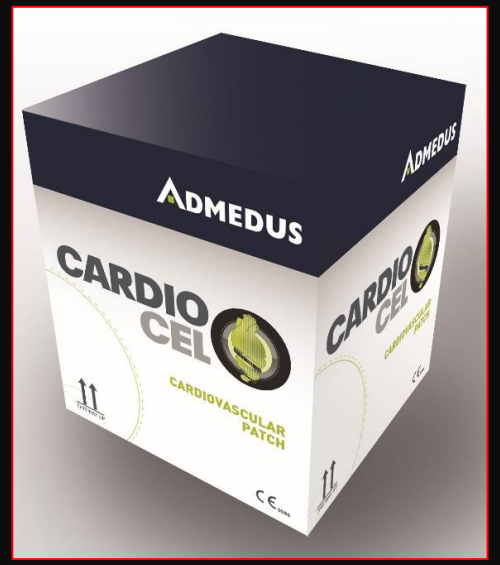
AAPCHS Asian Association for Pediatric and Congenital Heart Surgery

INSTITUT JANTUNG NEGARA
National Heart Institute



LeMaitre®

Clinical Experience in the application of Cardiocel in cardiac surgery

Dr. Sivakumar Sivalingam, M.Med, FRCS(C.Th)
Senior Consultant Cardiothoracic Surgeon
Clinical Director, Congenital Heart Surgery
National Heart Institute, Kuala Lumpur

4th Annual Scientific Meeting, Seoul Dragon City, May31st to June 1st 2024

Disclosures

No Financial Disclosures

Why me?

Surgeon using CardioCel

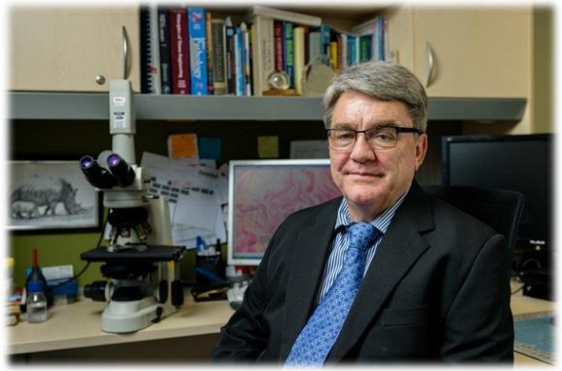
Publications

No conflict of interest

International CardioCel Outcomes Database

Tissue Engineering Process (TEP)History Developed by Prof. Neethling

- **Over 20 years of data,** 10 years of pre-clinical (animal) and 10 years clinical (human) study demonstrating the benefits of unique 21 Day Tissue Engineering Process.



- Pericardium taken from Australian Bovine and engineered in Perth, Australia.

- Results –CardioCel Bio Scaffold in different size, thickness and now unique 3D shapes for all heart components.

Potential Graft Concerns CardioCel TEP was created for…

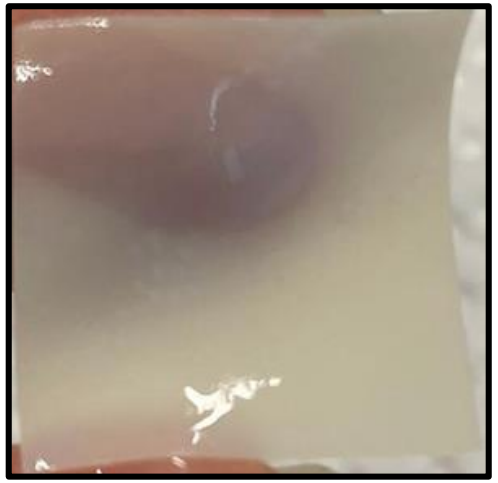
The 21 Day Engineering Process

Proprietary low monomeric aldehyde 0.05%
(12 x smaller than Standard GA).

The proprietary small chain, low molecular solution allows it penetrate deeper to crosslink with strength/durability but fully wash out after crosslinking stage to make a non-toxic product.

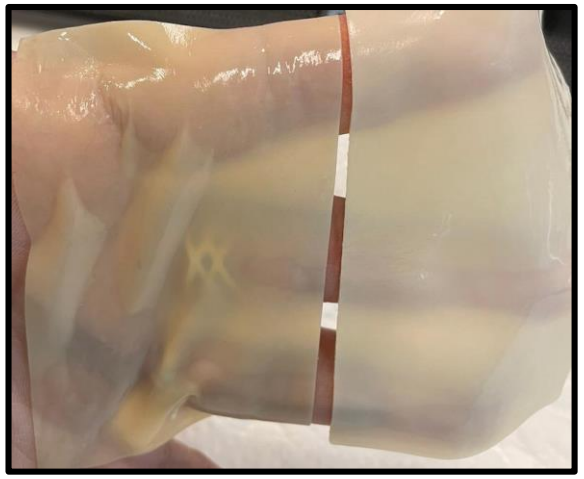
CardioCel is an **acellular**, pure collagen scaffold.
Cross-linked to be pliable, yet strong and durable
with **no toxicities**.

Cardiocel Patches



Cardiocel 2x2 cm

Cardiocel Neo



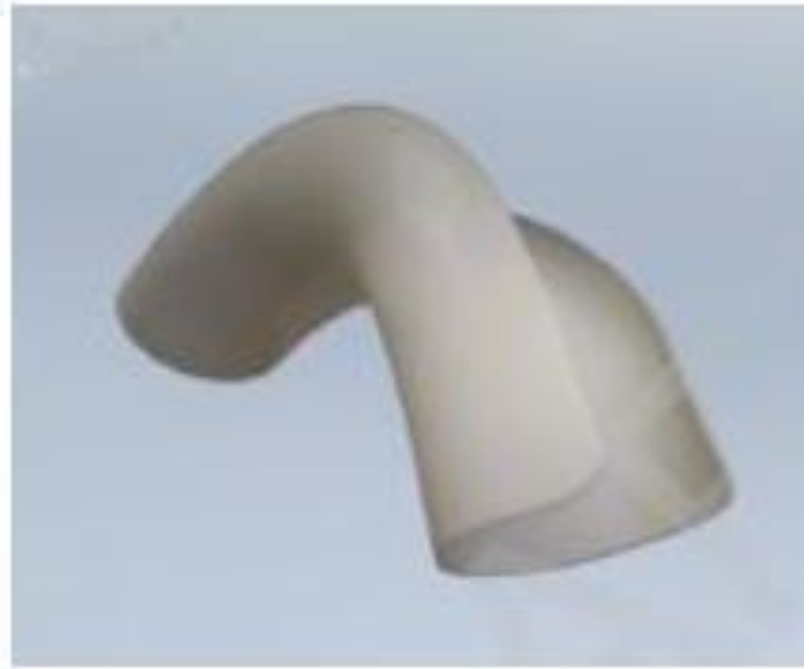
Cardiocel Neo Vs. Standard

Cardiocel 4x4 cm

Cardiocel 5x8 cm

CARDIOCEL 3D

CardioCel® 3D 30°



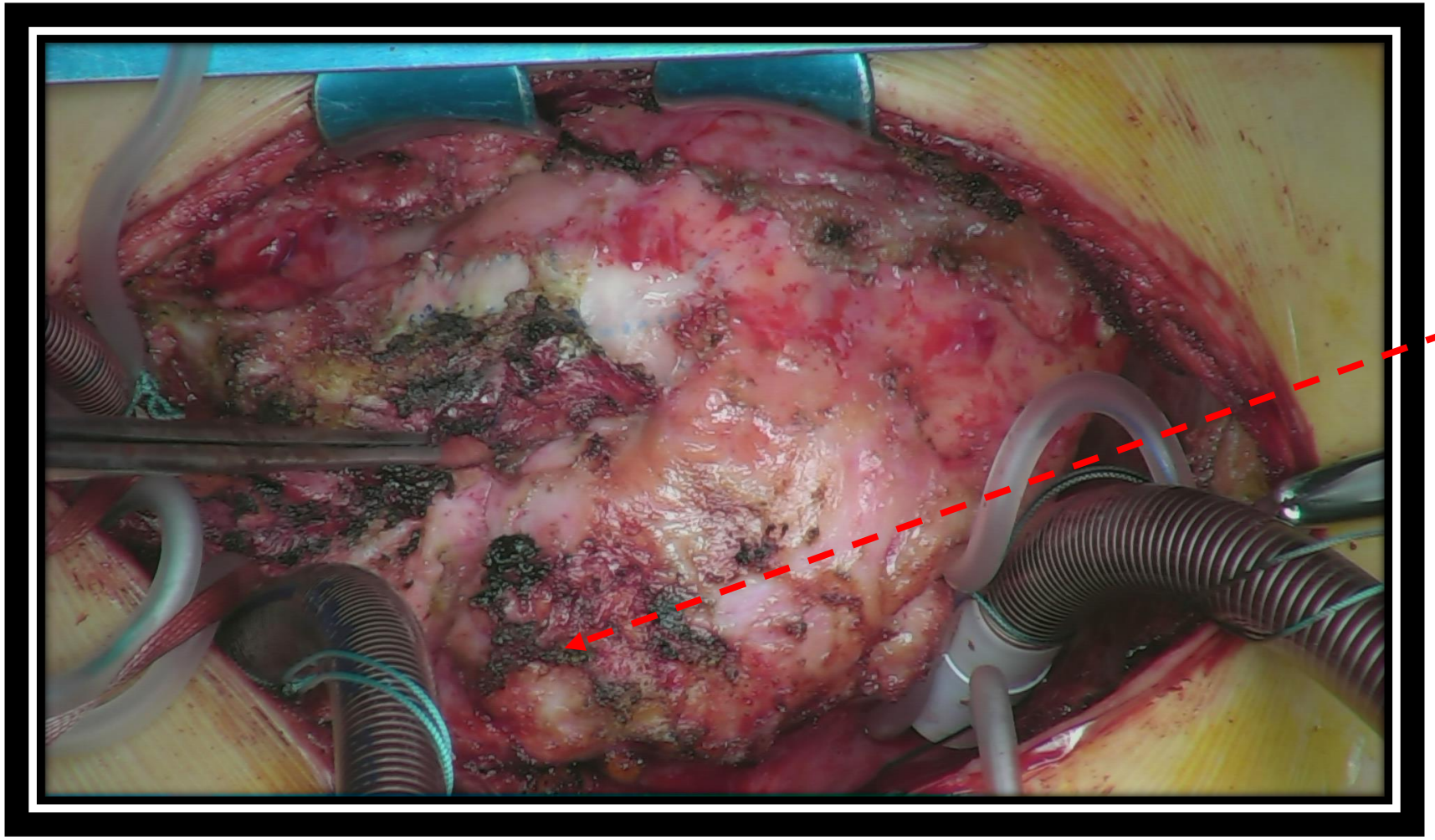
CardioCel® 3D 60°

Cardiocel Experience in IJN

- Since September 2015
- 228 patients had 236 implants
- Median Age(Months) – 53 months(2m – 35 years)
- Male : Female – 112:102

Etiology	Numbers
Ventricular Septal Defect	12
Monocusp valve	18
Branched PA reconstruction	82
Main Pulmonary Artery reconstruction	46
MAPCA	2
AV canal Defect	7
RVOT	5
Arch reconstruction	8
Fontan conversion	3
Ross and Konno	4
Truncus arteriosus	2
Tricuspid Valve	3
Mitral Valve	8
Aortic valve disease	21
Systemic vein baffle	3

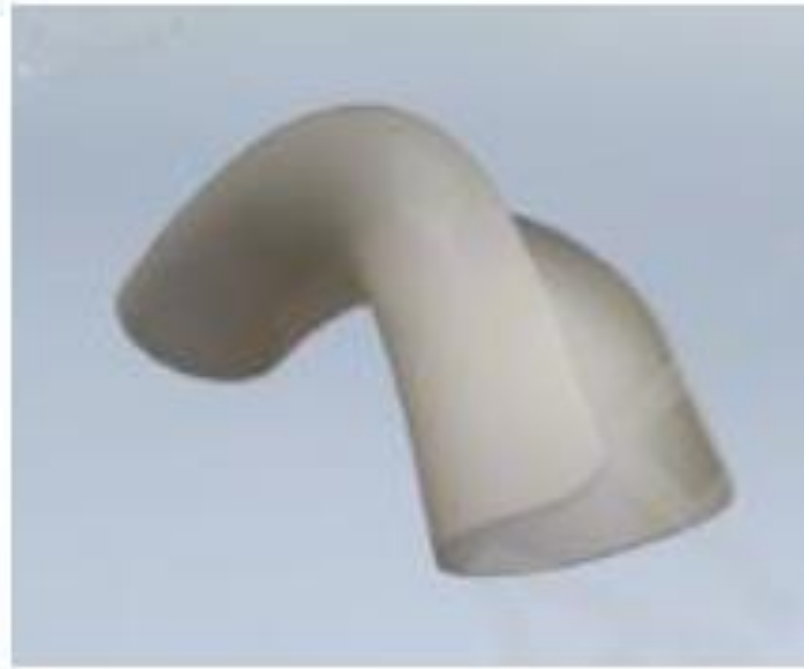
Re-operation after 5 years



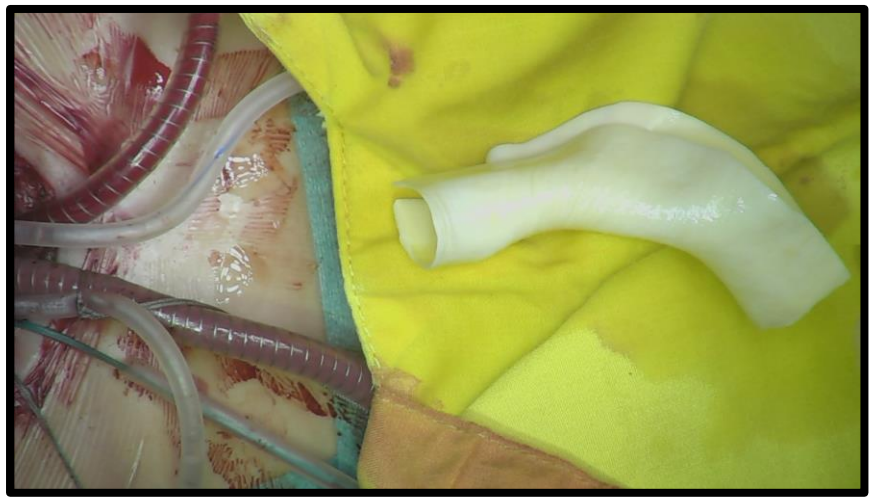
Cardiocel Patch reconstruction

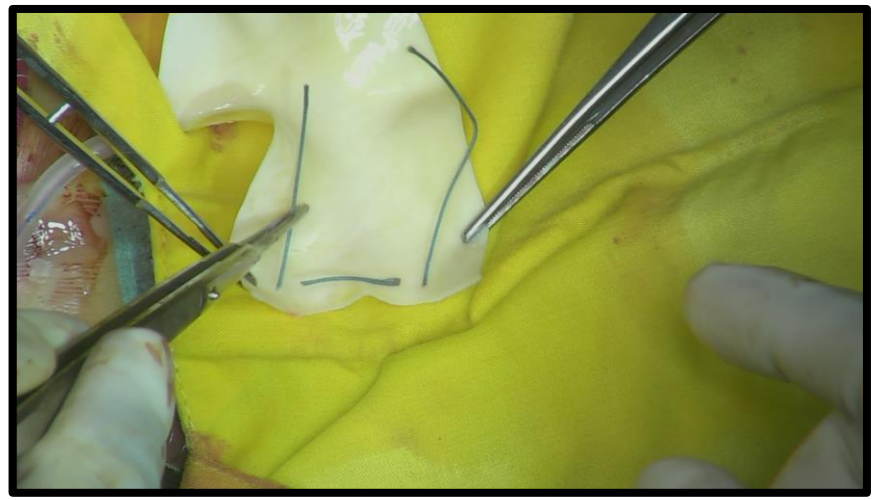
CARDIOCEL 3D

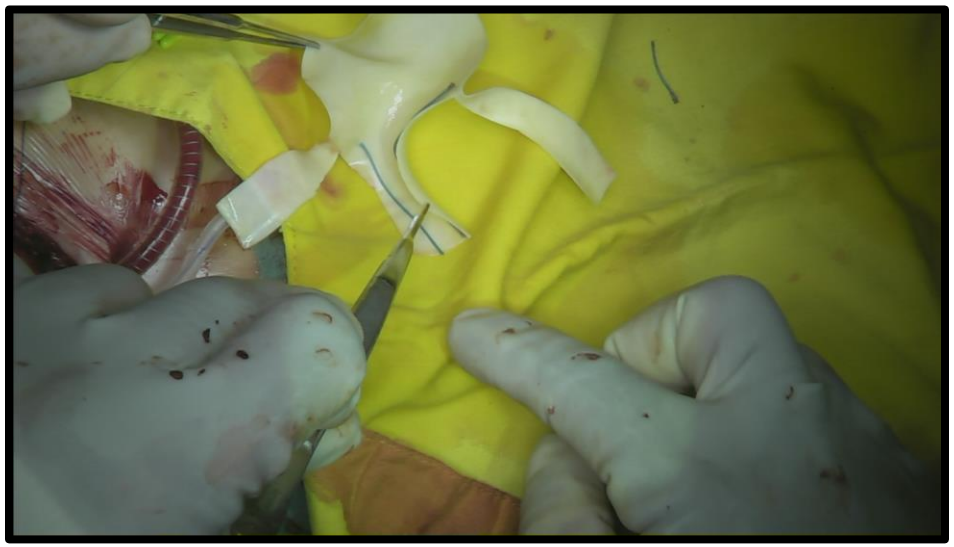
CardioCel® 3D 30°

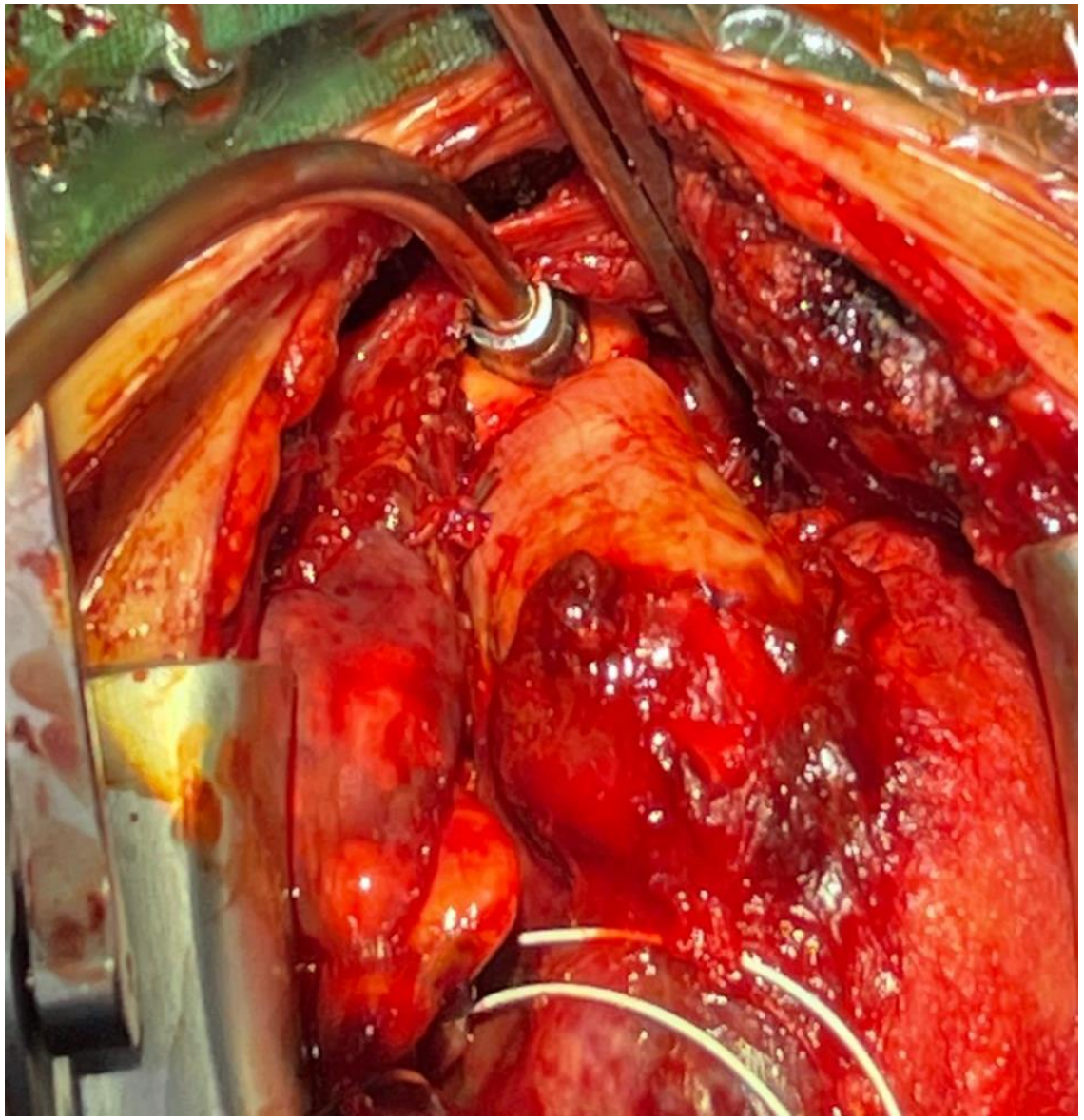


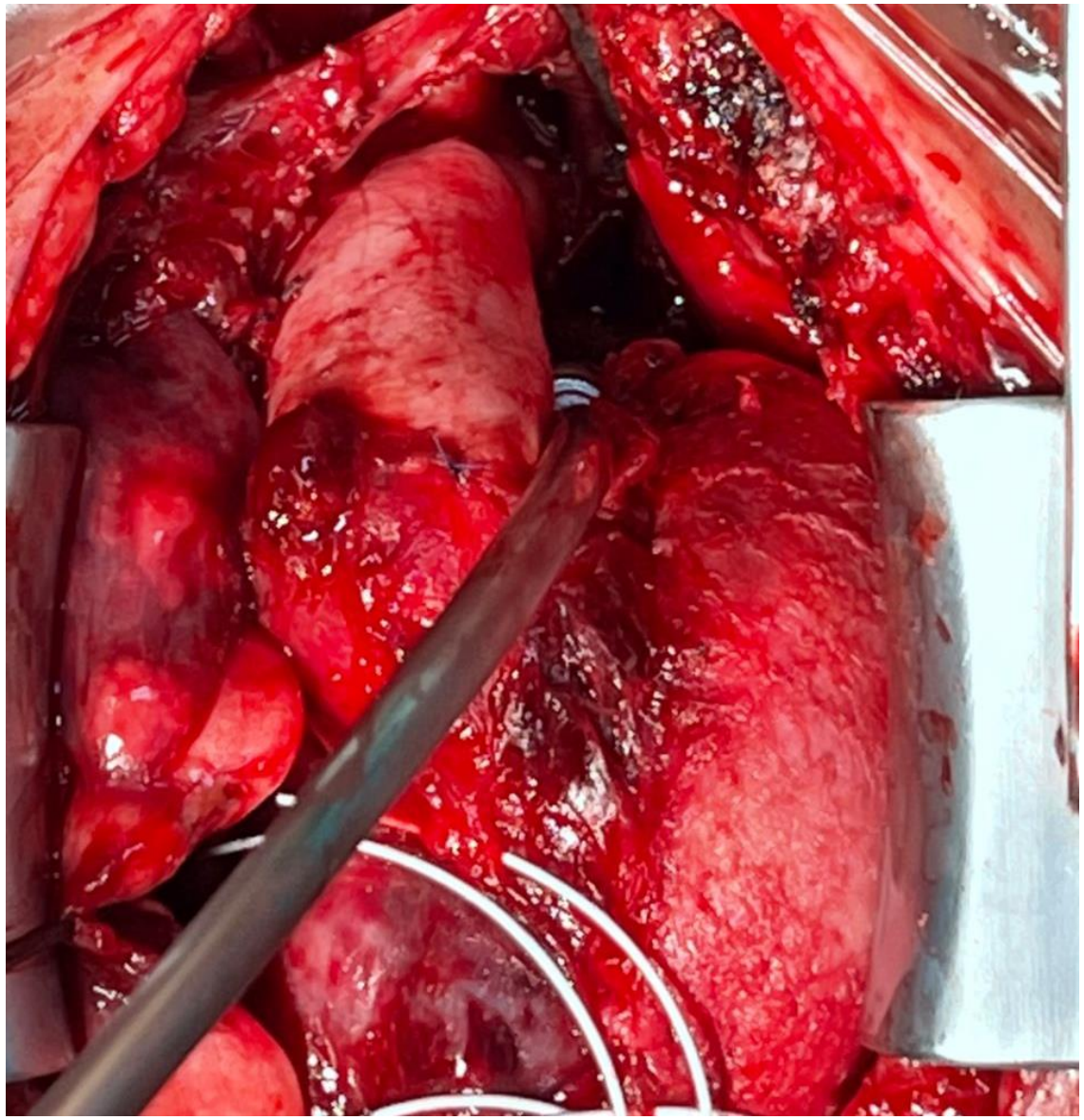
CardioCel® 3D 60°











Publications about CardioCel

Histology

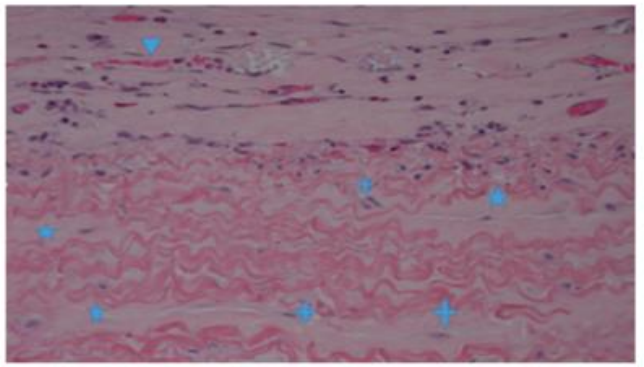
Seminars in Thoracic & Cardiovascular Surgery; 2017

Histologic Evaluation of Explanted Tissue-Engineered Bovine Pericardium (CardioCel)

Sudesh Prabhu, MCh,[,†,‡] Jane E. Armes, FRCPA,[†,‡,§] Douglas Bell, MBBS,[†] Robert Justo, FRACP,[*,†,‡] Prem Venugopal, FRCS,[*] Tom Karl, FRACS,[†,‖] and Nelson Alphonso, FRACS[*,†,‡]*

Semin Thoracic Surg 29:356–363

Keywords: remodeling, bovine pericardium, histopathology, CardioCel, congenital heart diseases



Remodeling of a CardioCel transannular patch graft after 502 days of implantation, seen as a fibroblastic infiltrate (†), surrounded by a newly interposed, pale, eosinophilic collagen (*) between the brightly eosinophilic graft collagen layers. Neovascularization (∇) is also demonstrated (hematoxylin and eosin, original magnification ×40).

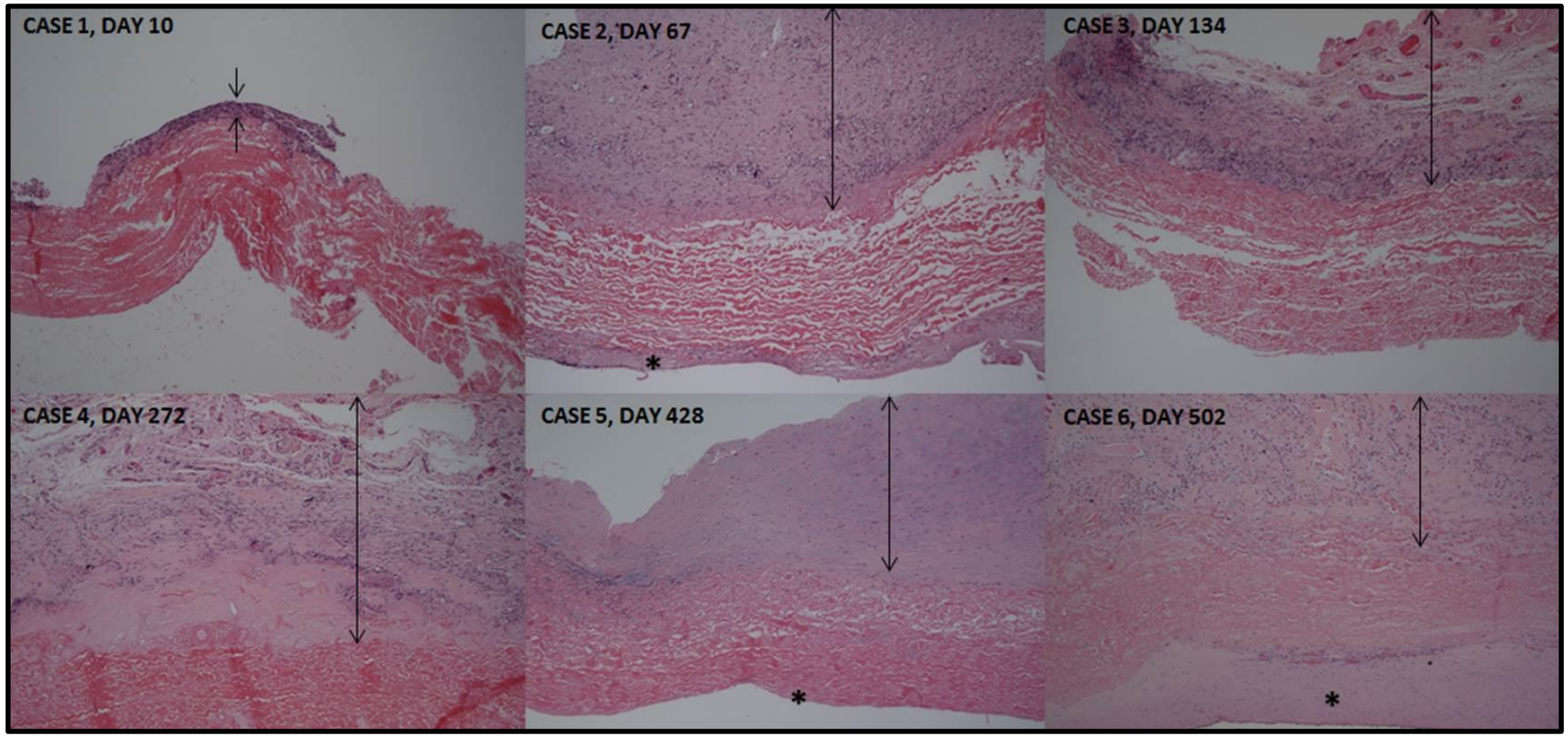
Histology study

- ✓ 6 specimens were surgically explanted
- ✓ CardioCel patch explantation was the primary indication for re-operation in cases 2 & 3
- ✓ CardioCel® explants were evaluated histologically
  - Hematoxylin and eosin
  - Masson's trichrome
  - Immunohistochemical staining

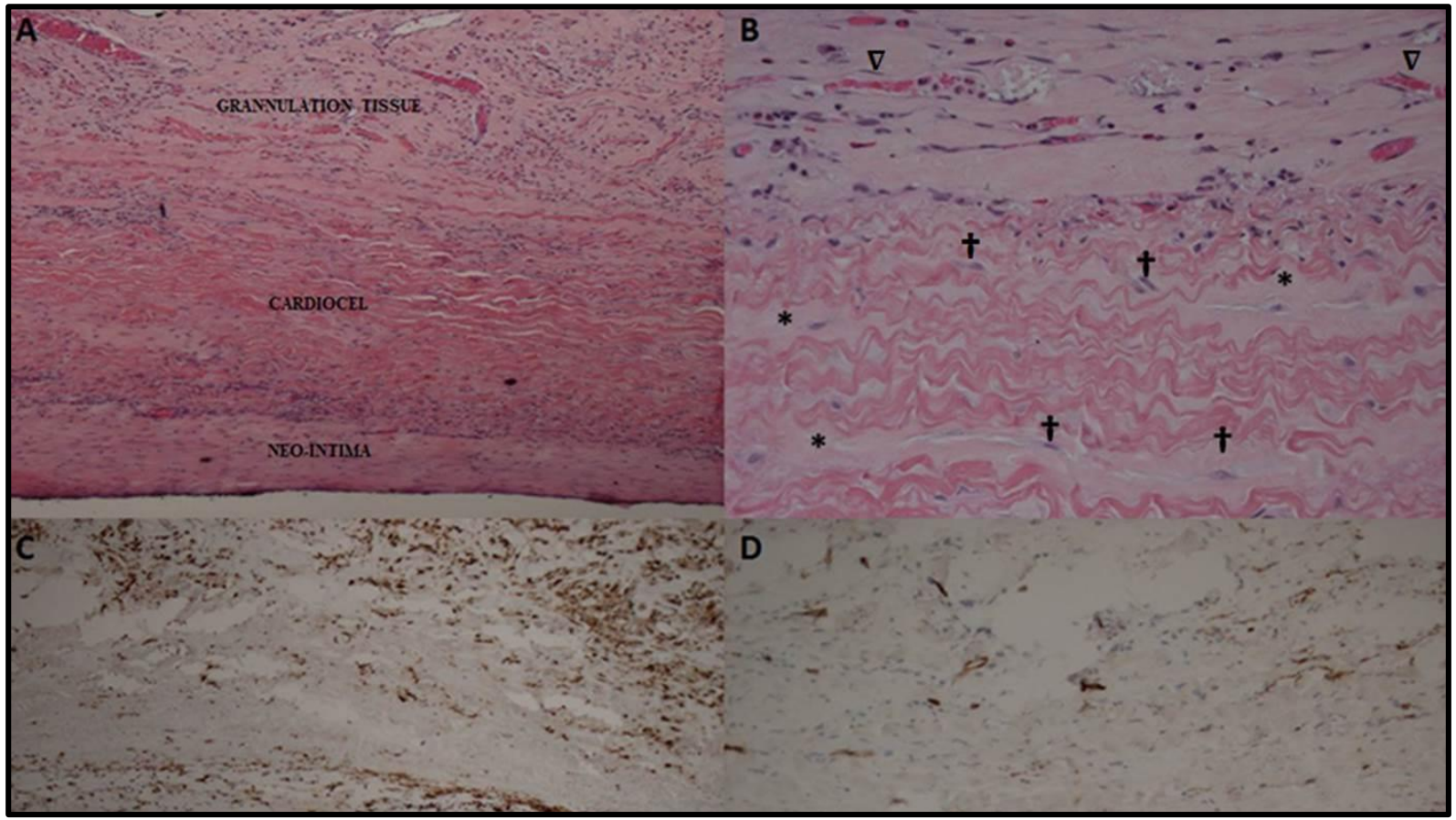
Explanted specimens

- ✓ Case 1 (10 days) Mitral valve repair
- ✓ Case 2 (67 days) Baffle for mixed TAPVD
- ✓ Case 3 (134 days) Type B interrupted aortic arch repair
- ✓ Case 4 (272 days) TOF trans-annular patch
- ✓ Case 5 (428 days) Reconstruction of PA bifurcation
- ✓ Case 6 (502 days) Augmented anterior pulmonary valve leaflet

Explant histology



Evidence of remodelling



Learnings

- ✓ No inflammatory cells within any CardioCel® patch
- ✓ No calcification
- ✓ Granulation tissue consistently thicker on the parietal surface
- ✓ Fibroblast infiltration increased with duration of implantation
- ✓ Neovascularisation evident in all specimens
- ✓ Endothelialisation
- ✓ Neo-intimal tissue layer formation

Wherever possible, visceral surface should be designated luminal surface

CardioCel 500

Annals of Thoracic Surgery; April 2019

Multicenter Experience With 500 CardioCel Implants Used for the Repair of Congenital Heart Defects

Douglas Bell, MBBS, Kim Betts, PhD, Robert Justo, FRACP, Nadine Forde, FRCPA, Prem Venugopal, FRCS, Antonio F. Corno, FRCS, Paul Smith, BS, Massimo Caputo, FRCS, Roberto Marsico, MD, Tom R. Karl, FRACS, and Nelson Alphonso, FRACS

University of Queensland School of Medicine, University of Queensland, Brisbane, Australia; Institute for Social Science Research, University of Queensland, Brisbane, Australia; Queensland Pediatric Cardiac Research, Queensland Children's Hospital, Brisbane, Australia; Queensland Health Forensic and Scientific Services, Brisbane, Australia; East Midlands Congenital Heart Center, University Hospital of Leicester, Leicester, United Kingdom; Bristol Heart Institute, Bristol Royal Hospital for Children, Bristol, United Kingdom; Johns Hopkins School of Medicine, Baltimore, Maryland; and School of Clinical Medicine, Children's Health Queensland Clinical Unit, University of Queensland, Brisbane, Australia

Methods

- October 2012 to November 2017
- 501 implants in 377 patients
- Multi-centre

1. Queensland Paediatric Cardiac Service, Brisbane
2. Bristol Heart institute, UK
3. Leicester Children's Hospital UK

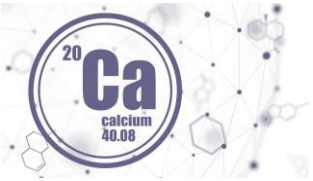
Cardiocel usage

	CardioCel Usage	Number of Implants (n=501)
1	VSD/ASD closure	183
2	PA reconstruction	103
3	Infundibulum/RVOT reconstruction	74
4	Aortic root/valve/arch	52
5	AVSD repair	38
6	Valve repair	30
7	Intra-atrial baffle	18
8	Other	3

Results

- ✓ Median follow-up: 31.7 months
- ✓ No differences in performance between the three centres
- ✓ 11 deaths across all centres – one related to CardioCel

Calcification

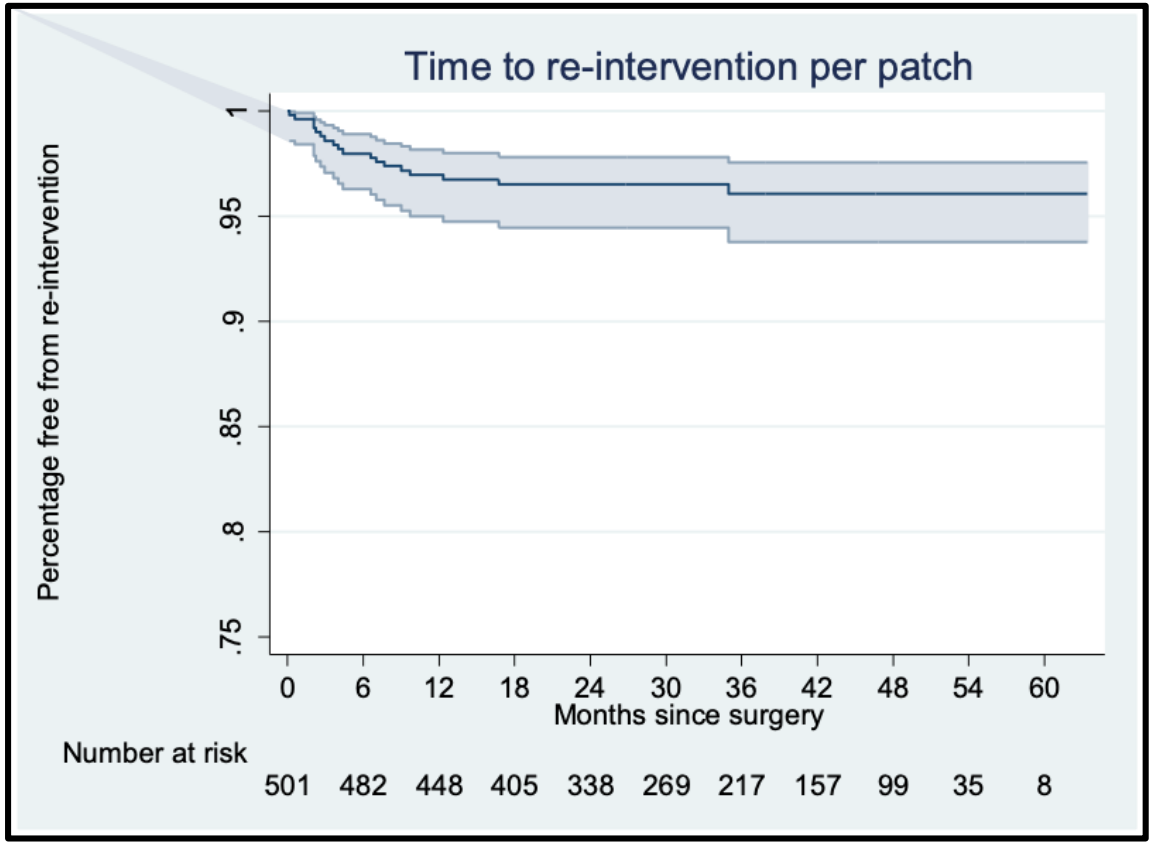


None observed

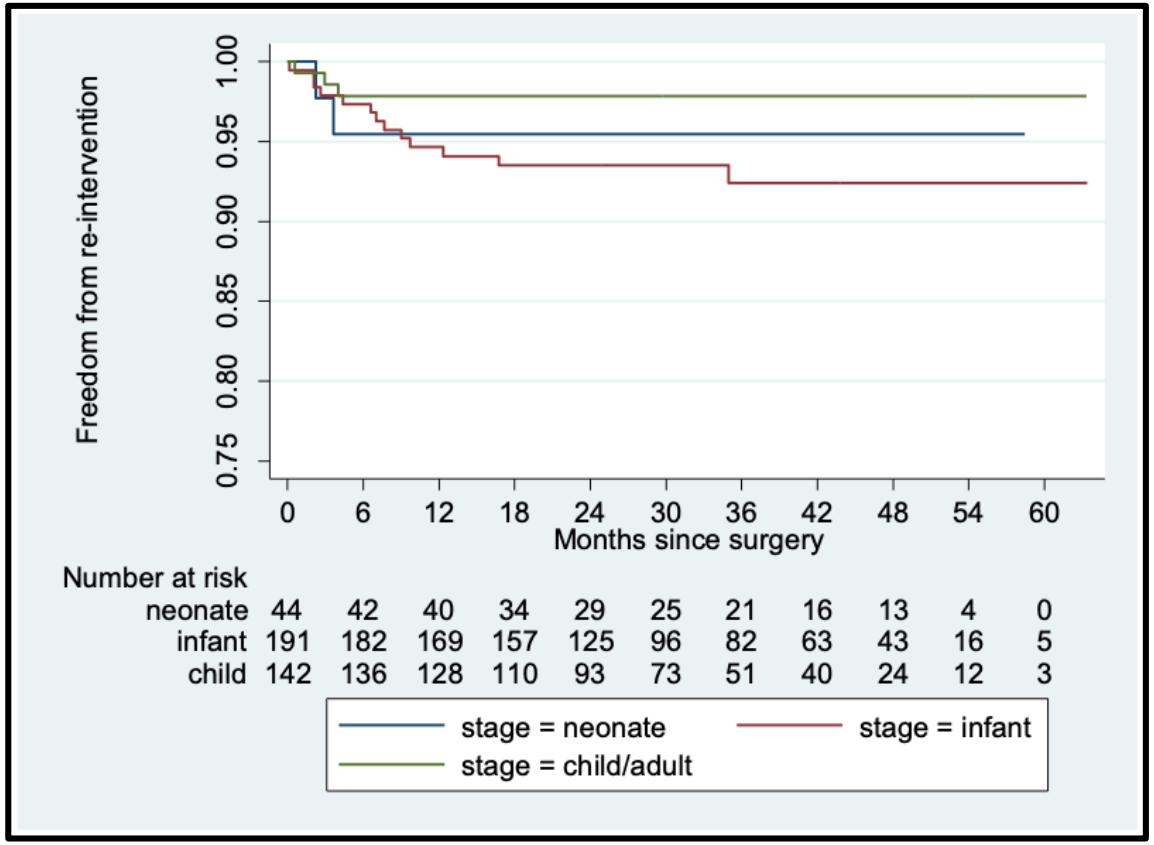
- ✓ Echocardiography
- ✓ MRI
- ✓ CT scan
- ✓ Histology in 6 explants (longest was 502 days in situ)

Freedom from reintervention

- ✓ Freedom from re-intervention at 3 and 5 years was 96%
- ✓ No interaction with country or center (p=0.29)

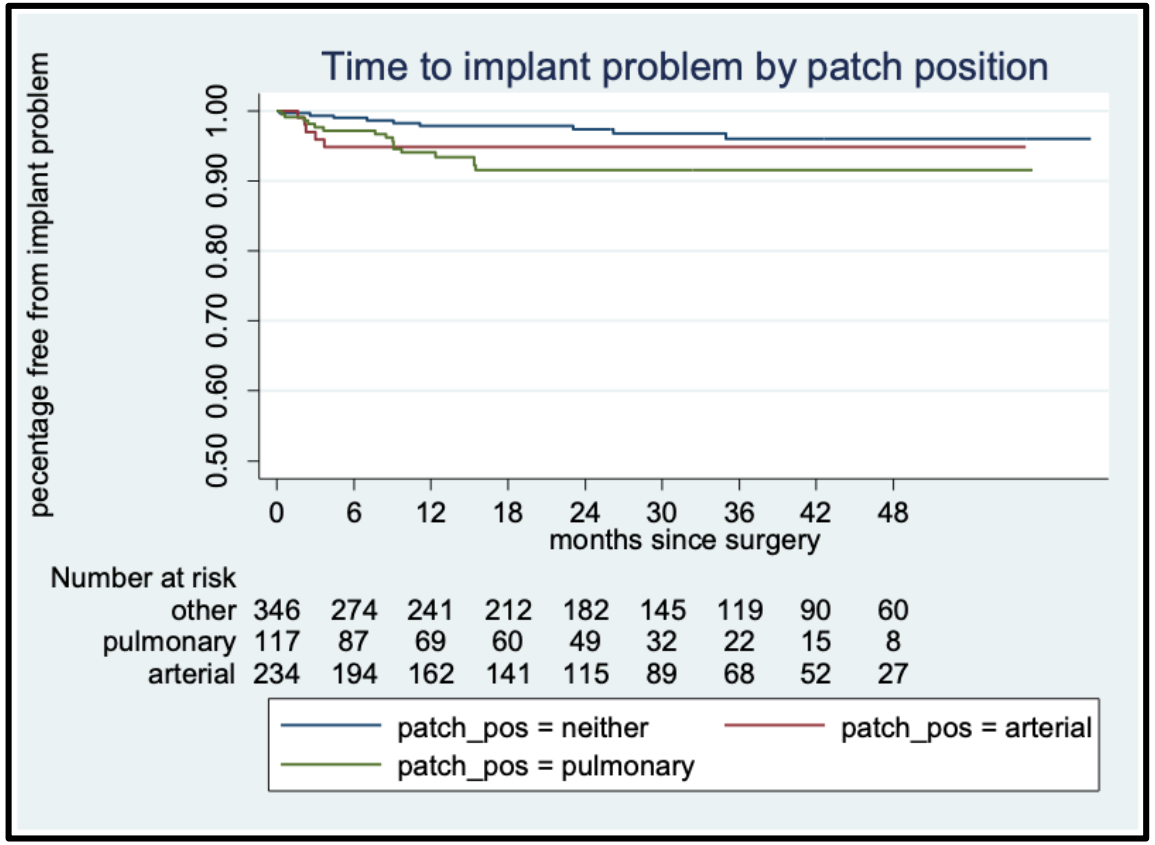


Reintervention by age



p=0.63

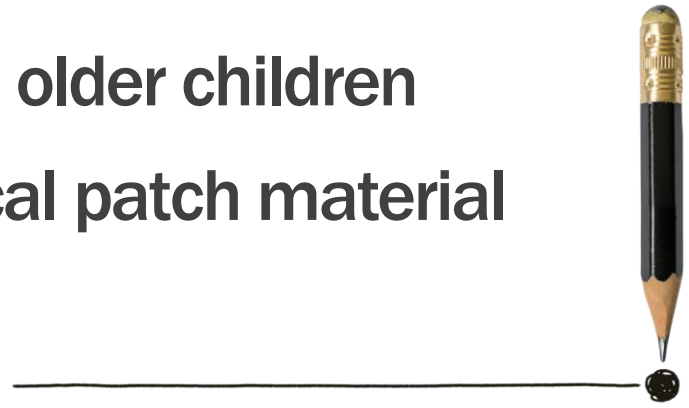
Reintervention by circulation



- ✓ Increased risk for re-intervention in the pulmonary arterial system compared with use in the systemic arterial system [HR = 2.87; 95% CI=(1.24, 6.66), p=0.014]
- ✓ 8/18 (44%) of all re-interventions were in the pulmonary circulation

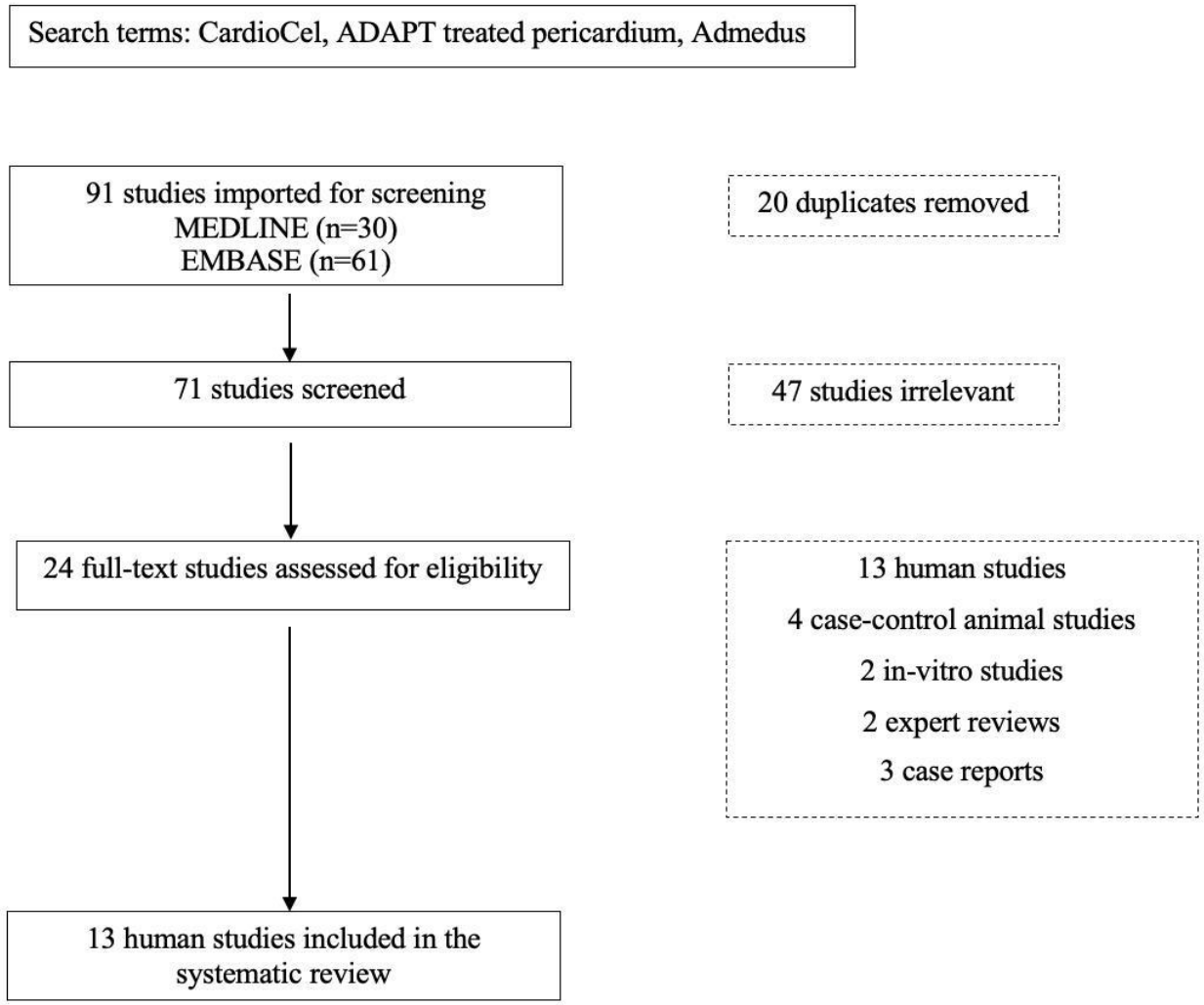
Learnings

- ✓ CardioCel® has good mid-term durability when used for the repair of congenital heart defects
- ✓ Higher probability of reintervention in the pulmonary circulation as compared to other sites
- ✓ Performs comparably in neonates, infants and older children
- ✓ Performance not compared with other biological patch material

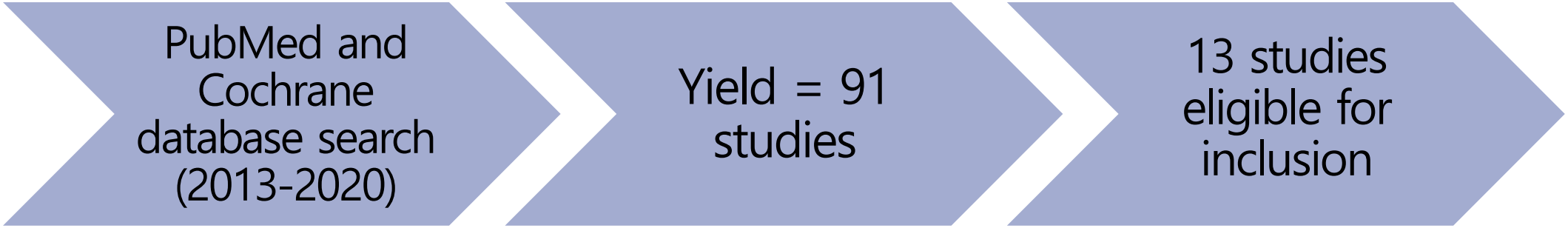


March 2023

Figure 1: Flowchart of search strategy



CardioCel systematic review



Human studies on CardioCel

Evaluation of a tissue-engineered bovine pericardial patch in paediatric patients with congenital cardiac anomalies: initial experience with the ADAPT-treated CardioCel® patch

William M.L. Neethling[a,b,c,*], Geoff Strange[d], Laura Firth[e] and Francis E. Smit[c]

Interactive CardioVascular and Thoracic Surgery 17 (2013) 698–703

PATIENTS	MEDIAN AGE (RANGE)	SITE	FOLLOW UP	RESULTS	
30	18 months (27 days-13 years)	• ASD • VSD • AVSD • RVOT • Aortic arch	12 months	SURGEON FEEDBACK • Handling quality • Seating quality • Efficiency	FOLLOW UP • No graft related deaths • No breakdown of repair • No thrombus • No calcification

Initial 2-year Results Of Cardiocel Patch Implantation In Children

Carine Pavy, Guido Michielon, Jan Lukas Robertus, Francois Lacour-Gayet, Olivier Ghez

Interactive Cardiovascular And Thoracic Surgery; 26 (2018): 448–453

PATIENTS	AGE (MEAN)	SITE (N)	FOLLOW UP	RESULTS

101	22 ± 36 months	• Septal defects (63)
		  ◦ ASD (3)
		  ◦ VSD (54)
		  ◦ CAVSD (4)
		  ◦ PAVSD (2)
		• RVOT (16)
		• Pulmonary artery (15)
		• Aortic arch (5)
		• Aortic root (4)
		• Valves
		  ◦ Aortic (6)
		  ◦ Mitral (3)
		  ◦ Tricuspid (1)
		  ◦ Senning (1)
			212 days (range 4-726)	• No difficulty in implantation
				• No infection
				• No graft related mortality
				• Five graft related re-interventions

Performance Of The ADAPT–treated CardioCel® Scaffold In Pediatric Patients With Congenital Cardiac Anomalies: Medium To Long–term Outcomes

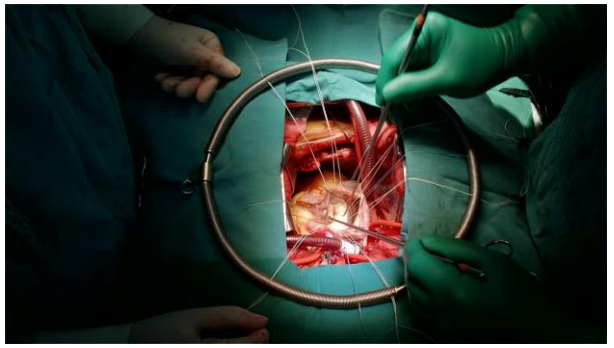
William Neethling, Alethea Rea, Guenther Forster, Kiran Bhirangi

Frontiers in Pediatrics 2020

PATIENTS	MEDIAN AGE (RANGE)	SITE OF IMPLANT	FOLLOW UP	RESULTS
30	18 months (27 days-13 years)	• ASD • VSD • AVSD • RVOT • Aortic arch	7.2 years (IQR 3.6-9.25)	FOLLOW UP • No graft related deaths • No breakdown of repair • No thrombus • No calcification on imaging studies (echocardiography and magnetic resonance imaging)

Mitral valve repair

Adults



Initial Experience And Early Results Of Mitral Valve Repair With CardioCel Pericardial Patch

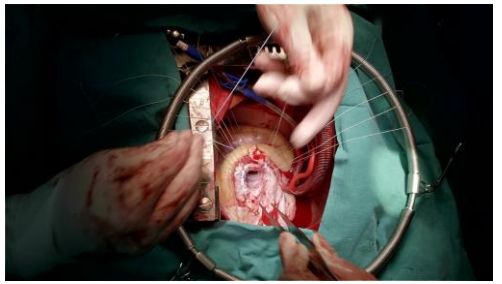
Anton Tomsic, Daniella D. Bissessar, Thomas J. Van Brakel, Nina Ajmone Marsan, Robert J. M. Klautz, Meindert Palmen

Ann Thorac Surg 2018;106:1241–5

PATIENTS	MEAN AGE	SITE OF IMPLANTATION	MEAN DURATION OF FOLLOW UP	RESULTS
30	57.2 ± 14.3 years	Mitral valve	1.7 ± 0.9 years	• One endocarditis • No failure of repair • No patch thickening • No calcification

Aortic valve repair

Children and adults

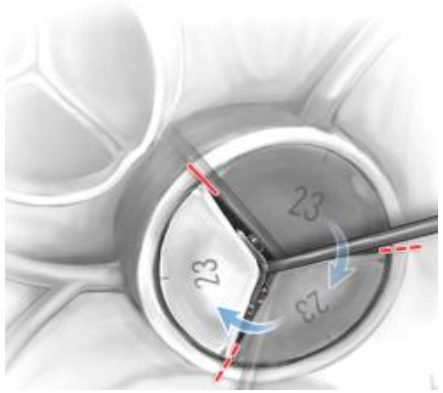


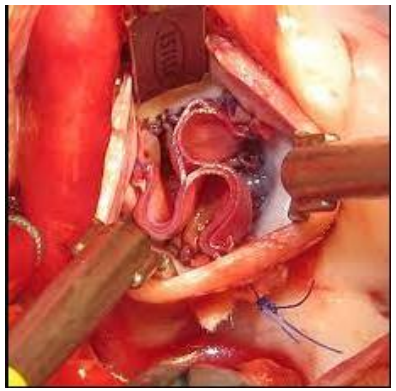
The Ozaki Procedure With CardioCel Patch For Children And Young Adults With Aortic Valve Disease: Preliminary Experience – A Word Of Caution

Sian C. Chivers, Carine Pavy, Ricky Vaja,Cesare Quarto, Olivier Ghez, Piers E. F. Daubeney

World Journal For Pediatric And Congenital Heart Surgery 2019, Vol. 10(6) 724–730

PATIENTS	AGE	SITE	FOLLOW UP	RESULTS
5	Mean 17.6 years	Aortic valve	Mean: 29.6 months Range: 22-36 months	• Reinterventions (n=2) • Regurgitation (n=1)





Results Of Aortic Valve Repair Using Decellularized Bovine Pericardium In Congenital Surgery

Sarah Nordmeyer, Peter Murin, Antonia Schulz, Friederike Danne, Johannes Nordmeyer, Johanna Kretzschmar, Daria Sumbadze, Katharina Rose Luise Schmitt, Olivermiera, Mi-young Cho, Nicodeme Sinzobahamvya, Felix Berger, Stanislav Ovroutski and Joachim Photiadis

European Journal Of Cardiothoracic Surgery; 54 (2018): 986–992

PATIENTS	MEDIAN AGE (YEARS)	SITE	MEDIAN FOLLOW UP (MONTHS)	RESULTS
40	9 (range 2 - 34)	Aortic valve	22 (range 6-42)	• **One death (calcified valve)** • **One endocarditis** • **8 re-operations (all showed thickened patches)**

Systematic Review

Learnings

Site of implantation	Neonates	Infants	Older children	Additional comments
Atrial septal defect	✓	✓	✓	
Ventricular septal defect	✓	✓	✓	
Complete atrio-ventricular defect	✓	✓	✓	
Trans-annular/right ventriculotomy	✓	✓	✓	Visceral surface directed towards lumen
Pulmonary artery	✓	✓	✓	Visceral surface directed towards lumen
Tricuspid valve	Insufficient data	Insufficient data	Insufficient data	
Mitral valve	Insufficient data	Insufficient data	Insufficient data	
Pulmonary valve	Insufficient data	Insufficient data	Insufficient data	
Aortic valve	Use with caution	Use with caution	Use with caution	
Aortic root	✓	✓	✓	Visceral surface directed towards lumen
Ascending aorta	✓	✓	✓	Visceral surface directed towards lumen
Aortic arch	Use with caution	Use with caution	Use with caution	Visceral surface directed towards lumen
Intra-cardiac baffle	Use with caution	✓	✓	Visceral surface directed towards the channel created by the baffle
Endocarditis	✓	✓	✓	Not immune to infection

CardioCel® for repair of congenital heart defects: nationwide results of over 1000 implants

Aditya A. Patukale [a,b,c], Supreet P. Marathe [a,b,c], Kim S. Betts [d], Michael Daley[c,e], Gautham Shetty[a,b,c], Abhishek Anand [a,b,c], Jessica Suna [a,b,c], David Andrews[f], Tom R. Karl [b,c], Christian Brizard [g], Prem Venugopal [a,b,c] and Nelson Alphonso [a,b,c,*]

[a] Queensland Paediatric Cardiac Service (QPCS), Queensland Children's Hospital, Brisbane, Australia
[b] School of Clinical Medicine, Children's Health Queensland Clinical Unit, University of Queensland, Brisbane, Australia
[c] Queensland Paediatric Cardiac Research (QPCR), Brisbane, Australia
[d] School of Population Health, Curtin University, Perth, Australia
[e] The Prince Charles Hospital, Brisbane, Australia
[f] Cardiothoracic Surgery Department, Perth Children's Hospital, Perth, Australia
[g] Department of Cardiac Surgery, Royal Children's Hospital, Melbourne, Australia

* Corresponding author. Clinical Directorate 7f, Queensland Children's Hospital, South Brisbane QLD 4101, Australia. Tel: +61-7-3068-3486; fax: +61-7-3068-3169; e-mail: n.alphonso@uq.edu.au

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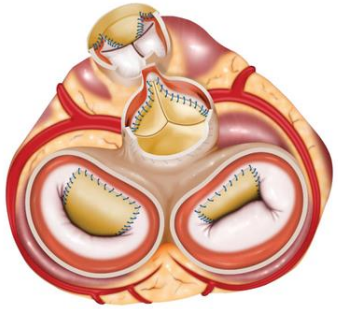
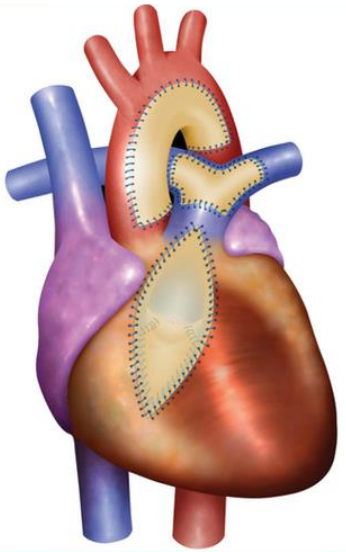
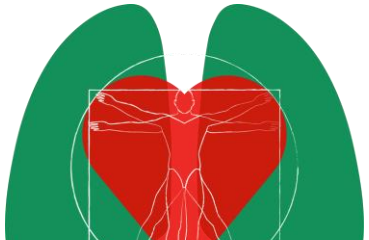
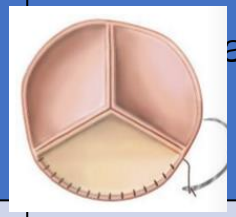
EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

- Objective : To assess the mid-term performance of CardioCel in the repair of congenital heart defects (CHD) using retrospective data from three Australian paediatric cardiac centres
- Study period: October 2012 to December 2019
- Primary endpoint: Need for CardioCel-related surgical or catheter reintervention
- Secondary endpoint: CardioCel-related mortality, thrombo-embolism, calcification, loss of function, hemodynamic compromise
- Inclusion criteria: All patients < 18 years of age with CardioCel used in repair of CHD

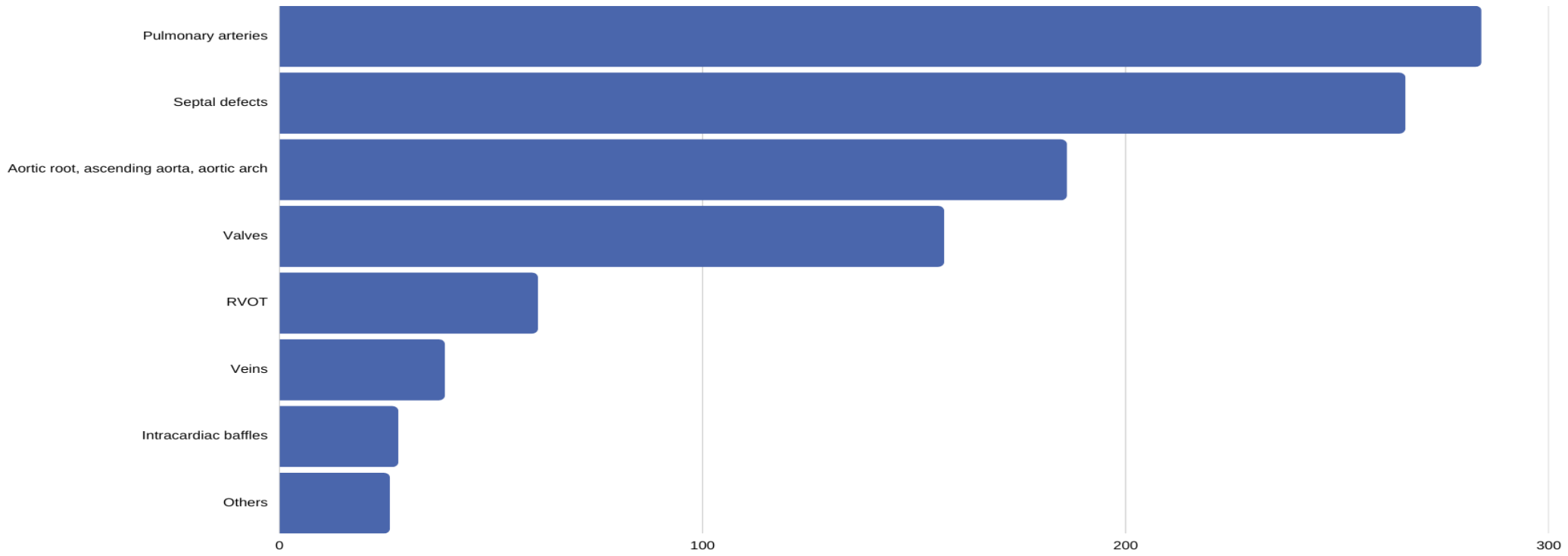




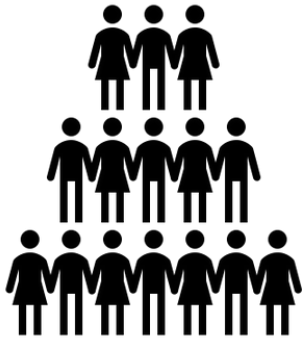


Age / CardioCel implant type	 ar	 eo		Total n (%)
Neonates	77	15	52	144 (12%)
Infants	386	41	17	444 (38%)
Children (1-12 yr)	354	63	12	429 (36%)
Adolescents (12-16 yr)	110	15	4	129 (11%)
Adults (>16 yr)	30	8	0	38 (3%)
Total n (%)	957 (81%)	142 (12%)	85 (7%)	1184

Patch usage by site

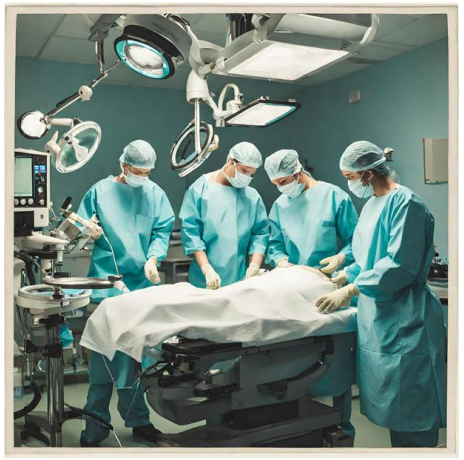


Results



752 patients
Median age: 1.0 year (IQR: 3.6 months – 7.0 years)
Age range: 0 days – 34 years

1184 patches



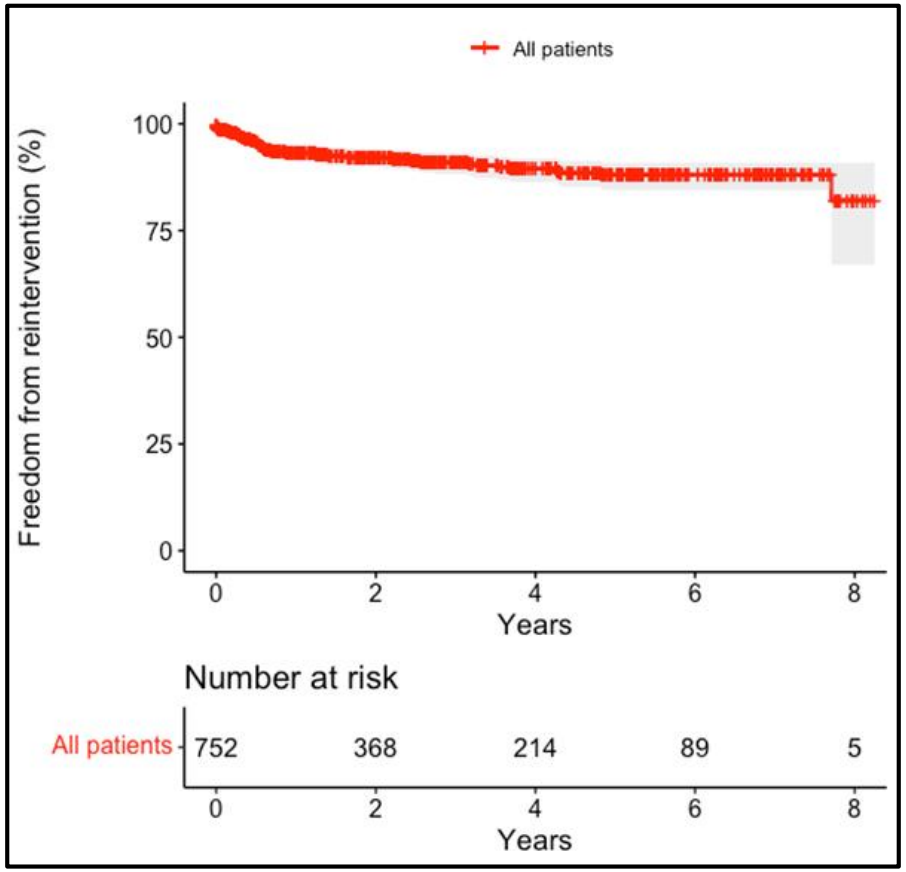
Implant-related reinterventions
67 (6.1%) patients

Follow-up

- ✓ Median follow-up: 2.1 years (IQR 0.6- 4.6)
- ✓ One patient died from CardioCel-related complication
  - ✓ 12-year-old with aortic stenosis
  - ✓ 1st operation: Aortic valve repair as neonate
  - ✓ 2nd operation: Aortic valve replacement with Konno in first year of life
  - ✓ 3rd operation: RVOT patch augmentation
  - ✓ 4th operation: Aortic valve replacement (upsize) with redo Konno, RVOT patch Cardiocel
  - ✓ Wound infection with VAC dressing
  - ✓ Dehiscence of RVOT patch and bleeding on POD#17

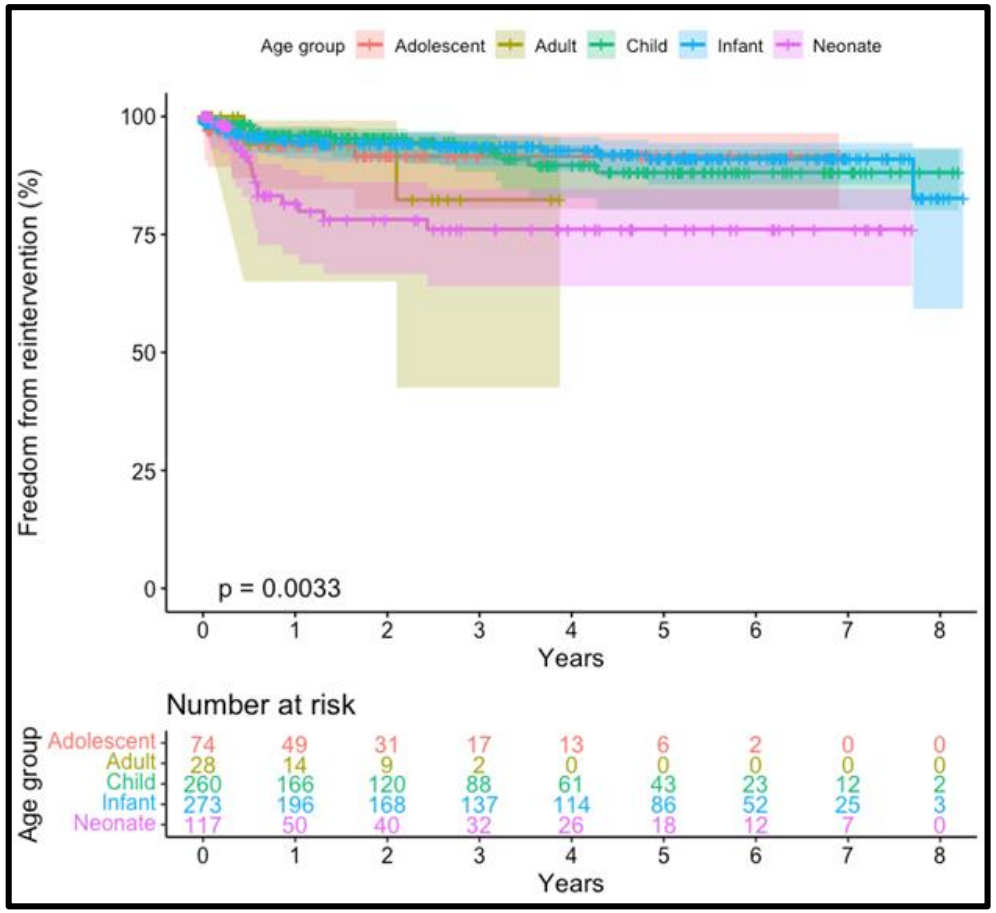
Freedom from reintervention

- 93% at 1 year
- 91% at 3 years
- 88% at 5 years



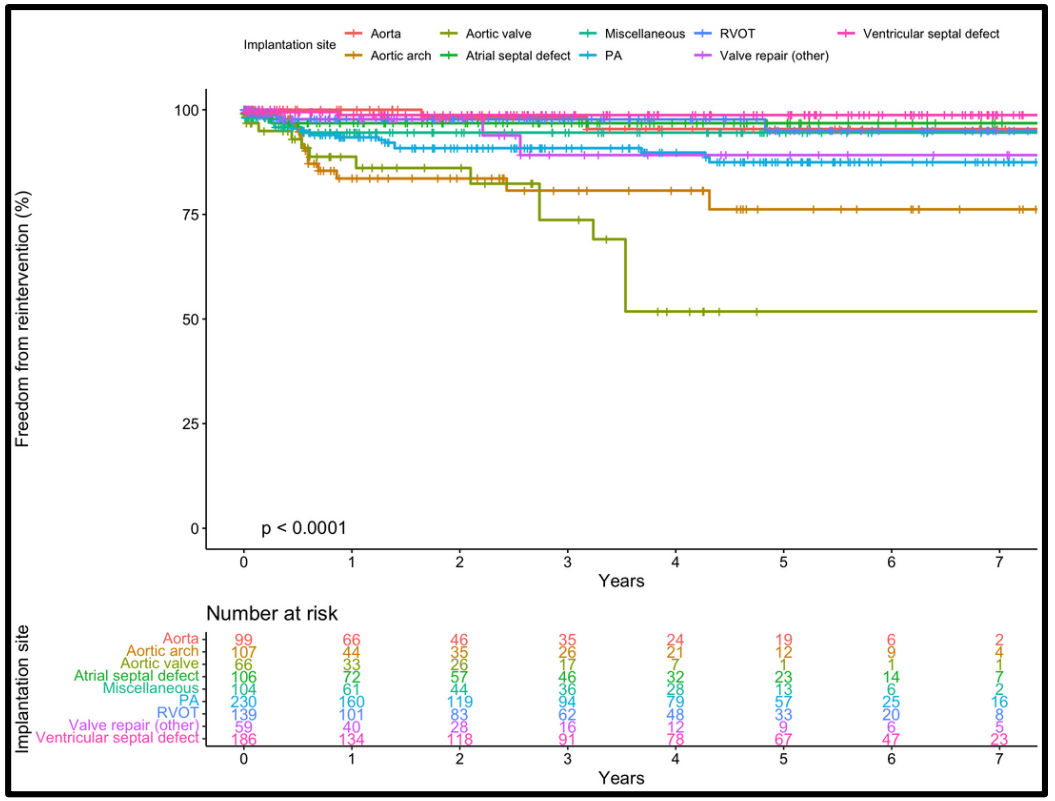
Stratification by age

- ✓ Neonates had greater risk of reintervention (p=0.003) than other age groups
- ✓ Sub-analysis in neonates: highest risk of intervention when used to augment pulmonary arteries [HR=1.12 (0.3, 4.13) p = 0.866]



Stratification by site of implantation

- Use of CardioCel for aortic valve repair (but not aortic arch) had a higher risk of reintervention as compared to other sites ($p < 0.01$)



Multivariable Cox regression analysis for predictors of reintervention

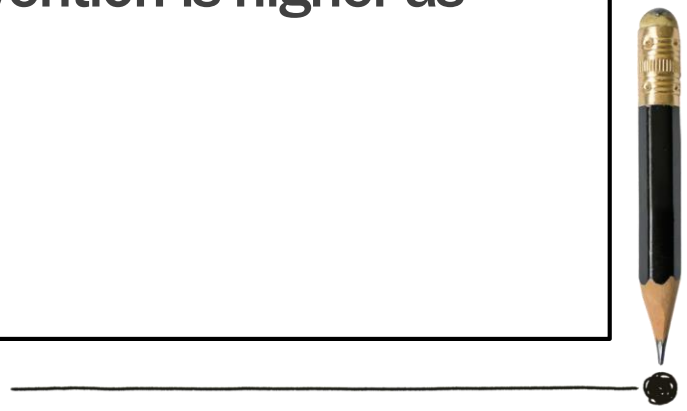
- ✓ Younger age at implantation (highest in neonates versus adolescent patients (HR=6.71, 95% CI=1.70, 26.52, p=0.007)
- ✓ Site of implantation - patches used for aortic valve repair had the highest risk of re-intervention (HR=7.15, 95% HR 1.66, 30.84, p=0.008)
- ✓ Gender and type of patch (CardioCel regular/ CardioCel Neo/ CardioCel 3D) were not risk factors

Secondary end-points

- ✓ Luminal narrowing: n=38 (3%)
- ✓ Thrombosis: n=2 (0.3%)
- ✓ Calcification: n=2 (0.3%)
- ✓ Aneurysmal degeneration: n=1 (0.13%)

Learnings

- ✓ CardioCel can be used to repair a variety of congenital heart defects
- ✓ Good mid-term results in the paediatric population
- ✓ Overall freedom from CardioCel related reintervention of 88% at 5 years
- ✓ Locations where probability of CardioCel-related reintervention is higher as compared to other sites
  - Repair the pulmonary arteries in neonates
  - For aortic valve repair at any age



A PROSPECTIVE, RANDOMISED, CONTROLLED STUDY TO EVALUATE THE PERFORMANCE OF CARDIOCEL® IN CONGENITAL CARDIAC SURGERY

THE 38TH EACTS ANNUAL MEETING | 9 – 12 OCTOBER 2024

Background / Study Objective

- A variety of biological patch materials are available for the reconstruction of the right ventricular outflow tract and pulmonary arteries in pediatric patients undergoing cardiac surgery
- These include autologous pericardium, CardioCel (ADAPT® treated bovine pericardium) and bovine pericardium

- The aim of this study was to evaluate the safety and effectiveness of CardioCel (study group) for reconstruction of the right ventricular outflow tract and pulmonary arteries compared to autologous pericardium and bovine pericardium (control groups)

Methods

- **Inclusion criteria**: Patients between 3 months to 12 years of age undergoing surgical repair of the right ventricular outflow tract and pulmonary arteries using biological patch material

- **Randomisation**: A total of 150 patients were prospectively randomised, with 50 patients assigned to each of the [3 groups (CardioCel, autologous pericardium and bovine pericardium). Randomisation was done using a computer-generated random number sequence.

- **Data collection:** Baseline and follow up data was collected prospectively from hospital records

- **Primary endpoint** was freedom from patch-related reintervention at 1 year

- **Secondary endpoints** were the length of ICU and hospital stay, re-exploration for bleeding, acute kidney injury and sepsis

Results 1 – Primary end point

- Median follow -up for the entire cohort was 1.1 years (IQR 0.8-1.2)
- There was no patch-related reintervention in any patient
- Freedom from patch-related reintervention for all 3 groups was 100% at 1-year

Conclusion

- CardioCel provides acceptable results when used for relief of right ventricular outflow tract obstruction and reconstruction of the branch pulmonary arteries

- There is no difference in the performance of CardioCel, autologous pericardium and bovine pericardium at one year when used for relief of right ventricular outflow tract obstruction and reconstruction of the branch pulmonary arteries


MY CHOICES

Septum, pulmonary artery, RV

Site of implantation	Neonates	Infants	Older children	Additional comments
Atrial septal defect	✓	✓	✓	
Ventricular septal defect	✓	(or Dacron)	(or Dacron)	Preferred in neonates
Complete atrio-ventricular defect	✓	✓	✓	
Trans-annular/right ventriculotomy	✓	✓	✓	Visceral surface directed towards lumen
Pulmonary artery	Pulmonary homograft (CardioCel Neo)	✓ ✓	✓ ✓	Visceral surface directed towards lumen

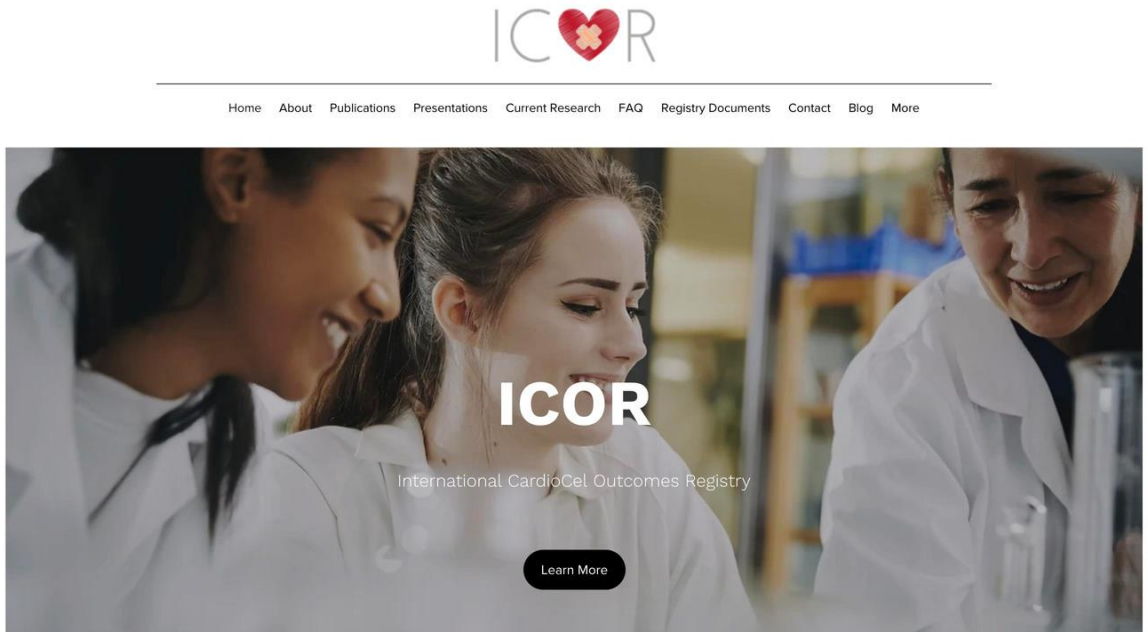
Valves

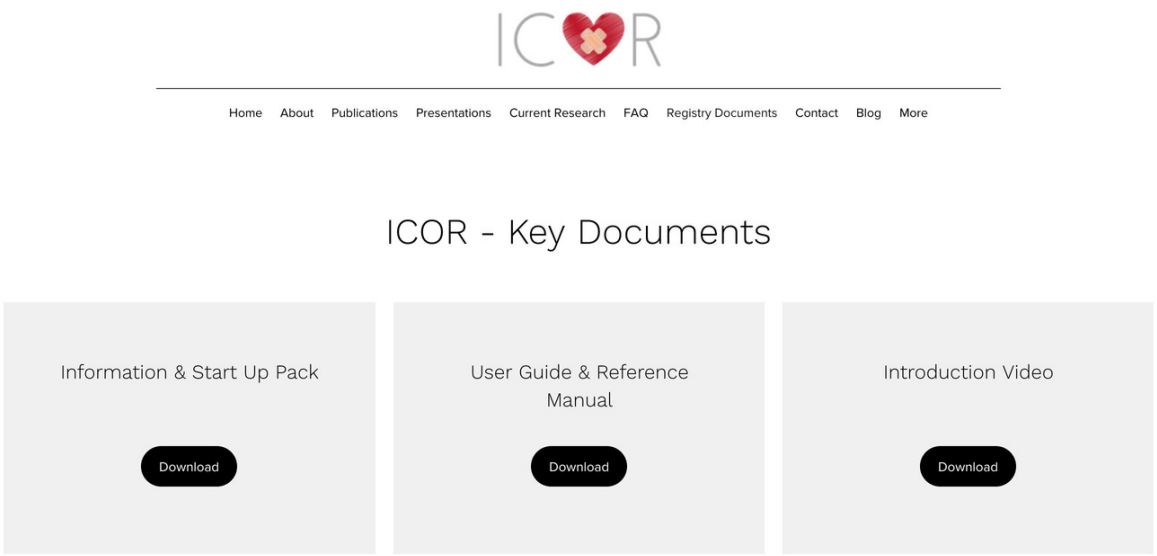
TOF –
Sung repair

Site of implantation	Neonates	Infants	Older children
Tricuspid valve	–	–	–
Mitral valve	CardioCel Neo	CardioCel Neo	CardioCel / CardioCel Neo
Pulmonary valve	–	0.1mm Goretex Cardiocel Neo	0.1mm Goretex Cardiocel Neo
Aortic valve	Autologous pericardium	Autologous pericardium	Autologous pericardium (CardioCel Neo)

Aorta, arch, baffle, endocarditis

Site of implantation	Neonates	Infants	Older children	Additional comments
Aortic root	✓	✓	✓	Visceral surface directed towards lumen
Ascending aorta	✓	✓	✓	Visceral surface directed towards lumen
Aortic arch	Pulmonary homograft	Pulmonary homograft	✓ (or Hemashield)	Visceral surface directed towards lumen
Intra-cardiac baffle	✓	✓	✓	Visceral surface directed towards the channel created by the baffle
Endocarditis	–	–	–	Not immune to infection





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