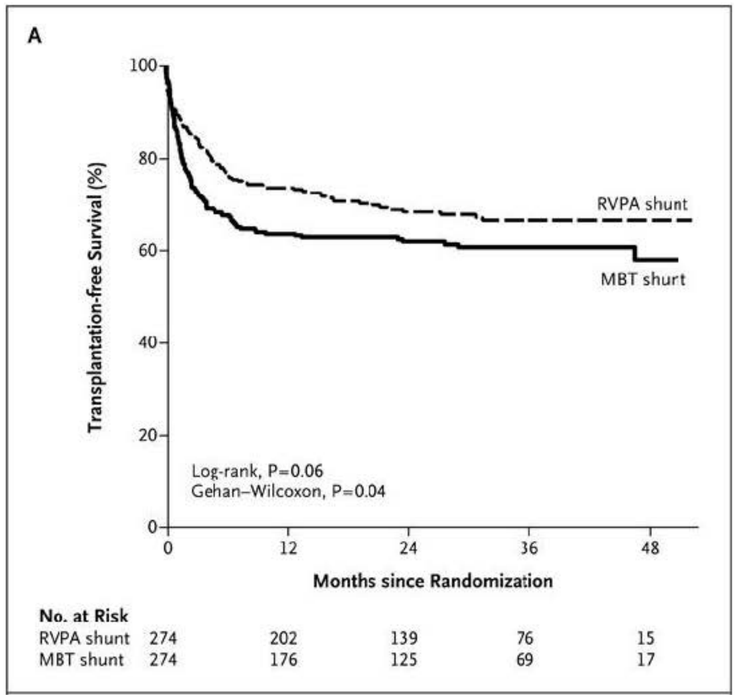
4.Associated cardiac malformations

5.Newborn clinical condition
- a.Stable
- b.Unstable, shock/MOF, systemic hypoperfusion

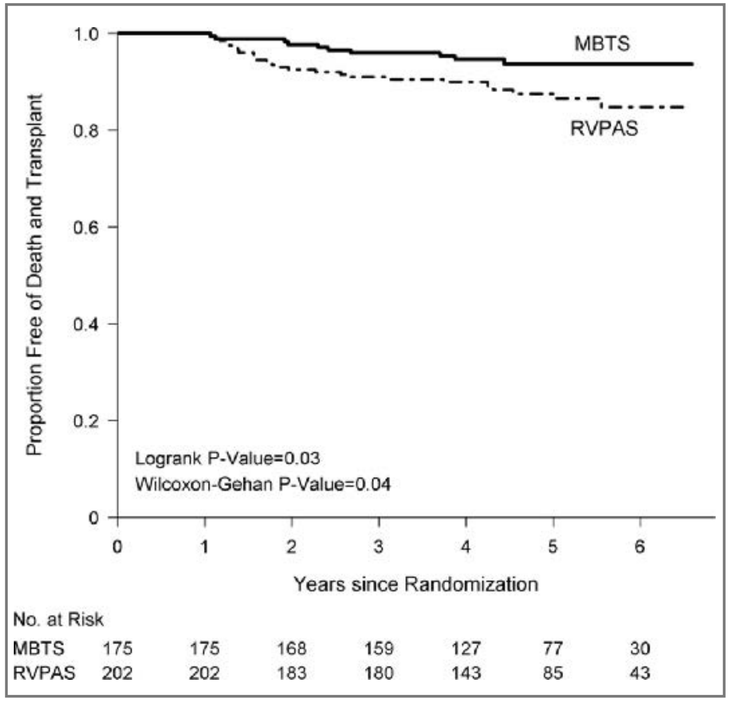


Tweddell JS et al. J Thorac Cardiovasc Surg 2012;144:152-9.

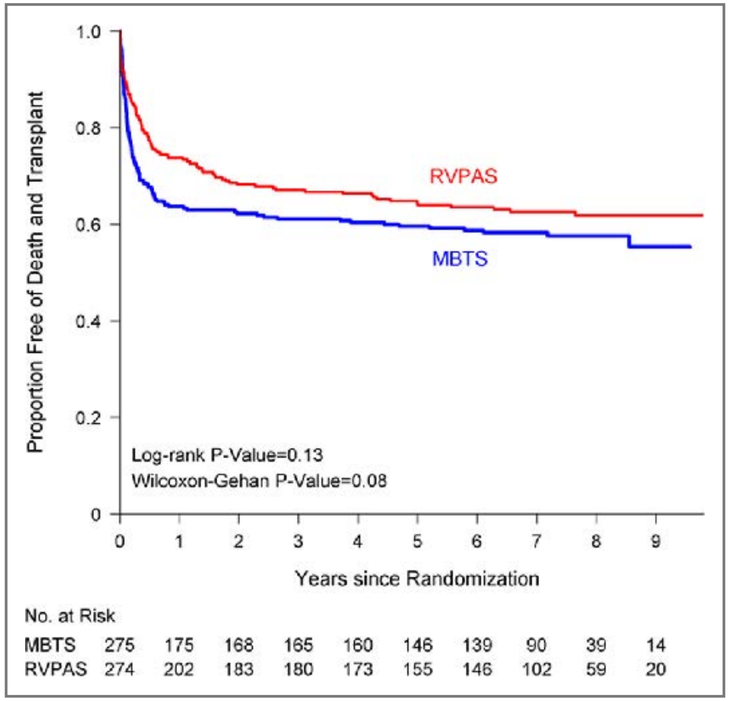
Single Ventricle Reconstruction trial



1 year



3 years (conditional)



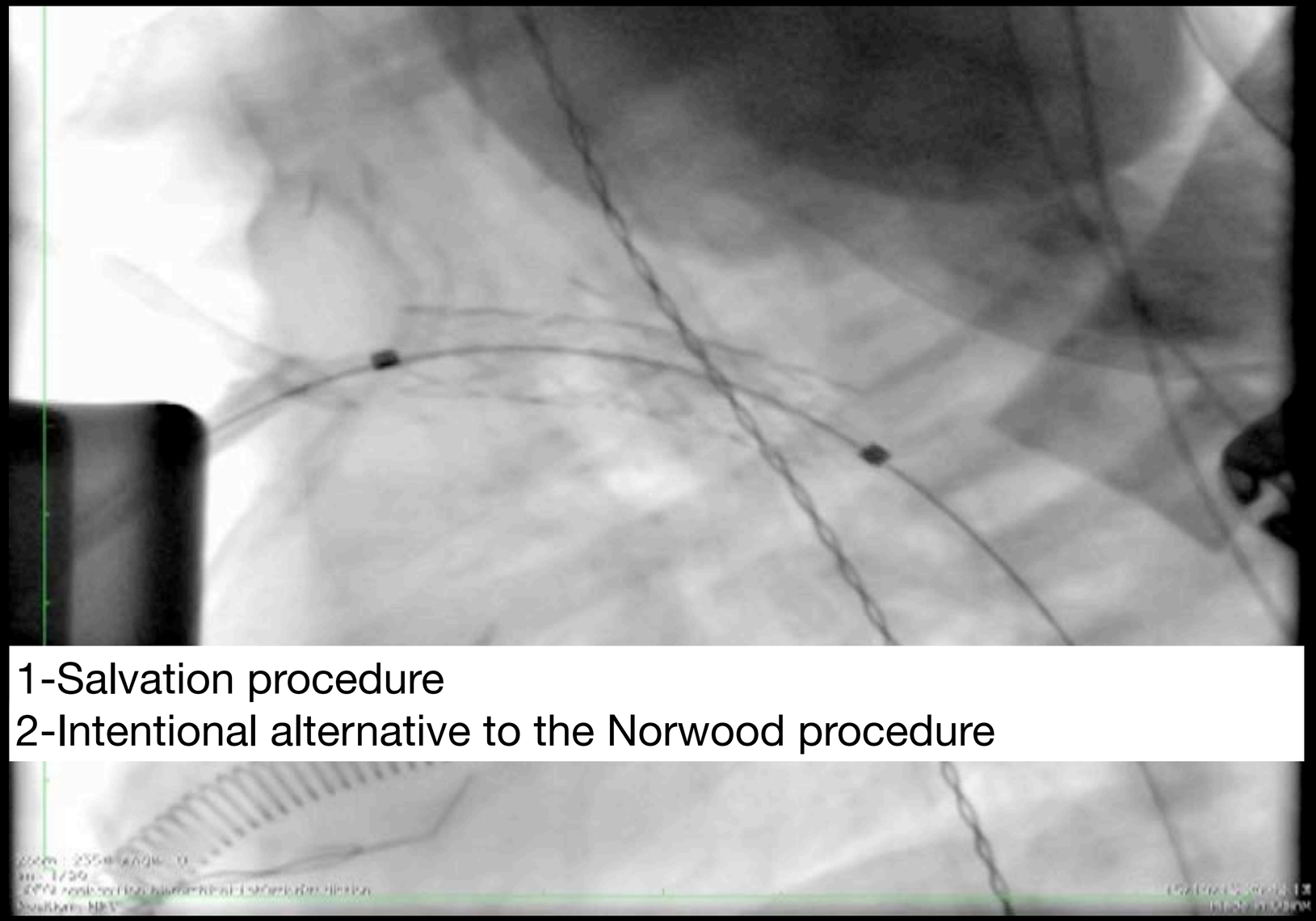
6 years

Term newborns AA RVPAS vs. Preterm newborns AS MBTS

Ohye RG, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. New England Journal of Medicine. 2010;362:1980-92.
Newburger JW, et al. Transplantation-free survival and interventions at 3 years in the single ventricle reconstruction trial. Circulation. 2014;129:2013-20.
Newburger JW, et al. Transplant-Free Survival and Interventions at 6 Years in the SVR Trial. Circulation. 2018;137:2246-2253.

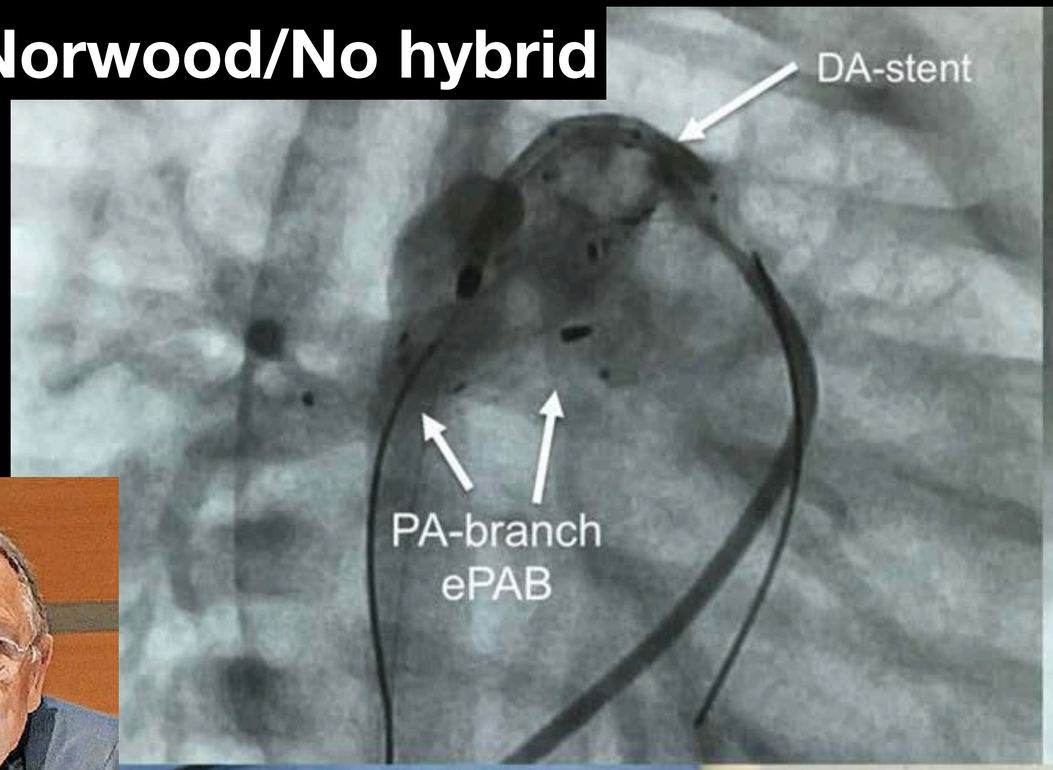
Hypoplastic left heart syndrome

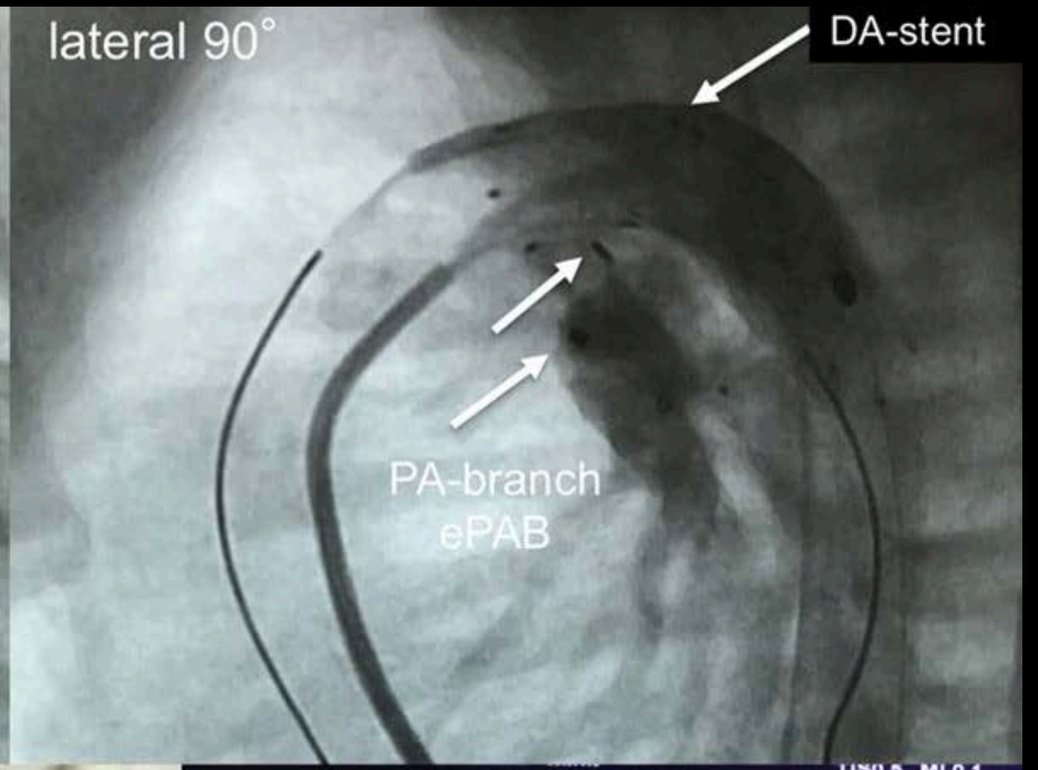
Norwood-Hybrid - *Angiographies after PA banding and ductal stenting*

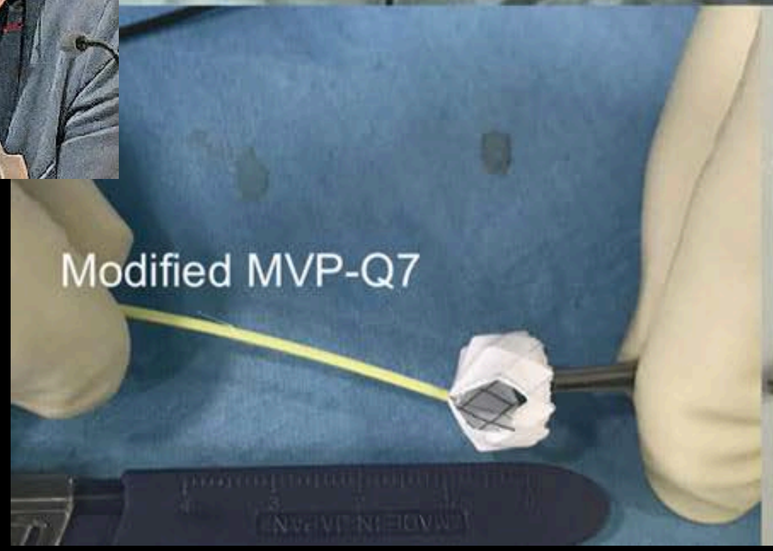


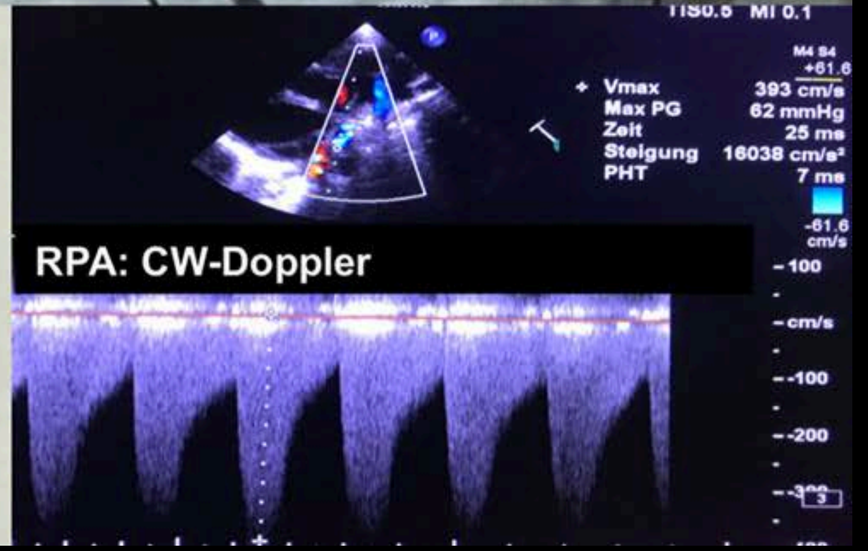
1-Salvation procedure
2-Intentional alternative to the Norwood procedure

No Norwood/No hybrid









Schranz D et al. Circulation. 2020;142:1402–1404.

The plan of action should set the ground for next stage

	Fetus	Neonate
Survival	Termination of pregnancy Planned delivery	Comfort care
Interventions	Aortic valve dilatation Atrial septum opening	Preoperative care Stage 1 palliation Transplantation
Suitability for subsequent stage	NA	Suitability for stage 2

Respective risks of surgical/hybrid approaches
-for interstage re-interventions
-for stage 2 complexity
-for extracardiac risk : neurodevelopment

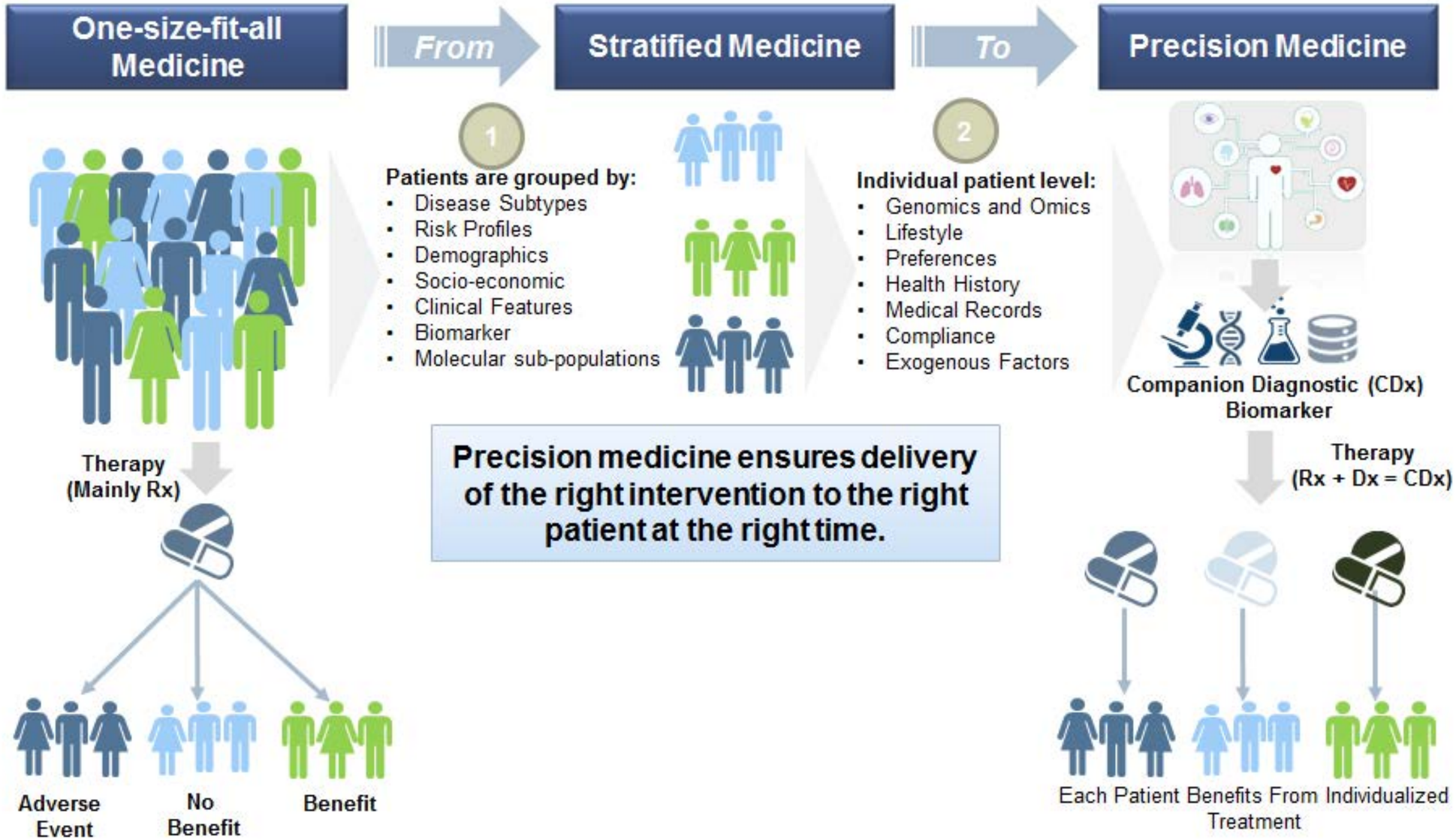
Wilder TJ, Caldarone CA. Apples to oranges: Making sense of hybrid palliation for hypoplastic left heart syndrome. JTCVS Open. 2020;4:47-54.

Stage 1 palliative intent has to be defined

Hybrid as alternative to Norwood	No convincing superiority
Salvage procedure	Procedure to stabilize hemodynamically unstable patients who are otherwise unsuitable for the Norwood operation.
Deferred Norwood	Strategy to utilize the hybrid approach to intentionally defer the Norwood operation for weeks to months. A Norwood is the second planned procedure.
Pretransplantation palliation	Strategy to utilize bilateral pulmonary artery banding to improve hemodynamic stability while awaiting a suitable organ for transplantation.
Univentricular-biventricular	Strategy to promote growth of left ventricular structures to increase probability of achieving a biventricular repair decision deferral typically with deliberate maintenance of a restrictive atrial septum.

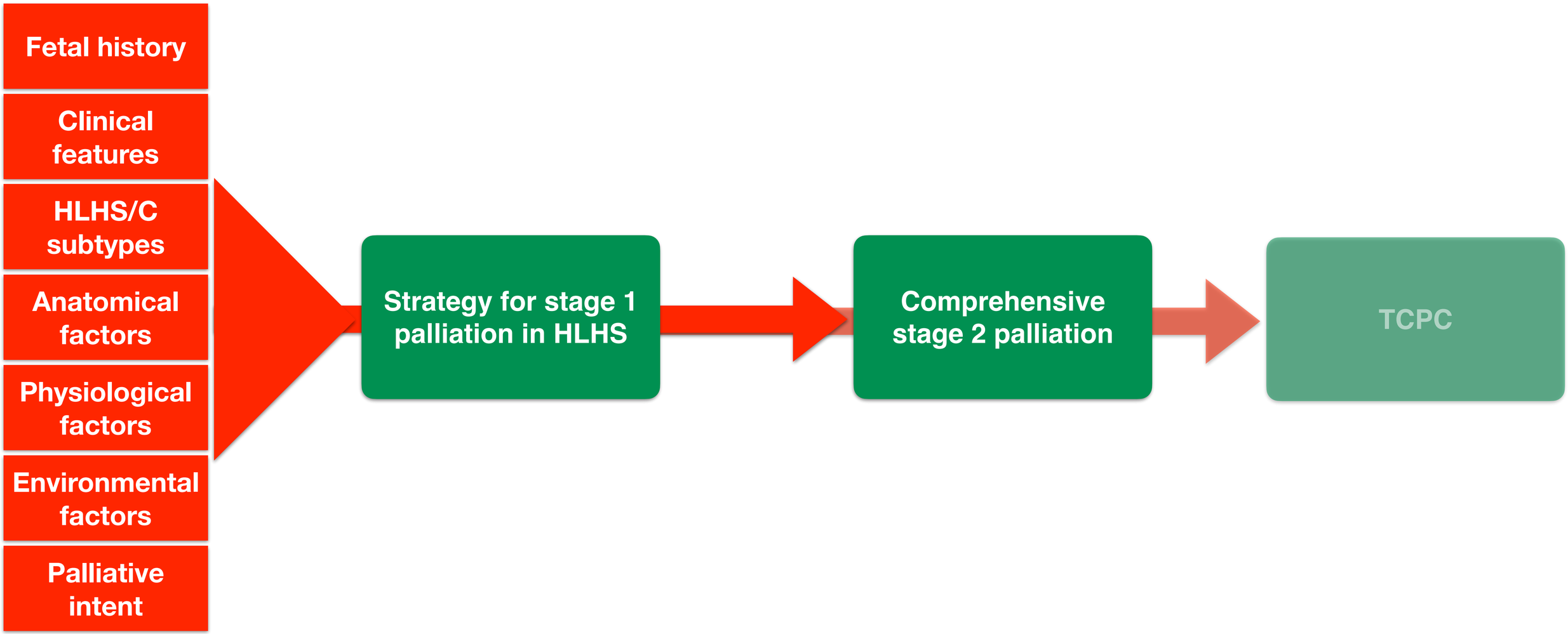
Wilder TJ, Caldarone CA. Apples to oranges: Making sense of hybrid palliation for hypoplastic left heart syndrome. JTCVS Open. 2020;4:47-54.

Transitioning from the « one-size-fits-all » to « precision medicine » model with multi-level patient stratification

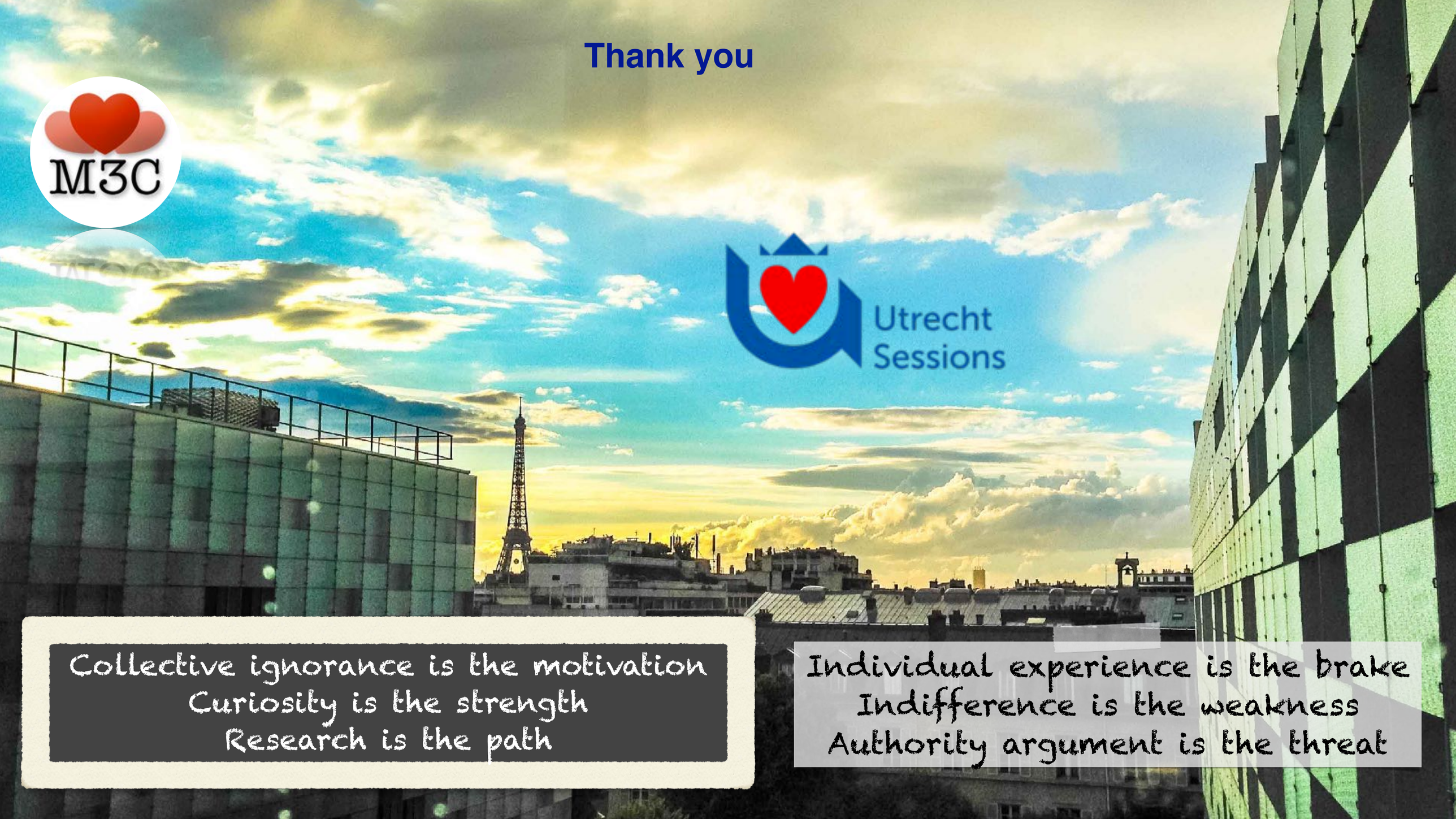


« Stratified medicine » in HLHS before stage 1

Towards precision medicine in HLHS ?



Thank you


M3C
Utrecht
Sessions
Collective ignorance is the motivation
Curiosity is the strength
Research is the path
Individual experience is the brake
Indifference is the weakness
Authority argument is the threat