Society for Heart Failure and Transplantation

SOCIETY FOR HEART FAILURE AND TRANSPLANTATION'S

THE REVIVAL

Promoting Academics to Improve Clinical Outcomes.

Anniversary EDITION

Society for Heart Failure and Transplantation

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Heart Transplant Surgeon, MS, MCh. (AIIMS, New Delhi), FACC.

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My Dear Colleagues,

It's such a pleasure to present to you the Print Edition of "The Revival". This is a compilation of all 13 articles from the inception of the Newsletter in February 2021. The journey was not easy with the Covid saga raging around all of us. Nonetheless, the issues of "The Revival" were hitting the circulation deadline dates each month. The efforts of Dr Talha Meeran, Dr V Nandakumar and Dr Jabir Abdullakutty and divine providence collectively have helped in the journey. I thank the guest authors who have dedicated their time and taken the effort to contribute their articles and enhance our knowledge with their experience.

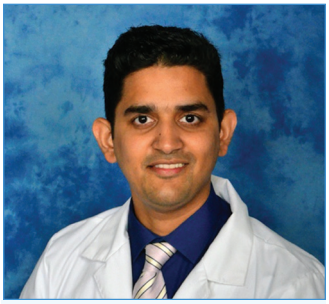
The vision of this Newsletter is to Promote Academics and improve Clinical Outcomes. I hope our beloved Readers have benefitted by this endeavour from our end. The executive committee of the Society for Heart Failure and Transplantation have backed us to the hilt and given us a very positive environment to work and this has helped us in achieving our goals in a seamless manner. The road map for this year will be to invite more Review Articles, which will have a greater breadth to each topic and keep all of us abreast with the current views and scientific data in heart failure. It has been the intent of this Newsletter to encourage Indian authors and give them a platform to showcase their clinical experience and writing talent. We will try to preserve that objective.

A super special mention is in order for Mrs Maithili Kulkarni our Genius Graphic Designer for conceptualisation of the original design, logo, formatting and infusing life and colour to our Newsletter. Mrs Maithili has faced the brunt of numerous edits and revisions from my side, and I thank her for her patience and positive work ethic.

To our dear readers, I thank you for your support and as always, wishing you a Happy Reading.

- Dr Manoj Durairaj
  Editor "The Revival"

SUB EDITOR



Dr Talha Meeran

MBBS, MD, FACC, Consultant Cardiologist, Dept of Advanced Cardiac Sciences and Cardiac Transplant, Sir HN Reliance Foundation Hospital, Mumbai.

Dear Colleagues,

REVIVAL was born during the peak of the 2nd COVID wave as a means to update and refine the SfHFT's CME programme. Owing much to the labour put in by the entire editorial team under the guidance of Dr Manoj Durairaj, REVIVAL has seen an increasing readership and has metamorphosed into a valuable resource for all those yearning to remain updated in our particular field.

This special 1st anniversary edition of REVIVAL comprises all the 13 articles published over the last one year. The scope of the topics covered over the last year have been wide and all-encompassing ranging from pediatric to adult related articles as well as heart & lung transplantation related articles. I would like to thank and congratulate the SfHFT president and entire SfHFT executive committee team for their constant support and encouragement.

Sincerely,
Dr Talha Meeran
Sub Editor "The Revival"

PRESIDENTIAL MESSAGE

Prof. (Dr) V. Nandakumar

Director & Chief, Division of Cardio Vascular/ Thoracic Surgery & Cardiac Transplantation, Metromed International Cardiac Centre, Calicut, Kerala.

Dear Colleagues,

Greetings from the Society for Heart Failure and Transplantation

Over the past two years 2020 and 2021 we had experienced the ill effects of Covid 19 which put off our physical meetings. Even during these adverse times, with the enthusiastic efforts of Dr Manoj Durairaj well supported by Dr Talha Meeran, the News Letter 'The Revival ' came out, the first issue being in February 2021. This was started with the idea of providing a platform for the members to present important aspects of heart failure and transplantation thereby to help raising the standards in the management of these patients. Every month it was released on time with high quality scientific material presented by experts in the respective field. Now the first 13 issues are compiled together as an Anniversary edition. This will cover a wide spectrum of topics ranging from paediatric heart transplantation, adult heart transplantation with complex issues like ABO incompatibility, current concepts in the management of heart failure patients, Lung Transplantation and Journey through heart transplantation in India to mention a few. Each topic is dealt with in a comprehensive manner yet highly informative in its contents.

Dr Manoj and Dr Talha have done a fantastic job in bringing out these issues without fail and this anniversary issue in a well designed manner.

- Prof. (Dr) V. Nandakumar
President

SECRETARY'S NOTE

Dr Jabir Abdullakutty

MD DM FSCAI FACC FESC FRCP

Senior Consultant Cardiologist, Lisie Hospital, Cochin, Kerala.

Dear Colleagues,

We were struggling in 2021, waging war against a cruel invisible enemy capable of devastating social and economic damages. Medical societies worldwide took a tremendous hit since their primary work of real-time scientific campaign in physical meetings and conferences were disrupted. Online meetings became the new norm. Many societies became a little dormant because of the lack of face-to-face discussions, which is crucial in exchanging ideas and formulating policies for scientific research and patient care. Despite the odds, Dr Manoj Durairaj and Dr Talha Meeran could do a fantastic job publishing the newsletter REVIVAl.
The newsletter was well received and appreciated well by the readers. It was highly commendable to publish the online newsletter with brilliant scientific articles every month. All the 13 review articles in 2021 Revival issues are of a high standard extending from primary Heart failure care to highly specialized therapies for advanced heart failure. It's our pleasure to bring an anniversary issue compiling all the 13 articles in 2021, which I think is a collectors issue for all those heart failure care providers. Thanks to our editor Dr Manoj Durairaj, sub-editor Dr Talha meeran and all the authors for their time and effort, which made the SfHFT proud to have this special anniversary issue of Revival. I am sure that this is the best new year gift that society can provide to its members and well-wishers. I wish you all a great year ahead.

- Dr Jabir Abdullakutty,
Secretary

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INDEX

PRE HEART TRANSPLANT WORK UP AND OUTPATIENT POST OP CARE FOR THE PEDIATRIC HEART TRANSPLANT PATIENT

Dr Swati Garekar is a pediatric cardiologist practising at Fortis hospital Mulund Mumbai.
She completed her MBBS from Seth GS Medical college and KEM Hospital Mumbai after which she did her MD pediatrics at the Children's Hospital of Michigan, Detroit. She went on to complete her 3 year pediatric cardiac fellowship at the same institution. She is interested in echocardiography, fetal echo, 3D printing of hearts, and heart failure/transplants.

INTRODUCTION:

Annually, around 5000 heart transplants occur around the world, of which 500 are pediatric ones. The number of heart transplants being performed in India is increasing and is fast becoming a practical option for our patients. This is true for the pediatric world as well. There is additional responsibility on the pediatric cardiac team as their patient has a much longer lifespan to be protected part of which is in a growing/evolving stage. The Indian scenario continues to have financial challenges apart from product (eg. appropriate lab tests, medications) and logistic (transport of organ) issues.

The following is a limited enumeration of outpatient evaluation of the pre and post heart transplant pediatric patient.

PRE TRANSPLANT WORK UP:

1. The primary responsibility of the team is to ensure that any treatable causes of heart failure have been detected and treated.

Ensure that the patient has been investigated thoroughly.

Some common (and potentially) treatable causes of pediatric heart failure are ALCAPA, LV outflow tract obstructions, systemic hypertension (secondary to eg. Pheochromocytoma), calcium and Vit D deficiency, certain SVTs masquerading as sinus tachycardias, Takayasu arteritis, and constrictive pericarditis.

The patient should also not have a contraindication to transplant: elevated non-responsive PVR, CHD with hypoplastic pulmonary arteries, active malignancy or associated with poor prognosis, advanced multi-organ failure, severe extracardiac malformations (syndromes etc) with poor quality of life and medical non-compliance issues in family.

2. Counselling session with family. This should include natural history of the condition and post heart transplant scenario for the patient. The mental and financial resources required by the family post transplant also needs to be discussed.

3. Judging the severity of heart failure.

a. Growth percentiles serially followed

b. Quality of life. (playing is everything for a child!)

c. Hospitalizations for heart failure or home inodilator therapy.

d. Detailed echocardiogram

e. 12 lead ECG

f. Diagnostic cardiac catheterization with calculation of cardiac output and PVRi and response to or oxygen, sildenafil or iNO if transpulmonary gradient is high. Cardiac cath is recommended for all patients especially patients with non-DCM findings in the echo evaluation. Moderate persistent PH in a DCM patient should also warrant a cardiac cath.

g. Serial values of NT pro BNP (or BNP)

h. Serum ST-2 level may be considered.

4. End organ health assessment

a. CBC with differential

b. BUN, Creatinine, electrolytes

c. Liver function tests

d. Lipid profile

e. Chest XRay

f. Urine routine, microscopy and urine protein/creatinine ratio

g. Abdominal ultrasound

h. Additional imaging if pt has CHD

5. Infection surveillance (serology needed yearly if on the transplant waitlist for a long time). If child receives a live attenuated vaccine then they need a 4wk waiting period before being placed on the waiting list.

a. HIV

b. HBS Ag

c. HCV Abd. HSV IgG and IgM

e. EBV IgG and IgM

f. CMV Ig G and IgM

g. Varicella IgG

h. Measles, Mumps, Rubella IgG

i. Mantoux test

6. Labs specific for Transplant

a. Blood grp

b. Panel Reactive Antibody (PRA)

c. Lymphocyte immunotyping; subtyping

d. Chest XR less than 6mo old film

e. Echo less than 3 months old report

f. ECG less than 3 months old tracing

g. Updated Height and Weight every 3 months

POST TRANSPLANT OUT-PATIENT CARE OF THE CHILD

1. The family must be asked to survey their home to ensure that cleanliness. The walls/ceilings should be inspected for damp spots. An isolated corner/room can be devoted for the child.

2. No visitors for 3 months

3. All family members should receive age appropriate vaccines; preferably non live one. If younger children in the house get the live vaccine (eg. MMR), then appropriate contact precautions should be taken to isolate the heart transplant patient.

4. Diet:

a. Avoid eating food prepared in hotels, street food etc as far as possible and especially in the first year post transplant.

b. Wash fruits and vegetables thoroughly before using. Avoid raw veggies including sprouts for the first 3 months. Avoid undercooked meat, unpasteurized milk and juice prepared outside the house.

c. No intake of orange (eg Nagpur orange) as it interferes with Tacrolimus. Grapefruit is also to be avoided. (Grapefruit is distinct from grape).

d. Follow a healthy diet for the whole family. This means whole grains, fruits and vegetables and less of sugar, salt, oil and packaged food for the whole family.

5. Purchase a weighing scale for home use. Record weight weekly initially and then monthly.

6. Strict adherence to OPD appointments.

7. Inform if vomiting after tacrolimus/mycophenolate dose; unexplained fever; diarrhea, weight change

8. No immunization for 6 months post transplant.

9. No live attenuated vaccines to be given at-all post transplant. The list includes measles, mumps, rubella, varicella, oral rotavirus, nasal flu vaccine, oral typhoid vaccine, BCG, oral polio.

10. Annual flu (non live) vaccine is recommended.

11. May return to school 3 months post transplant. Plan must be individualized based on the local situation.

12. Endomyocardial Biopsy: 1 month post transplant and then annually. More frequent biopsies may be required.

13. Coronary angiography for detection of coronary allograft vasculopathy (CAV). IVUS /OCT are better suited for CAV detection compared to coronary angiography alone but cost is an issue. Left and right heart catheterization with recording of hemodynamics at the time of biopsy.
If a coronary angiogram was not done on the donor heart (>40years old), an angiography maybe done along with the 1month endomyocardial biopsy.

14. Standard Medications

a. **Tacrolimus:**

i. Child to eat and drink nothing for 1 hour before and after tacrolimus. Current recommendations mention no need for NBM status pre and post.

ii. Usual dose is 0.1mg/kg/day divided into 2 doses PO

iii. Trough levels (mcg/L) to be maintained post transplant:

1. 0-6months:10-12
2. 7mo-1yr:8-10
3. 1yr to 36 months post transplant: 6-8
4. >3yrs post transplant: 5-7

b. **Mycophenolate:**

i. Dose is 20mg/kg/day divided into 2 doses PO

ii. Watch out for side effects: WBC count and diarrhoea

c. **Prednisone**

i. Dose is 5mg/day or 0.1mg/kg/day

ii. To be continued for 6months to 1 year if rejection free (wean off)

d. **Valgancyclovir for 3months for CMV prophylaxis.**
Dose : BSA x Creat clearance x 7. (Creatinine clearance by Schwartz formula; max value to be taken as 150ml/min/1.73m2). The tablet strength is 450mg and in general, the dose is 1 tablet OD ; to be adjusted for renal impairment if required.

e. **Sulfamethoxazole-Trimethoprim (Bactrim)** for 6 months

for Pneumocystis and Toxoplasmosis prophylaxis. Dose 80mg TMP (+400mg sulphamethoxazole) component tablet once a day. BSA adjusted dose: 150mg/m2 of TMP component per day. Some protocols give it thrice a week only.

f. **Statin.** Rosuvastatin may be used >10yr age. 5-10mg q HS. The practice of starting a statin is not uniform for all centres.

15. Pediatric cardiology Clinic visit

a. Every month for the 1st 3 months and then every 3 months for the first year. Every 6months for the 2nd year and then annually or more frequently as reqd. This visit includes height, weight, BP, pulse oximetry check, complete physical exam, check list for side effects of medications and PTLD surveillance (weight loss, fever without focus, "tonsilitis").

b. Echocardiogram: same schedule as above, with emphasis on ventricular systolic and diastolic function and PA pressure evaluation

c. ECG: same schedule as above

d. Holter monitor annual; if CAV present

e. Exercise stress test annual if CAV present

16. Blood tests

a. Monthly Tac level for the first 2 years; then 3 monthly or more frequently as indicated.

b. CBC every month for first 6months and then 3 monthly to 6monthly thereafter.

c. BUN, Cr similar to CBC

d. CMV IgG titre if negative pre op. If positive, then CMV PCR after 6months.

e. EBV IgG titre every 3 months if negative pre op. EBV PCR every 3 months for the first year esp if asymptomatic increase in titre. Serum LDH levels may be added.

f. Creatine Kinase (CK) level at 6months, if on statin.

g. Annual: CBC, Lipid profile, CMV IgG if preop negative; CMV PCR if pre op positive, EBV IgG if preop negative, EBV PCR if preop positive; varicella IgG, Liver function tests, BUN, Creatinine with GFR calculation, lytes, serum Glucose, calcium, Vit D 25(OH) level, serum calcium, HbA1c, iron studies, NT pro BNP, Urine routine and microscopic and protein/creatinine ratio, DXA scan for bone density (may make once in 2 years if normal).

CONCLUSION:

1. Pediatric heart transplant is a viable option for end stage pediatric heart failure in India.
2. Pre operative work up begins with ruling out treatable causes of heart failure
3. Further tests are used to determine extent of heart failure and timing of listing for heart transplant in addition to some specific pretransplant labs
4. Pre operative counselling (regarding their expectation from the procedure) of the family and the child is essential.
5. The first 1 year post transplant is most stressful for the medical team and the family as it involves extra care and surveillance.
6. Basic post operative medications are Tacrolimus and Mycophenolate currently. Modifications are made for individual patients.
7. Surveillance post-transplant revolves around detecting drug induced organ dysfunction, new infection, tumour detection and signs of rejection and coronary allograft vasculopathy.
8. Lifestyle should be focused on returning to a normal life with a focus on healthy diet, daily exercise and strict compliance with medications and tests.

HEART FAILURE AND HEART TRANSPLANTATION IN CHILDREN AND FOR CONGENITAL HEART DISEASE: CURRENT SCENARIO

Dr K Ganapathy Subramaniam

Dr K. Ganapathy Subramaniam is senior consultant cardiac surgeon at MGM Healthcare and visiting consultant at Institute of Child Health, Egmore. He finished his M.Ch (Cardiac Surgery) at AIIMS (New Delhi) and Pediatric Cardiac Training at Dr K. M. Cherian unit at Frontier Lifeline and Sydney, Australia. He looks after the Pediatric and Congenital heart disease program at MGM Healthcare, and is a part of the Heart and Lung transplant Unit at MGM Healthcare under the leadership of Dr K.R. Balakrishnan.

His areas of interest include complex congenital and neonatal cardiac surgeries. Heart transplantation. Lung transplantation in Pediatric patients and in patients with Congenital heart disease and Mechanical Circulatory support.

He has played an active role in setting and helping transplant programs across the country and was involved in the developing transplant program in Pune, Kolkata, Bangalore. Hyderabad, Jaipur and Vijaywada. He works along with Aishwarya Trust to make Pediatric Cardiac Surgery accessible to underprivileged people.

History and Prevalence

Heart transplantation is an accepted modality of treatment for children with heart failure refractory to medical therapy. The first Pediatric transplant for an Ebstein's anomaly was attempted by Adrian Kantrowitz in 1967 on Dec 6 (within 3 days of the first heart transplant) and the child survived for 6.5 hrs. In 1984, Leonard Bailey and his team at Loma Linda did the first Xenotransplantation in much publicized Baby Fae. She received a baboon heart for Hypoplastic Left heart syndrome and survived for 18 days.

According to registry of International society for Heart and Lung Transplantation, pediatric cardiac transplants represent about 10-15% of total transplants performed world wide which range between 500-700 procedures.

Indications

The indications vary according to the age. In infants, it is congenital heart disease which cannot be palliated surgically. This includes, Hypoplastic Left Heart Syndrome with severe ventricular dysfunction or tricuspid regurgitation, severe form of Ebstein's anomaly and congenital cardiomyopathy. In older children dilated and various forms of cardiomyopathy form the common indication. In an older age group, an increasing number of heart failure children, are the ones with previous palliation, especially those with a failing Fontan circulation. The youngest child in our series of 102 transplants was 12 months old. Dilated and restrictive cardiomyopathy form close to 75% of the indication for transplantation. Congenital heart disease form 11% (12/102) of the patients and majority are patients with single ventricle physiology.

Selection and Timing of Surgery

Selection of patients and timing of transplantation is crucial, but what is even more important is the selection of the donor. Worsening activity levels not improving with medical therapy, feed intolerance, recurrent admissions for heart failure symptoms with need for inotropes for stabilization and increasing Brain Natriuretic Pepide (BNP) levels (which are usually increased more than 10 times the recommended upper normal limit at the time of transplantation) can be used for deciding about timing for transplantation. Worsening abdominal pain due to hepatic congestion is a common complaint in pediatric population.

In failing single ventricle physiology patients – worsening cyanosis, protein losing enteropathy (PLE) and single ventricle dysfunction with worsening arrhythmias and valve regurgitation are indications. The failing single ventricle palliation with normal ventricular function is a high risk subset due to our lacunae in understanding of the altered circulatory and lymphatic physiology. Fortunately, all patients with PLE respond to transplantation with normalization in 3-4 weeks.

An early Fontan failure (<6 months) is a particularly high risk subset and these patients are better managed by taking down the Fontan to a Glenn stage and then transplanting them. The best subsets for transplantation are the single ventricle physiology patients with protected pulmonary circulation with ventricular dysfunction with no previous palliation. The patients with single ventricle and ventricular dysfunction tend to perform better following transplantation than those with normal ventricular function at least in the short term. The problem of sensitization due to: previous surgeries (redo sternotomy), transfusion, homograft use and difficulties in hemodynamic evaluation of pulmonary vascular resistance (PVR) are other challenges in this subgroup.

Evaluation of the Donor

Evaluation of potential donor is done usually with the help of transthoracic echocardiography. While blood group matched donor is necessary for older children, ABO incompatible cardiac transplants with results comparable to blood group matched donors are possible in neonatal and infant population. In presensitised individuals with high Panel Reactive Antibody levels, a negative Complement Dependent Cytotoxicity (CDC) cross match is preferred prior to transplantation. The use of older and heavier donors, whose heart can fit into the pericardial cavity of the recipient is frequently used. This is not always a disadvantage as these hearts can pump against the higher pulmonary vascular resistance compared to age and weight matched donors. Cutting down on the pericardium on the left side and opening the pleura widely, leaving the chest open till the donor heart adapts and leaving a small atrial communication are other maneuvers which can be used while using oversized donors. Custodiol (HTK) cardioplegia is used routinely and the median cold ischemic time is 200 minutes and the maximum is 330 min with good outcome in our experience.

While assessing the donor left ventricular function is easy, what we need is to identify if the donor right ventricle heart can pump against the increased pulmonary resistance of the recipient. A conductance catheter which can generate pressure volume loops of the donor can help decide the suitability of the heart particularly in patients with borderline elevated PVR. This is a study in progress.

A particular problem with the use of oversized hearts in pediatric population is the 'Big heart Syndrome'- they can present with hypertension , poor sensorium,seizures, cortical blindness and other neurological symptoms, which requires aggressive control of blood pressure in the postoperative period to prevent neurological morbidity. With preemptive management of increasing blood pressure in the immediate postoperative period, this syndrome has become uncommon of late.

Preoperative Stabilization

Preoperative stabilization of the recipient is paramount. Mechanical circulatory support (MCS) should be considered if there is end organ dysfunction setting in not responding to inotropes. Waiting time death rate, before the organ is available after listing for transplantation, is between 15-30 % and efforts should be made to reduce this using priority allocation and use of MCS.

Extracorporeal membrane oxygenation is the most easily available temporary mechanical support in our setting. ECMO can be converted to ventricular assist device without the oxygenator using extracorporeal centrifugal pumps.
We have bridged 10 of our patients with MCS with 70 % 5 year survival rate. The results in patients whose end organs are functioning normally with decreased pulmonary resistance are understandably better, though bleeding and sepsis could be of concern. Long term pumps though available for use in grown up children are prohibitively expensive for most of our population. We have experience with HVAD (Medtronic, Minneapolis) and Berlin Excor and have used Virtual Reality and 3-D printing to size and site the inflow cannula prior to surgical implantation.

Technical Aspects of Pediatric Heart Transplantation

The technical aspects of transplantation need close attention. Gentle handling of the donor heart, preventing distension are as important as the implantation of the organ. Extended donor organ harvest including the arch, branch pulmonary arteries, innominate vein and donor pericardium may be needed depending on the anatomic needs of the recipient. While explanting the recipient heart, the dictum is to stay close to the myocardium. Leaving a large cuff of recipient tissue can help manage systemic venous anomalies. An orienting suture on the anterior most aspect of the donor and recipient heart can help avoid twisting of the anastomosis. It should be ensured that there is enough adventitia on the recipient and donor aorta particularly in the area between the aorta and the pulmonary artery. Bleeding can be troublesome, if suturing is done only to the media devoid of adventitia of either the aorta or the PA. Discrepancies in size and abnormal relationship of the great vessels can be overcome by careful suturing and having extra length of great vessels. The dictum is to keep the PA as short as possible and leave the aorta long. We usually measure the PA and Left atrial pressure on the table before going on bypass of the recipient. If the transpulmonary gradient (Mean PA pressure – LA pressure) is high (> 12 mmHg) a small atrial communication is left in the donor heart to help in the management of posttransplant RV dysfunction.

Fontan patients have a condition which is opposite to a typical patient with cardiomyopathy. They have smaller hearts, large and dilated aortas and small and thin walled pulmonary arteries and left atrial wall, which is contrary to what happens in a typical dilated cardiomyopathy patient. Oversizing in Fontan patients has be done extreme cautiously as the pericardial cavity is usually small and cutting down on the pericardium and pleura may not be possible because of adhesions. Handling stented pulmonary arteries, multiple redo surgeries and bleeding can make this subset extremely challenging.

Immunosuppression and Posttransplant surveillance

Immunosuppression is by using induction with Basiliximab

(12mg/m2) 30 min before initiation of cardiopulmonary bypass along with Inj. Methylprednisolone (20 mg/kg) given at the time of initiation of CPB and during aortic cross clamp release. Maintenance therapy is with Tacrolimus started on 2nd postoperative day at a dose of 0.5- 1mg(0.05 – 0.3mg/kg depending on tacrolimus metabolizer status) aiming for a trough level of 8-12ng/ml, mycophenolate mofetil (10-20mg/kg/dose twice daily and Prednisone, which is tapered and stopped by 6 months.

Endomyocardial biopsies (EMB) for rejection surveillance is done prior to discharge and once yearly in our unit as recommended protocol biopsies by western centres, are not possible due to financial and logistic reasons. Any drop in ventricular function or new onset valve regurgitation should be aggressively investigated and anti-rejection measures initiated. Donor derived cell free DNA can be used to perform liquid biopsy and limit the number of EMB in the future.

Outcomes

The outcomes of pediatric transplantation in our unit are comparable to the survival reported in literature with 89% 90 day survival and 5 year survival of 73%. Severely elevated Right atrial pressure (> 18mm Hg), presence of ascites, elevated creatinine (>1.5mg/dl), lower INTERMACS category (very sick patients), presence of Pulmonary artery stenting were risk factors for mortality. The duration of cold ischemia and Preoperative PVR did not have effect on short or long term survival.

Early mortality in our experience is mostly due to right ventricular dysfunction and sepsis. A falling urine output, increasing central venous pressures, falling pulmonary artery pressures and worsening liver function are indicators of RV dysfunction, can be initially managed with inotropes, inhaled Nitric Oxide, but may necessitate institution of ECMO to support failing RV. Long term mortality may be due to infection, unrecognized rejection or graft vasculopathy.

Summary

The children with successful outcomes have very good quality of life and demonstrate rapid catchup growth. The renewed zeal towards life which the children show after successful transplantation needs to be seen to be believed. More awareness needs to be created about organ donation in pediatric hospitals and patients need to be referred reasonably early. Pediatric heart failure and its comprehensive management including patients with previously operated congenital heart disease requires dedicated specialized team and our country has the talent and skill to provide it.

SALIENT POINTS:

1. Pediatric Cardiac Transplantation is a proven modality for managing endstage heart failure and for managing Congenital heart disease where further palliation is not possible.
2. There is a need to increase awareness regarding pediatric organ donation and to refer early for consideration of transplantation.
3. ABO incompatible transplants are possible in neonates and infants with comparable outcomes.
4. An affordable durable mechanical circulatory support for pediatric population is the need of the hour.
5. Oversized hearts can be safely used for pediatric population.
6. Failing Single Ventricle physiology are particularly challenging subsets where liver and renal dysfunction and sensitization can adversely influence outcomes.
7. PLE resolves following heart transplantation.
8. Panel reactive antibody levels, Endomyocadial biopsies, immunosuppresion should be tailored to our needs.
9. Good early outcomes and acceptable mid term outcomes are possible even in our set up.
10. Xenotransplantation, Immune tolerance, Donation after circulatory death, Organ care and transport systems , increasing number of adults with single ventricle physiology will make Cardiac Transplantation for pediatric and congenital heart disease an exiting area of study.

ABO INCOMPATIBLE HEART TRANSPLANT IN A YOUNG INFANT

Dr Mukesh Goel

Senior Consultant, Cardiothoracic Surgery Heart & Lung Transplant Indraprastha Apollo Hospital, New Delhi

Dr Mukesh Goel completed MCh in CTVS from GB Pant hospital, New Delhi in 2001. He joined Escorts Heart Institute and got trained in beating heart CABG. He is presently associated with Indraprastha Apollo Hospital, New Delhi as Senior Consultant Cardiac Surgeon.

He is credited with carrying out the first heart transplant at Apollo Hospital, New Delhi. He is the coordinator of Heart & Lung Transplant & ECMO at the Institute.

His interest include CABG, aortic surgery, MICS MVR, LVAD, ECMO, Heart & Lung transplantation.

ABO incompatible heart transplant is contraindicated due to very high risk of hyper acute rejection due to preformed anti A/anti B blood group antibodies. Children needing heart transplant have very high waiting list mortality due to paucity of suitable organs. Children with O blood group have disproportionately high competition for organs while organs from those with less common groups like B and AB go waste. Complement system is not fully developed in newborn infants and they don't produce isohaemagglutinins with absent or very low anti A/B titers. Thus, the factors for acute rejection are not present in infants and small children and this fact is useful for ABO incompatible pediatric heart transplant. We present one ABO incompatible heart transplant in five-month-old boy.

A four month old boy was transferred on ventilator and inotropes from UAE . Child was in cardiogenic shock with no recordable pulse and blood pressure. Child was resuscitated with fluid, inotropes and diuretics. He was put on broad spectrum antibiotics. Child stabilized in next forty eight hours and became alert with warm peripheries and adequate urine output. He had already developed gangrene of right hand and foot with ischemic changes in tip of left fingers and toes. His Echo showed non compacted left ventricle with significant dilatation and severely depressed ejection fraction (15%). He also had severe mitral regurgitation (MR) contributing to low cardiac output and pulmonary edema. His chest xray had picture of pulmonary edema and areas of consolidation in right lung. He was treated with inotropes and ventilation twice in last three months in UAE.

Initial plan was to implant biventricular assist device (Berlin heart) and to wait for the donor heart. However, presence of limb gangrene and lung consolidation made us to decide against BiVAD. A decision was taken to do " Pulmonary artery banding" to increase right ventricular afterload and shift interventricular septum to left to influence severity of MR and pulmonary congestion. PA Banding was carried out two weeks after arrival. Tracheostomy was also done to prepare for long ventilator support. His MR came down quite a bit in postoperative period, pulmonary edema improved and inotropes and diuretic requirement came down. He got stabilized but remained dependent upon Mirinone and Lasix infusion. His ventilator requirement also came down to minimal support with periods of spontaneous respiration. We were, however, not able to wean him off inotropes, diuretics and ventilaory support completely. His PRA was nil.

One month after his arrival, information was received about a twenty-month-old girl child with brain death consequent upon traumatic brain injury. Her blood group was AB while that of our child was O. We decided to accept the AB group heart for O group child keeping in mind the rarity of pediatric donors, uncertainty of availability of size and group matched organ, doubtful survival of child during waiting period and immature immune organs in children. Anti A & B titers of the child were done which were 1:1 for both meaning no antibodies against A & B antigens were detected. Blood products were arranged to eliminate anti A/ B antibodies in plasma and platelets (AB plasma and platelets) while red cells were of O group. Rituximab (monoclonal antibody) was administered in a dose of 375mg/m2 before induction.


Image by fujikama from Pixabay

The rest of the immunosuppression was what is routinely used including Tacrolimus, Mycophenolate, and methyl prednisolone/ prednisolone. Cold ischaemia time was 140 minutes. Transplanted heart regained normal rhythm and contraction after reperfusion and was weaned off cardio-pulmonary bypass with milrinone and dobutamine. Inotropes were weaned off in next four days. He was on spontaneous respiration with intermittent ventilaor support after five days of transplant mainly because of pre-existing right lung consolidation.

Anti A & B titers were measured daily for initial five days and alternate days subsequently. These have remained 1:1. CD 19 levels to monitor Rituximab were measured after ten days of first dose and were nil.

Heart transplant is well established as effective therapy in children with end stage heart failure. Post transplant five years survival is close to 80% in experienced centers. However, concern of hyperacute rejection in ABO incompatible transplant hampers efficient utilization of organs in paediatric group and also causes high wait-list mortality. In children, antibodies against carbohydrate blood group antigens start developing by age of six to eight months after colonization of gut by E.Coli by that age which has cross reacting antigens at its surface. This fact can be utilized for ABO incompatible transplant in young children with similar results to those with ABO incompatible transplant. Lori J West et al described ten children with ABO incompatible transplant who had similar survival and suffered no more rejection episodes compared to children with ABO compatible transplant. Partial B cell tolerance may be a factor in preventing future development of antibodies against donor blood group antigens.

The results of ABO incompatible transplant in children are at par with that of ABO compatible transplant. One should not shy away from ABO incompatible transplant in young children, as wait-list mortality is very high otherwise.

SALIENT POINTS:

1. Children requiring heart transplant have disproportionately high wait-list mortality due to paucity of size and blood group matched donors.
2. Immune system and blood group antibodies responsible for hyperacute and acute rejection is not fully developed in children.
3. ABO incompatible heart transplant can safely be done and has comparable results to that of ABO compatible transplant.
4. The need of special immune suppression techniques is rare .
5. B cell tolerance (accommodation) develops against donor antigens later on.

PERIOPERATIVE MANAGEMENT OF HEART TRANSPLANT PATIENTS

Dr Manoj Kumar Sahu

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His interest areas are Thoracic organ transplantations, Extracorporeal membrane oxygenation and Pediatric Cardiac Intensive care.

Introduction

Heart transplantation (HTx) is accepted worldwide as a Gold Standard treatment option for End Stage Heart Disease. Heart Transplantation provides a substantial improvement in survival and quality of life. However, transplantation is not without risk, and transplant recipients will suffer some form of complication, which can range from mild to potentially fatal. Bleeding, kidney failure, primary graft dysfunction, allograft rejection, infection and immunosuppressant management remain the challenges in the early post-operative period.

Preoperative Evaluation of the Recipient:

Rule out active psychiatric diseases and assess family support

CT/MRI of the brain, chest, abdomen and carotid doppler are done to rule out pathologies in brain, lungs, liver and kidney.

A complete cardiovascular testing is performed with electrocardiogram, echocardiogram, coronary angiogram and right heart catheterization to measure the pulmonary artery pressure and document reversible pulmonary vascular disease prior to transplant.

Screening for endocrine diseases like diabetes, thyroid dysfunction and hematological disorders is done.

The recipient should be immunized against Influenza, Hepatitis & Pneumococcus

A complete list of laboratory investigations include the following -

- Blood grouping (ABO), Panel Reactive Antibody (PRA)
- Complete blood count, thyroid function tests, glycosylated hemoglobin (HbA1c)
- Biochemistry- renal & liver function tests, Lipids, Electrolytes, amylase, lipase etc.
- Coagulation parameters – Prothrombin time, International normalisation ratio and activated partial thromboplast in time
- Cardiac and inflammatory/infective biomarkers - CPK(MB), BNP, Trop-I, procalcitonin (PCT)
- Serology-Titers for HIV, Hepatitis, Cytomegalovirus (CMV), Ebstein-Barr virus (EBV), Varicella zoster virus(VZV), Toxoplasma, Rubella, HSV.
- Microbiological cultures (bacteria / viral / fungi / tuberculosis)
- Skin swab for methicillin resistant staphylococcus aureus (MRSA)

Preoperative orders before surgery:

Informed Consent, Part preparation & nil by mouth for 8 hours

Arrange Leukocyte depleted, irradiated CMV negative cross matched blood & products

Vitamin K 10 mg intramuscular injection

Antibiotic Prophylaxis (as per protocol)

Immunosuppressants - Tacrolimus 1 mg & Mycophenolate mofetil 500 mg per oral stat dose

Tab. Eltroxin 25 mcg oral stat dose

Tab. Sildenafil 25mg oral stat dose in selected patients

Intraoperative Management-

Arrival of donor heart in the operating room and starting recipient surgery is coordinated well, Surgery is performed under cardiopulmonary bypass (CPB), mild hypothermia at 32^0C. Methylprednisolone 500 mg IV is given at the time of aortic cross clamp (ACC) removal. Appropriate inotropes/vasodilators are initiated while weaning from CPB, in some instances mechanical support like Intra aortic balloon erpulsation (IABP)/ Extra corporeal membrane oxygenation (ECMO) may be required. Chest is closed after thorough hemostasis and placing four epicardial pacing wires

Postoperative Management of HTx Recipient in the ICU

All HTx patients are received in intensive care unit (ICU)- sedated, intubated & ventilated.

These patients are nursed in single or double-bed rooms preferably with reverse isolation.

Strict asepsis is mandatory. Medical staff must disinfect their hands & put on gloves before performing any procedure. Visitors must be restricted.

Arrival in ICU- establish the hemodynamic monitoring & re-establish the mechanical ventilation.

Arterial blood gas is done to check oxygenation & ventilation, Activated clotting time is tested and residual heparin effect may be neutralized with protamine.

The aim is to achieve adequate cardiac output (CO). Optimize preload, afterload with appropriate fluids, inotropes and vasodilators. Ensure adequate organ perfusion and recovery.

The goal is to rehabilitate the patient to normal life – Early extubation, physiotherapy, mobilization, enteral nutrition and psychosocial assistance are the expected norms. Most patients are maintained on inotropic and chronotropic support for 36-72 hours. Extubation is typically achieved when hemodynamics are stable and bleeding is no longer a risk. Invasive monitoring and mediastinal drains are removed after mobilizing the patient, day 3 onwards. A patient who has an uncomplicated course may get discharged from the ICU within 72 hours, but most of them stay in ICU for 5 days
on average.

Immunosuppressant (IS) therapy– Most transplant centers use triple drug regimen (tacrolimus, mycophenolate mofetil (MMF) and prednisolone as maintenance IS therapy. Tacrolimus 1mg & MMF 10mg/kg are started orally preoperatively few hours before surgery.

Methylprednisolone is started intraoperatively at 500mg/iv / at the time of ACC release and then continued postoperatively at same dose/iv/ 8 hourly (2 more doses) - followed by - 1mg/kg/day iv in 2 divided doses, till the target tacrolimus blood level is achieved. Then methylprednisolone is converted to oral prednisolone which is tapered gradually and kept going at a dose of 5mg per day

Tacrolimus and MMF are again re-started from postoperative day 2 onwards keeping close watch on renal function. We monitor the blood Tacrolimus levels twice a week and aim at the target trough levels-1st 2 months =10–15 ng/ml, 2–6 months = 8–12 ng/ml, and after 6 months = 5–10 ng/ml). **MMF is continued** at - 500 - 1500 mg twice daily (check with WBC counts, target 5000–7000/µl)

Induction agents (IA) – are required in certain special situations/cases like marginal donor hearts/preoperative renal impairment/or if some center has been using IA as a protocol. IL-2 Receptor Antagonists (Basiliximab) - 12 mg/m2 up to 20 mg per dose over 30 min on day 0 and day 4.

Other Postoperative medications include– Antibiotics, analgesics as per protocol. Pulmonary vasodilators like (Sildenafil) are started from day 0 if indicated for pulmonary artery hypertension. Other important medications like Valganciclovir (antiviral drug) for CMV prophylaxis, trimethoprim-sulfamethoxazole for Pneumocystis carinii and Voriconazole for antifungal prophylaxis are mandatory - started from day 2 onwards, once the patient is stabilized with good hemodynamics and normal kidney function.

Early Postoperative problems and management-

a) **Bleeding–** Watch closely for cardiac tamponade

b) **Sinus node dysfunction–** Maintain target heart rate of 100/ min, normal sinus rhythm & intact A-V conduction is helpful in achieving good CO.

c) **Ventricular dysfunction–** treated using inodilators (dobutamine/ milrinone).

d) **Increased pulmonary vascular resistance (PVR)–** managed with inhaled nitric oxide(iNO), sildenafil and avoiding hypercapnia, hypoxia, acidosis and hypothermia.

e) **Vasoplegia and severe hypotension– Maintain** optimal preload (CVP of 10-12 mmHg) and MAP > 70 mmHg. vasoactive and inotropic agents are adapted accordingly.

f) **Hypertension– may** be due to larger heart size (big heart syndrome), baroreceptor dysregulation and drug (calcineurin inhibitors) effects and it is controlled with iv vasodilators(NTG/ SNP) initially and then by calcium channel blockers

g) **Primary graft failure (PGD)–** manifests as heart failure

without any anatomic or immunologic etiology. IABP/VA ECMO are initiated early to support the failing heart if doesn't respond to pharmacotherapy.

h) **Renal dysfunction–** These patients need appropriate fluid management, optimal filling pressure and diuretics If the recipient becomes anuric/oliguric/ serum creatinine rises sharply- hemodialysis is instituted and initiation of tacrolimus is delayed.

i) H**yperacute Rejection–** occurs within 1st 24 hours, intraoperatively and manifests as failure to wean off CPB

Intraoperative endomyocardial biopsy (EMB) is done to confirm the diagnosis.

The condition is treated with high dose corticosteroid (CS), Plasmapheresis, iv IgG

Cytolytic therapy- Rituximab, IV Cyclosporin / Tacrolimus and MMF (if no response to No-2)

Inotropes and vasopressors to stabilize the hemodynamics and implementation of mechanical circulatory support devices (MCSD) if hemodynamics deteriorates despite maximal pharmacotherapy

j) **Acute Cellular Rejection (ACR)–**

An endomyocardial biopsy (EMB) should be performed as early as possible

Pulse steroid therapy (high dose methylpresdnisolone) is given as first-line therapy for symptomatic ACR irrespective of ISHLT EMB grade (1R, 2R or 3R).

Cytolytic IS therapy with Polyclonal Antibody - anti-thymocyte antibodies (ATGAM)/ Monoclonal Antibody (OKT3) – are administered in addition to steroids if hemodynamic compromise is present and especially if there is no clinical improvement within 12 to 24 hours of pulse therapy

Inotropes, vasopressors and MCSD are required to maintain adequate CO until recovery of heart allograft function occurs

k) **Antibody Mediated Rejection (AMR)–** is the antibody-mediated response to mismatched HLAs (existing antibody to donor specific antigens on graft endothelium). AMR results in graft ischemia, thrombosis and cell death in minutes to hours and is uniformly fatal.

Ventricular dysfunction without significant ACR on EMB is an indirect indication of AMR

Treatment- Pulse steroids, Iv IG, Plasmapheresis and Rituximab (anti B-cell CD-20)

CONCLUSION:

1. Heart Transplantation still remains the gold standard for ESHF patients
2. A thorough pre-operative evaluation of recipients is done to rule out the contraindications for HTx, they are immunized before, their PRA, blood group and weight etc. are recorded.
3. Storage and Transport of hearts from distant places (outstation hearts) need to be addressed diligently, Ischemia time exceeding 4 hours is a big risk for allograft rejection/PGD postoperatively.
4. Early postoperative period is heralded by many complications starting from bleeding, tamponade, arrhythmias, to dangerous ones like PGD and acute allograft Rejection
5. The transplant centre should have adequate back-up to manage PGD or Rejection with antirejection drugs and the circulatory assist devices like ECMO/VAD etc.
6. Infection is a major challenge, which needs to be diagnosed and treated timely
7. Renal failure is a major risk in the early postoperative period, can be averted with judicious management of fluid and IS therapy.
8. Hyperacute rejection occur intraoperatively soon after weaning CPB, or may fail to wean off CPB - diagnosed with EMB and treated immediately while supporting the heart pharmacologically and mechanically.
9. **Acute rejection episodes are to be diagnosed & treated early and efficiently with pulse steroid therapy, upregulation of immunosuppressants and other measures (e.g., plasmapheresis, iv IG, IAs etc.).**

VALVE SURGERY AND HEART FAILURE

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- Fellowship from the Royal Australasian College of Surgeons
- Advanced fellowship from Mayo Clinic , USA
- Member of ACS/ STS/EACTS/ HVS/ASCVTS/SfHFT/INSHLT/SCS/Mayo alumni
- Fellow of IACTS and C S Sadasivan Orator- 2020
- PI for six major trials: STICH/CORONARY/SIRS/BACE/LAAOS/PROMOTE
- Reviewer for IJCTVS/Asian Annals and EACTS- annual meeting .
- Organized live workshops for 20 consecutive years at GKNMH
- More than 25 years of experience in the practice of specialty with more than 10,000 procedures to credit
- Areas of interest: Reconstructive Valve surgery / Aortic surgery /surgery for heart failure

Preamble

The definition of Heart Failure (HF) is very wide and has various gaps. Several recent trials like the PARADIGM, VICTORIA, PARAGON etc. in heart failure have had different definition points. Different Societies have had definitions that are very variable and multi-factorial, some relying on haemodynamic criteria which are very difficult to apply clinically.

The 2021 guideline from AHA/ ACC defines the diagnosis of Heart Failure with reduced ejection fraction as anything <40 %.

The 2021 consensus statement by the Heart Failure Societies of America/Europe and Japan tries to address some of the gaps and grey zones and they have proposed a new universal definition for Heart Failure. This consensus statement defines HF *as a clinical syndrome with current or prior* symptoms and/ or signs caused by a structural and/or functional cardiac abnormality as determined by EF <50%, and corroborated by *at least one* of the following:

- Elevated natriuretic peptide levels
- Objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities such as imaging or hemodynamic measurement at rest or with provocation.

Most of the definitions have addressed the left ventricle. Right heart failure (RHF) is commonly secondary to left heart failure and is associated with a dilated right atrium and right ventricular dysfunction, associated with WHO group 2 pulmonary hypertension. Most of the time in valvular heart disease there is a component of right heart failure and biventricular failure.

Valvular Heart Disease (VHD), especially Aortic stenosis (AS), aortic regurgitation (AR) and mitral regurgitation (MR) can result in heart failure. VHD is acknowledged as a specific disease and so most heart failure clinical trials exclude significant VHD.

The focus of this article is to address valve surgery and heart failure. Primary diseases of the valve will eventually result in heart failure, mostly aortic and mitral regurgitation. Heart failure can itself result in valvular regurgitation which commonly occurs in mitral and tricuspid valves. For the ease of understanding and to have a clear idea the article would address, a clinical situation where the patient has a surgically correctable valvular lesion associated with ventricular dysfunction. This article does not dwell into the surgical techniques and procedures available as it is beyond the scope. The content is based on the current consensus document in heart failure (Ref 1), the 2020 AHA guideline on Valvular heart disease (Ref 2), and the ACC 2021 Update to Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment (Ref 3).

Heart valve abnormalities can clinically present as acute or chronic heart failure. We will look at each valve separately as the clinical scenario and the cause can be different.

Aortic Valve:

Critical aortic stenosis and acute aortic regurgitation secondary to endocarditis or acute aortic dissection, can result in acute heart failure. Treatment is pretty straightforward and needs to be addressed based on the underlying condition, which could be either a valve or a root

replacement procedure as indicated. Most of the time the left ventricle (LV) fails due to the sudden increase in volume and once the mechanical issue is resolved the LV recovers completely.

In Aortic Stenosis (AS) the timing of intervention is simple i.e- when the patient is symptomatic. The onset of symptoms is an indication of surgery. Symptomatic AS (stage D1) – Aortic Valve Replacement (AVR) is a **class IA** recommendation. In asymptomatic individuals with critical AS a LV function < 50 % is a class IB-NR indication(Ref 2). In asymptomatic AS which is critical (V max > 5 m/s) it is also wise to look at BNP levels. If it is elevated greater than 3 times the baseline; it is a class IIa indication for surgery. The simple take-home message is that there is no contraindication for offering a valve procedure to patients with AS based on their poor left ventricular function. The risk stratification may vary but not the indication. The other argument today is whether it is a Surgical AVR (SAVR) or Transcatheter AVR (TAVR). This has to be a Heart Team decision (**IA**).

Aortic regurgitation (AR) again is similar and may present late as it is asymptomatic for long. So one may see more patients with LV dysfunction at the time of presentation. Here again, presence of symptoms is an indication of surgery. If asymptomatic and if the EF <55 % it is an indication. However, even if the EF is >55% one has to look at the Left Ventricle End Systolic Dimension(LVESD). Surgical intervention is indicated if the LVESD is >50 mm or indexed is >25mm/m2. Another parameter in asymptomatic patients is to look at serial imaging studies to see if there is a drop in EF or increase in Left Ventricle End Diastolic Dimensions (LVEDD) to >65 mm which will signify the development of heart failure and surgery may be indicated (**2b**). Transcatheter Aortic Valve Implantation (TAVI or TAVR) is a class 3 (**Harm**) recommendation in patients with AR who have an indication for SAVR. Here as well, the take-home message is again related to symptoms. If the patient is symptomatic – offer surgery irrespective of LV function.

Surgical procedures may vary from valve repair to replacement. If replacement it could be a mechanical or a bioprosthetic valve. In terms of approach, it could be a TAVR or a SAVR. There could be additional procedures that need to be done on the root or ascending aorta depending on associated conditions and genetic background of the patient.

Mitral Valve:

Acute mitral stenosis in a native valve is unknown. Rarely an acute obstruction to a left Atrio-Ventricular valve is due to a prosthetic valve obstruction or a myxoma. They present as acute pulmonary edema and an urgent surgical correction is indicated. Chronic Mitral Stenosis (MS) most commonly is rheumatic in origin and presents quite early before the onset of LV dysfunction. The indications of surgery are clearly defined and depending on the morphology of the valve a Percutaneous Mitral Balloon Commissurotomy (PMBC) or surgical repair/ replacement is carried out. There is no contraindication to surgery even with LV dysfunction. Most of the time, these patients have more right ventricular (RV) dysfunction and tricuspid regurgitation (TR) due to a long-standing mitral obstruction.

Mitral Regurgitation (MR) is the focus when it comes to the left ventricle. It can be acute or chronic and can also be primary or secondary.

Acute MR presents as an acute emergency with acute pulmonary edema and varying degrees of LV dysfunction. The causes include Post Myocardial Infarction (MI) MR, an acute chordal rupture in degenerative disease, infective endocarditis, or prosthetic valve dehiscence. Acute post-MI – MR is most commonly seen with inferior wall MI and the majority of patients present with cardiogenic shock. More than 2/3rd of the cases are due to partial rupture of the postero-medial papillary muscle. Left untreated more than 75% of them die within the first 4 weeks. Surgery also carries a high risk close to 15-40% but with a 5-year survival of close to 60%. The management of most cases of Acute MR is surgical which maybe repair or replacement. An acute chordal rupture in a degenerative etiology should be repaired (if possible). Infective Endocarditis (IE) and valve dehiscence are dealt with as the need be. A total chordal preservation mitral valve replacement will be a better option especially in the setting of a partial or complete papillary muscle rupture in Post MI acute MR. Sometimes an Acute MR can be dynamic due to dysfunction secondary to ischemia where revascularization alone may correct the problem.

Chronic MR can be primary or secondary.

Primary MR if symptomatic is an indication for surgery irrespective of LV function. However, if asymptomatic a drop in EF<60% or a LVESD >40 mm is an indication for surgery (**Class I recommendation**). If degenerative in origin then a repair should be attempted in a centre of excellence which is again a **class I recommendation**. All the above recommendations even though class I are all supported by
a **LOE B-NR.**

Secondary MR can be ischemic or non-ischemic. Ischemic MR (IMR) is a result of asymmetrical dilatation of the LV whereas non-ischemic is usually symmetrical. Both cases are ventricular disease rather than a valve problem.

The most common clinical scenario is an IMR. It is a surrogate marker of poor outcomes. 5-year survival is only 40% if MR is present and the mortality is also directly related to the quantum of MR. 5-year survival of 47% with Effective Regurgitation Orifice (ERO) <2 cm2 vs 29 % with ERO >2 cm2. Relative risk ratio of cardiac death is 1.56 if ERO<2 cm2 vs 2.38 if ERO >2 cm2.

The mechanism proposed is multifactorial which includes annular and LV dilatation, regional LV dysfunction, papillary muscle dysfunction or displacement and leaflet tethering. Current Magnetic Resonance Imaging (MRI) studies have shown that it is just not a LV dilatation but a loss of balance between systolic torsion and diastolic recoil. Consequent to this the saddle shape is lost with flattening and stretching of the septo-lateral diameter and apical tethering of the posterior leaflet. The tenting height is a marker of severity. The leaflets are not normal. Studies from transplanted hearts have shown that the leaflets are biochemically different with altered extracellular matrix. There is a delayed closure leading to central and commissural leaks. Current echocardiography studies have also shown that papillary muscle dysfunction is protective and decreases MR. Also, LV End Diastolic Volume (LVEDV) has a poor correlation to severity. The ratio of LV mass to EDV is constant in secondary chronic MR. An EF of <55% with severe MR indicates advanced myocardial dysfunction. LV End Systolic Volume Indexed (LVESVI) – is the most accurate indicator of ventricular contractility and the best predictor of outcome and cardiac death.

Echocardiography forms the gold standard for evaluation and assessment of severity. The severity of MR as per the recent guideline is the same as for degenerative etiology. An Effective Regurgitant Orifice Area (EROA) >0.4 cm2 and a Regurgitant Volume >60 cc are suggestive of severe MR. The decision to intervene should be made on preoperative assessment and not under general anaesthesia.

Vena contracta width is more predictive of severity than EROA. EROA in secondary MR has its limitations as it is affected by loading conditions of the LV and a stress echo paradoxically decreases EROA and MR severity in Functional MR (FMR) and IMR. EROA estimation based on doppler flow convergence is also affected because of the crescentic shape of the regurgitant orifice.

Severity of MR: AHA 2020 Guideline

Parameter	Mild	Moderate	Severe
EROA (cm2)	< 0.2	0.2 - 0.4	> 0.4
Regurgitant Vol (ml)	< 30	30 - 60	> 60
Vena Contracta (mm)	< 3	3 - 6.9	>7

Treatment of secondary MR is primarily GDMT (Guideline Directed Management and Therapy). This is a **Class I recommendation (2020)**. In patients undergoing CABG with severe MR, mitral valve procedure is indicated as a **2a** recommendation. In patients with severe MR who are symptomatic in spite of GDMT and if EF >50% MV surgery is a **2b-B-NR** indication. In patients with severe MR with EF <50 % Transcatheter Edge-to-Edge (TEER) is a **2a-B-NR** indication provided the LVESD<70 mm and the PA systolic<70 mm Hg.

Surgical options are MV Repair or Replacement. The 2020 guidelines give a **2b-B-R** recommendation for a chordal preserving MVR in symptomatic MR with EF <50 % against an undersized annuloplasty. Repair is the most commonly done procedure as the operative mortality is significantly lower than MVR when CABG is associated. The mechanism is complex and the fact that the recurrence of MR is high suggests that most of the time the exact mechanism is
not addressed.

Two standard techniques are a) an undersized annuloplasty (Figure 1a) and b) an edge-to-edge repair (Fig 1b).

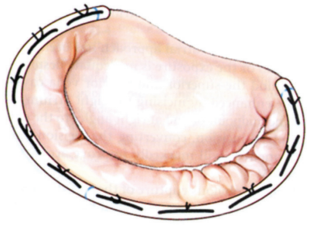

Figure 1a) Schematic diagram showing an undersized annuloplasty performed

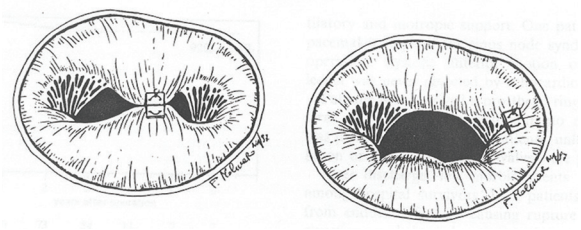

Figure 1b) Schematic diagram showing an edge-to-edge repair performed

The choice of rings is many and there is no ideal one. The choice between a band and ring is also not very clear and largely depends on the surgeon's choice and comfort. The general consensus is in favour of a complete rigid ring, however not supported by any definitive studies. There are other techniques like neo-chords, chordal cutting, papillary muscle traction to correct displacement etc. but are not standardized.

There are certain situations where the controversy or lack of clear consensus still exists-

1) Should moderate MR be addressed during CABG ?
There have been many trials and the recent CTSN RCT is the only definitive trial that compared this. 300 patients were randomized to either CABG only or CABG plus undersized annuloplasty. The primary endpoint was not clinical but LVESVI. There was no difference between the two groups in terms of MACE also. MV repair group had less MR at two years but no clinical difference. They also observed that improvement in lateral wall motion correlated with

improvement in MR irrespective of treatment arm. Hence, the answer to the question is NO. However, there are a few caveats. If the lateral wall is scarred and is not grafted added then fixing the MR may be a good option to improve symptoms and quality. On the contrary, if the lateral wall is viable with a good target vessel that is graftable then one may defer fixing the moderate MR. Probably, it is not justified to replace the valve for sure in moderate MR. Either repair it or leave it alone. Poor predictors of recurrence include a LVEDV >5, coaptation depth of <10 mm and AP diameter
>37 mm and a tenting area >1.6 cm sq.

2) MV Repair or Replacement?

This question arises in the setting of severe MR and symptomatic patients. The CTSN looked at it. They randomized 251 patients to either MV repair or a total chordal preserving MVR. At one year the degree of residual or recurrent MR was higher in the repair group but the perioperative mortality was higher in the replacement group. At one year there was no other difference however in clinical outcomes. The CORE group from Australia in their meta-analysis also observed the same. Repair may be preferred if there is significant viable myocardium on the inferolateral wall and if the target vessel is grafted. A scarred lateral wall probably will dictate a choice of replacement.

The current 2020 guideline gives a **2b-B-R** recommendation in favour of total chordal preserving replacement in this setting as against an undersized annuloplasty.

3) Role of Percutaneous Techniques?

The Mitra-clip which is based on the principle of Alfieri stitch is the only percutaneous repair technique now approved for MR. Initially applied for a degenerative disease it is extended to secondary MR as well based on the COAPT trial. It is a **2a-B-R** recommendation in FMR in patients with LVEF of 20-40 % and LVESD<70 mm and PA pressure<70 mm Hg.

Percutaneous mitral valve replacement is still under trial and innovation. There are close to 20 plus devices under investigation for native valve disease. However, a valve-in-valve is being done fairly regularly in many centres for bioprosthetic valve failure in patients who are unfit for a reoperation.

4) BACE Device

The BACE or the Basal Annuloplasty of Cardia Externally is a collar around the base of the heart with silicone bags that can be filled with saline and adjusted remotely under TEE guidance. This addresses the mitral annulus and also supports the infero-basal wall of the ventricle as a containment device. This can be done off-pump and has currently got the CE mark (Fig 2a-b).

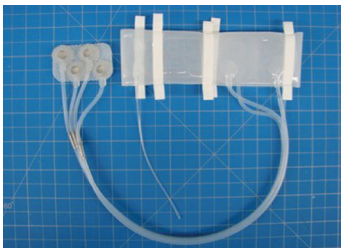

Figure 2a) Photograph of a BACE device

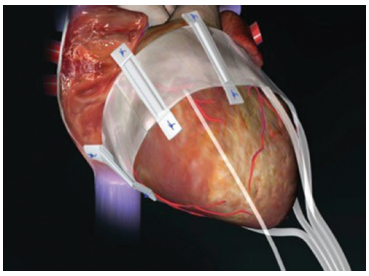

Figure 2b) Schematic diagram showing as to how does a BACE device wrap around the heart and treats secondary MR

Tricuspid Valve:

The most common cause of tricuspid regurgitation (TR) is secondary to left-sided valve disease.

Severity of TR :

Parameter	Progressive TR	Severe TR
Jet area	<50 % of RA	>50 % of RA
Vena Contracta	<7 mm	>7 mm
ERO	<0.4 cm	>0.4cm
Rvol	<45ml	>45 ml

In patients with severe TR who are undergoing left-sided surgery fixing the tricuspid valve is a **Class I –B-NR** recommendation today. In progressive TR who is undergoing a left-sided surgery if the tricuspid annular end-diastolic dimension is >40 mm or with symptoms of right-sided failure then the TV has to be addressed as a class **2a-B-NR** recommendation.

Isolated TV surgery may be considered in the absence of left-sided disease if the patient has symptoms of right-sided failure, either due to primary or secondary TR if there is no pulmonary hypertension. Progressive RV dilatation is also a **2b** indication in asymptomatic cases.

The common scenario is a severe TR a few years after a left-sided surgery. In this setting, if the patient has symptoms of right-sided failure isolated TV surgery can be advised as a **2b-B** recommendation provided there is no pulmonary hypertension and severe RV systolic dysfunction.

The choice of procedure is most often a repair. Repair of the TV valve should be undertaken with the same systematic

process that is done for a mitral valve. An incomplete ring annuloplasty is a preferred technique. There are special rings which may also be used. Sometimes, especially when going in as a redo after a left-sided surgery one should have a low threshold to replace the valve.

TR in Transplanted hearts:

TR in transplanted hearts is a very common occurrence. The majority of the cases range from mild to moderate and are managed medically. Sometimes, it can be severe and causes severe right heart failure symptoms. Concomitant TV annuloplasty in donor's hearts is advocated by some but is not universally accepted. The decision to surgically correct the tricuspid valve should be taken with extreme caution even if the RV function is good. Anatomical etiologies do better than functional ones. There is emerging data that suggest that replacement with a biological valve is more durable and also gives access to Endo-Myocardial Biopsy (EMB).

SALIENT POINTS:

- Valvular heart disease is one of the established causes of heart failure. As it is a separate entity, most HF trials do not address primary valve disease. It can also be the effect, especially in mitral and tricuspid valves.
- The definition of heart failure is constantly changing and as per the 2021 consensus statement, it is defined as: symptoms and signs with EF <50 % (HFrEF), elevated NP levels and evidence of pulmonary or systemic congestion. (AHA/ACC 2021 <40 %)
- Symptomatic aortic stenosis or regurgitation is a class I indication for intervention irrespective of left ventricular function. Critical AS is a **Class I-A** recommendation (2020).
- Acute MR of whatever etiology is a surgical disease and needs emergent intervention.
- Symptomatic Chronic MR should be surgically corrected irrespective of ventricular function.
- Secondary MR most commonly is ischemic in origin and surgical correction provides symptomatic relief but does not improve survival. No concrete evidence to show that correction of moderate MR helps.
- Standard repair commonly involves a reducing annuloplasty with a rigid complete ring and an edge-to-edge repair if need be as an adjunct. A total chordal preserving MVR for severe MR may be preferred.
- TEE can be done in patients who are high risk for surgery provided EF>20 % and PA pressure <70 mm Hg
- TMVR is still not a validated procedure, however, Valve-in-Valve is a practiced option in patients who are at high risk for a redo-procedure.
- BACE device is an external annuloplasty system that addresses the MR as well as the basal LV.
- Tricuspid Valve disease is mostly secondary to left-sided disease. Severe TR or moderate TR with an annulus >40mm should be corrected during left-sided surgery.

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6

USE OF SWAN GANZ CATHETER AND HEMODYNAMIC MONITORING IN CONGESTIVE HEART FAILURE

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Dr Bagirath Raghuraman is presently working as Senior Consultant interventional and Transplant Cardiologist, Program Director, Heart Transplant, at Narayana Institute of Cardiac Sciences, Narayana Health City, Bangalore. Apart from training in Interventional Cardiology at The Rotenburg Cardiovascular Clinic at Fulda, Germany, he underwent training in advanced management of heart failure and cardiac transplantation at Papworth hospital, Cambridge, United Kingdom. He also underwent training in the use of cardiac assist devices in the management of heart failure at the University of Minnesota, Minneapolis, USA. Apart from this, he underwent training in Balloon pulmonary angioplasty for Chronic thromboembolic hypertension (CTEPH) at the Tokyo Medical University Hospital, Tokyo, Japan.

His area of expertise apart from interventional cardiology has been management of heart failure, mechanical circulatory support devices, cardiac resynchronisation therapy and cardiac transplantation.

Introduction:

Pulmonary artery catheters or the Swan-Ganz catheters are balloon floatation catheters that are used for the evaluation and management of critically ill patients, and for the evaluation of unexplained dyspnoea or pulmonary hypertension. They are useful for collecting detailed hemodynamic data, including direct assessment of filling pressures and cardiac output, and also for calculation of pulmonary and systemic vascular resistance

Pulmonary artery catheter (PAC) can be used to make the following measurements:

1. Central venous pressure (CVP)
2. Right-sided intracardiac pressures (right atrium, right ventricle)
3. Pulmonary arterial pressure (Pap)
4. Pulmonary capillary occlusion pressure (PCOP; pulmonary capillary wedge pressure [PCWP])
5. Cardiac output (CO)
6. Mixed venous oxyhaemoglobin saturation (SvO2)

The PAC can indirectly measure the following calculated parameters:

- SVR = 80x [Mean artery pressure – CVP] /CO)
- Pulmonary vascular resistance (PVR = 80 x [mean Pap – PCWP]/CO)
- Cardiac index (CI = CO/body surface area)
- Stroke volume index (SVI = CI/heart rate)
- Left ventricular stroke work index (LVSWI = [mean systemic artery pressure – PCWP] x SVI x 0.136)
- Right ventricular stroke work index (RVSWI = [mean Pap – CVP] x SVI x 0.136)
- Oxygen delivery (DO2 = CI x 13.4 x haemoglobin concentration x arterial oxygen saturation)
- Oxygen uptake (VO2 = CI x 13.4 x haemoglobin concentration x [arterial oxygen saturation – venous oxygen saturation])

The indications for hemodynamic monitoring are:

1. Unexplained or unknown volume status in shock
2. Severe cardiogenic shock (eg, acute valvular disease, suspected pericardial tamponade)
3. Indicated in patients with discordant right and left ventricular failure.
4. Suspected or known pulmonary artery hypertension - Indicated for the hemodynamic differential diagnosis of pulmonary hypertension.
5. Indicated to assess response to therapy in patients with precapillary and mixed types of pulmonary hypertension.
6. Indicated for cardiac transplantation or ventricular assist device workup.
7. Severe underlying cardiopulmonary disease (eg, congenital heart disease, left-to-right shunt, severe valvular disease, pulmonary hypertension) who are undergoing corrective or other surgery.
8. Indicated in patients with severe chronic heart failure requiring inotropic, vasopressor, and vasodilator therapy.

1. Invasive hemodynamics is indicated in patients with high cardiac output, low SVR, elevated PCWP and RA pressure
2. Indicated in some patients with systolic heart failure such as fulminant myocarditis and peripartum cardiomyopathy where there is a possibility of recovery.
3. Indicated in selected patients with cardiogenic shock or other severe hemodynamic collapse, with anuria or oliguria, or with uncertain hemodynamic parameters and inadequate response to therapy.
4. Uncertainty regarding hemodynamics after therapy:
    - Possibility of right left mismatch
    - Investigate intrinsic pulmonary hypertension
    - Investigate unusually low or high SVR
    - Recurrent or refractory symptoms
    - Cardio - renal syndrome
5. Failure to wean from intravenous inotropic infusions.
6. Uncertainty regarding baseline hemodynamic profile
    - Symptoms and severity are disproportionate to clinical examination, often requiring assessment during exercise.
    - Ambiguity regarding clinical assessment
7. Management of Decompensated Heart Failure with uncertain contribution from other conditions:

    A. Cardiac causes
    - Ongoing ischemia
    - Primary valvular heart disease

    B. Noncardiac causes:
    - Severe pulmonary involvement
    - Renal insufficiency
    - Hepatic insufficiency
    - Sepsis

C. Postoperative respiratory insufficiency or hypotension unresponsive to treatment (refractory hypotension)

In patients with advanced heart failure, invasive hemodynamics can be used to achieve the following therapeutic targets:

1. LV filling pressure (reflected by PCWP) of <16 mm Hg
2. RA pressure < 8 mm Hg
3. SVR between 1000 - 1200 dynes-sec/cm−5

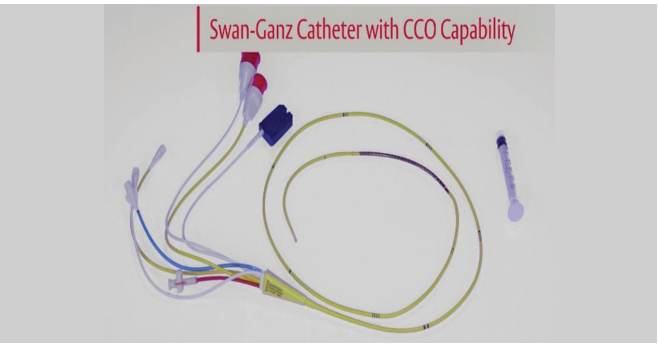
Multiple studies (large, small, randomized and meta-analyses) have reconfirmed that there is no benefit in terms of either hospital stay or survival by the use of invasive hemodynamic monitoring. As a consequence of this finding, most societal guidelines no longer support their routine use. However, many clinicians who monitor critically ill patients, value the information obtained from PAC placement in selected patients as discussed above.

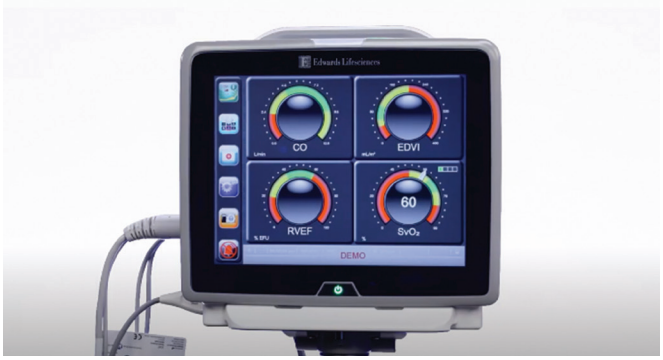
Common challenges faced by a cardiologist managing heart failure:

1. Patient has worsening renal parameters.
2. Patient has persistent hypotension despite maximal doses of inotropes.
3. Patient is not improving on treatment – whether patient is refractory to medications?
4. Unable to optimize the patient and make him/her suitable for cardiac transplantation.
5. How to minimize the side effects of the medications?
6. How to titrate the dosages so that I can give the right dose of medications?
7. When can I wean off intravenous supports – not too early / not too late?

How is hemodynamic monitoring done?

1. Right internal jugular vein access
2. Sheath inserted by Seldinger technique.
3. A Swan Ganz direct flow catheter is inserted into the sheath over a guidewire and maneuvered and positioned in the pulmonary artery.
4. The pressure transducer of the Swan Ganz catheter is connected to a Continuous cardiac outcome monitor.
5. Arterial access – radial or femoral sheath for arterial pressure monitoring
6. After catheter placement, measurement is taken with patient's bed head end angle of 30°





The goal of hemodynamic tailored therapy is to achieve low or near normal filling pressures without a drop in cardiac output or peripheral perfusion. This can be achieved by a careful balance of inotropes, vasodilators, and diuretics.

The 2013 ACCF/AHA and 2010 HSFA guidelines

The guidelines reiterate that there is no benefit in the routine use of invasive hemodynamic monitoring in normotensive patients who are being treated for ADHF who have a good response to vasodilators and diuretics.

The HSFA guidelines recommends invasive hemodynamic monitoring in the following clinical scenarios:

- Heart failure which is refractory to therapy
- Uncertain volume status and cardiac filling pressure
- Significant hypotension (Systolic BP < 80 mm Hg) or worsening renal insufficiency during therapy
- Requirement to assess degree and reversibility of pulmonary hypertension, as part of cardiac transplantation work up.
- To document adequate hemodynamic response to inotropic therapy, where long-term outpatient infusion therapy is indicated or planned.

Risks and complications of invasive hemodynamic monitoring:

1. Bleeding
2. Infection
3. Arrhythmias
4. Rare catastrophic events like Pulmonary artery rupture
5. Pulmonary infarction.

Clinical Trial evidence:

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) was a randomized controlled trial that enrolled 433 patients with severe and symptomatic heart failure despite adequate therapy. The patients were randomized to receive therapy guided by clinical assessment and PAC versus clinical assessment alone. The results showed that the use of PAC did not significantly alter the days alive and out of hospital during the first 6 months (133 versus 135 days), duration of hospitalization (8.7 versus 8.3 days) or mortality (43 versus 38 deaths) as compared to clinical assessment alone. The results of the ESCAPE trial led to a decline in the use of PAC in AHF management.

THE FINAL WORD:

Echocardiography does compare with PAC to a certain extent which is outlined by the skill of the echocardiographer. However, the absolute numbers generated by a PAC are the "Gold Standard" and leaves no ambiguity in the mind of the end user.

Both the ACC / AHA and the ESC guidelines suggest that invasive hemodynamic monitoring is potentially useful in selected patients with persistent heart failure symptoms despite standard therapies, require vasopressor support, or have uncertain volume or perfusion status.

RIGHT HEART FAILURE IN PULMONARY HYPERTENSION

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Dr Prashant Bobhate is a Paediatric Cardiologist and Pulmonary Hypertension specialist working as Consultant Paediatric Cardiologist and heading the pulmonary hypertension clinic at Kokilaben Dhirubai Ambani hospital, Mumbai. After completion of MBBS from Lokmanya Tilak Municipal Medical college and MD Paediatrics from Seth GS medical college and KEM hospital Mumbai, he did his Fellowship in Paediatric Cardiology at Fortis Escorts Heart Institute, New Delhi.
He has done Fellowship in Pulmonary Hypertension at Mazankoski Heart Institute, Stollery Children's Hospital at University of Alberta, Edmonton, Canada. He has played a pivotal role in setting up a one of its kind Pulmonary Hypertension Clinic in Western India. Apart from the routine investigation and management of patients with PH, this clinic has performed 19 Potts shunt (Highest Single Centre experience in the World) and has 24 patients on prostacyclin therapy. The clinic also has a dedicated Cardiopulmonary Rehabilitation Centre, which helps in rehabilitation of the patients with PH. He is current Convenor of the "Pulmonary Vascular Research Institute" in India and heads their Indian Taskforce since 2018. Along with his clinical work, Dr Prashant takes keen interest in clinical research and has published more than 20 original articles in national and international peer reviewed journals and 6 chapters in textbooks of paediatric cardiology, cardiology and pulmonary hypertension.

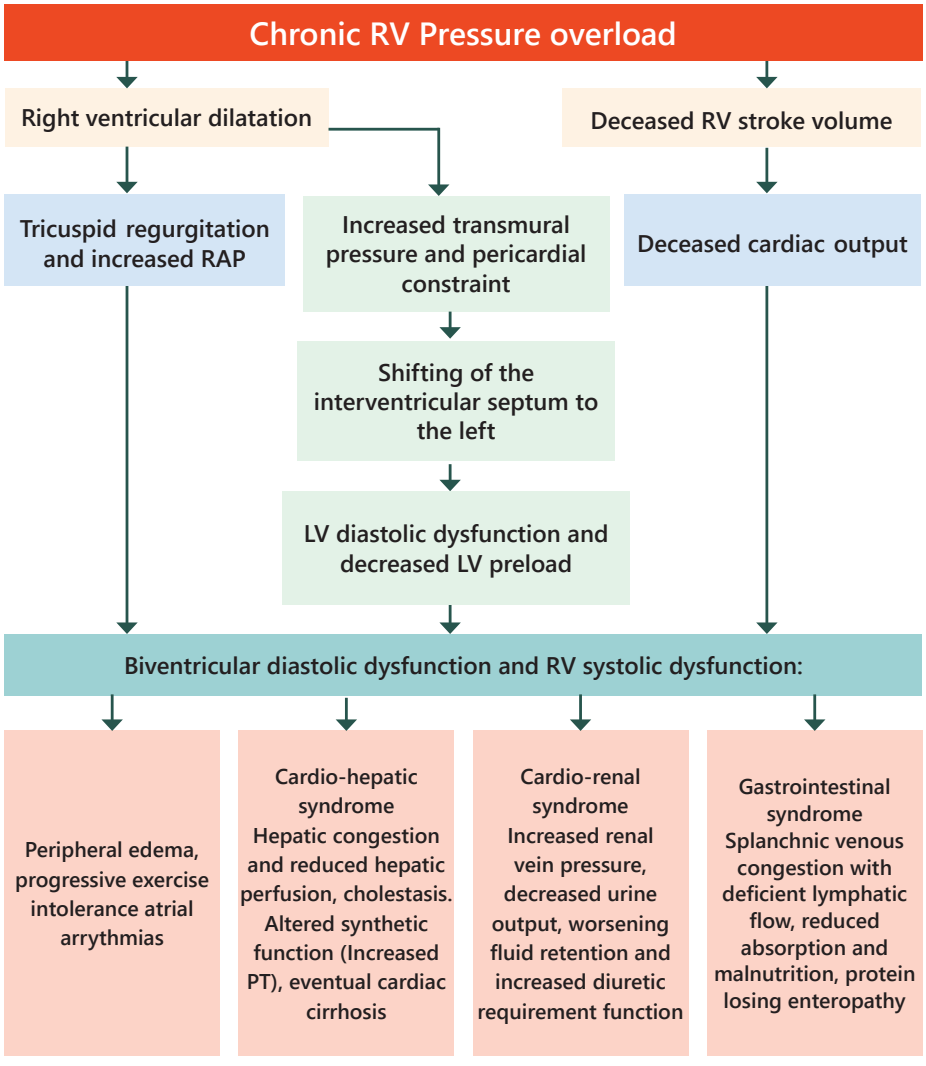
Right heart failure in pulmonary hypertension:

Advanced pharmacological management of PAH has renewed the current interest in the evaluation and management of right ventricular dysfunction (RVD) and right heart failure (RVF). RVD is defined as an abnormal structure or function of the right ventricle, whereas RHF is a clinical syndrome with signs and symptoms of heart failure.

Normal RV ejection fraction (RVEF) is determined by adequate preload (systemic venous return), native contractility of the right ventricular wall, afterload (PAP and PVR), and pericardial compliance. Ejection of blood into a highly compliant and low resistance pulmonary circulation ensures that the energy expenditure required for normal RV output is much less as compared to the left ventricle. Thus RVEF is highly sensitive to afterload, and minimal increase in the afterload has detrimental effects on RVEF. (1) Patients in RHF generally exhibit elevated right-sided filling pressures (right atrial pressure >8 mm Hg) and reduced cardiac index (<2.5 L/(min " m2).

Pathophysiology and clinical manifestations:

Although RV failure can be acute or chronic, in pulmonary hypertension, it is usually chronic secondary to persistently increased afterload. An initial compensatory phase of myocyte hypertrophy and remodeling is gradually replaced by a decompensated



phase associated with myocyte loss and fibrosis. The decompensated phase is usually associated with elevated right atrial pressures and PVRi with a decrease in cardiac output. Decreasing mean Pap with persistently elevated PVR is an ominous sign of end stage RHF.(2)

Clinical manifestations:

- Increased mortality
- Decreased functional capacity
- Cardio-hepatic and cardiorenal syndromes
- Malnutrition and cachexia
- Coagulopathy

Symptoms:

- Exertional Dyspnea, fatigue
- Peripheral edema
- Abdominal fullness or ascites
- Exertional chest pain (angina)
- Presyncope and syncope

Examination:

- Elevated JVP
- RV S3
- Loud P2 (pulmonary hypertension)
- TR murmur which increases on inspiration (Carvello sign)
- Right ventricle heave

Evaluation of right heart failure:

Imaging:

Cardiac echocardiography is the first line of imaging in a patient with right heart failure. It is widely available and enables a rapid assessment of RV size and function. Parameters suggestive of pulmonary hypertension are: septal flattening, RV dilation, dilated and non collapsing IVC, high RVSP estimated from tricuspid regurgitation jet, dilatation of pulmonary artery, decreased pulmonary artery acceleration time. Two important parameters of RV function assessment by 2 D echo are fractional area change (FAC) and TAPSE. FAC < 34% and TAPSE < 17 mm suggest RV dysfunction. 3D echo and speckle tracking/ strain imaging are more reliable estimates of RV function. MRI is the gold standard in the assessment of RV function. It also helps in the assessment of RV fibrosis with late gadolinium enhancement. High cost and accessibility is the limitation of MRI.(3)

Biomarker:

There is a long list of biomarkers, but most of them lack specificity. BNP/NTproBNP levels correlated with hemodynamic parameters, echocardiographic indices of RV overload, New York Heart Association functional class, and mortality in patients with PH and RVF. (5). More recently, circulating endothelial cells and micro-RNAs have also been identified as biomarkers in PAH, with possible implications on outcomes. (4)

Treatment:

Treatment of RHF is supportive and symptomatic and revolves around decreasing preload, afterload and improve contractility.

Preload optimization: (Diuretics, salt, and fluid restrictions): The goal of optimal fluid management in chronic RHF is to maintain sufficient preload for adequate cardiac filling while providing relief from right ventricular volume overload, interventricular dependence, and congestion. Loop diuretics and a combination of diuretics like loop diuretics and thiazides may be helpful to augment natriuresis via sequential nephron blockage. Sodium restriction (<3g/day) and fluid restriction (<1.5-2l/day) are reasonable in patients with PAH and RHF. (2)

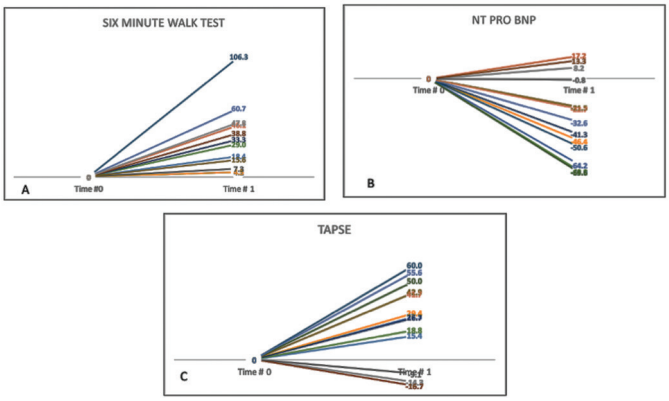
Afterload reduction: Afterload reduction is the cornerstone in the treatment of RV failure with pulmonary hypertension. For patients with group 1 PAH, therapies include PDE (phosphodiesterase)- 5 inhibitors, endothelin receptor antagonists, activators of soluble guanylate cyclase, and prostacyclin analogs. There are no approved therapies for groups 2, 3, and 5 PH beyond treating the underlying disease.

PDE5 inhibitors: Phosphodiesterase 5 inhibitors like sildenafil and tadalafil are established, effective, and well-tolerated in patients with group 1 PAH. Improvement in pulmonary vascular remodelling, right ventricular contractility, and antiproliferative effects have been demonstrated after the use of PDE5 inhibitors. This results in an improvement in functional capacity and reduced clinical events. (5)

Endothelin receptor antagonist: Endothelin -1 has been implicated in the pathogenesis of PAH. ET receptor antagonists (Bosentan, Ambresentan, and Macitentan) have been demonstrated to improve heart failure symptoms, exercise capacity, and clinical worsening in patients with PAH. Although due to superior clinical study design, Macitentan is the only oral, pulmonary vasodilator that has demonstrated mortality benefit in PAH. Elevation in hepatic transaminases, peripheral edema, and anemia are common side effects of these medications. (6)

Prostacyclin analogues: Prostacyclin analogues were one of the first medications which were approved by the US FDA for use in PAH. (7) Unfortunately, they are not yet marketed in India. These can be imported by patients for

their personal use. We currently have 22 patients who are on inhaled iloprost, two patients on subcutaneous treprostinil, and one on oral selexipag. All these patients were started on prostacyclin analogues as add-on therapy on an existing combination of PDE5 inhibitors and endothelin receptor antagonists. Improvement in functional class, decrease in NT pro-BNP, and improvement in echocardiographic parameters have been demonstrated with the use of these medications. (Figure)



Interventional palliative bridge therapy:

Patients who remain in the high-risk category despite maximal medical treatment or deteriorate on the same would be candidates for interventional therapies such as atrial septostomy or a Potts shunt as a bridge to transplant.

Atrial septostomy

Atrial septostomy or the creation of a non-restrictive interatrial communication decompresses the right atrium.
It has been shown to improve cardiac output in patients with severe PAH at the expense of causing desaturation. Beneficial effects of the same have been shown to improve functional class and decrease the incidence of syncope in PAH. Relative contraindications for atrial septostomy include mean right atrial pressure of more than 20 mm Hg, resting arterial oxygen saturation < 90%, and patients with impending death. Interatrial communication is known to decrease in size over time, decompresses the right ventricle only in diastole, and has not been demonstrated to reduce the need for pulmonary vasodilators.

Reverse Potts shunt

Decompressing the right ventricle by creating an unrestricted communication between the left pulmonary artery and the descending aorta has recently emerged as a promising management strategy for patients with PAH.

The advantage of a reverse Potts shunt is that it provides high oxygen saturated blood to the coronary arteries and the central nervous system and only causes the lower body's desaturation. Another benefit arises from its effect on pulmonary hemodynamics by the relief of RV pressure overload in systole and diastole pressure, with a subsequent reduction in PA pressure and shifting of the interventricular septum towards the left ventricle with an improvement in systolic and diastolic ventricular performance In our own experience, a reversed Potts shunt was performed in 20 patients with significant improvement in the functional class, echocardiographic parameters, and reduction in medications. (8)

Lung transplant

Bilateral lung transplant or heart and lung transplant may be an option for some children with PH. However, despite improvement in immunosuppression medications, the overall survival after lung transplant remains limited. Besides, it is limited by its availability and financial constraints in low and medium-income countries such as India. Among all causes for a lung transplant, the patients with PAH as an indication for transplant have the worst survival. Median survival after lung transplantation has been reported to be 4.9 years. (9)

CONCLUSION:

- Pulmonary hypertension is a chronic progressive disease eventually leading to right heart failure
- Suspicion and early diagnosis is important for good long term outcomes
- With current medications survival has improved significantly in patients with PAH
- Upfront combination therapy with PDE5 inhibitors and endothelin receptor antagonist significantly improves morbidity as well as mortality
- Prostacyclin analogues are the need of the hour, currently they are not marketed in India but can be imported, early institution of prostacyclin analogues helps improve functional class, right ventricular function and survival
- Palliative procedures like reversed Potts shunt and atrial septostomy can be used a bridge to transplant
- Lung/ heart and lung transplant needs to be considered in treatment refractory patients.

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LUNG TRANSPLANTATION – AN OVERVIEW

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Dr T. Sunder currently heads and directs the Lung transplant programme at Apollo Hospitals, Chennai. He graduated (1987) from Stanley Medical College, Madras and got his Masters in General Surgery (1992) from his own Alma Mater. After a brief period in the Department of Cardiothoracic surgery at Madras Medical College, Chennai, he underwent further training in England for a period of 11 years. He qualified in Fellowship Examination Cardiothoracic Surgery (2002) and was a Consultant Cardiothoracic Surgeon in England.

He joined Apollo Hospitals, Chennai in 2003 and helped start the department of heart lung transplantation programme with his colleagues.

His special areas of interests include cardiopulmonary transplantation, mechanical circulatory support, pulmonary hromboendarterectomy, thoracic oncology. His academic interests include biostatistics and data analysis.

He serves as an Associate Editor for the Indian Journal of Thoracic and Cardiovascular Surgery, which is the official publication for the Indian Association for Cardiothoracic & Vascular surgeons.

He is also the Section editor for heart and lung transplantation for the Journal of Practice of Cardiovascular Sciences.

He is passionate about photography and enjoys landscape and architectural photography.

This article strives to give a brief overview of all aspects of lung transplantation(LT) – which is now an accepted therapy in appropriate patients with end stage lung disease (ESLD). This article aims to give a bird's eye view of LT to the pulmonologists and the general physicians. This article would also be of interest to the intensivists, anaesthetists and cardiothoracic surgeons interested in cardiopulmonary transplantation. A list of suggested further reading is provided at the end of this manuscript for those interested.

LT is-relatively a very young therapy when compared to renal transplantation and is now only 38 years old. Although first performed in 1963, the first two decades following the first attempt was fraught with complications – predominantly related to ischaemic complications in relation to the bronchial anastomosis and those related to immunosuppression and this procedure did not gain widespread acceptance, given its dismal outcomes. It was in 1983 a successful long term survivor was reported after LT and subsequently there were long term survivors following LT.

1. How does LT differ from other solid organ transplantations?

Except for skin, small bowel and lungs, all transplanted solid organs are "inside" the human body with no direct communication with the environment. The surface area of the lungs is also quire large with increased antigenic load. This in combination with direct environmental exposure makes the practice of lung transplantation more challenging.

2. REFERRAL FOR LT

Ideally early referral is preferred. A simple rule of the thumb is to consider referral to the transplant unit when the patient is being prescribed supplemental oxygen and long term oxygen therapy (LTOT). Prompt referral would allow the time required to meet the transplant unit, clarify doubts, allow adequate time for decision making and organising finances. Referral could be of 2 types.

2.1 Referral for candidacy assessment: This is to check and see if the patient is a transplant candidate. The outcome of this assessment would be one of three possibilities

i) The patient is not yet a candidate for LT – will have to be followed up

ii) The patient is a candidate and may be considered for wait-listing

iii) The patient is not a candidate and cannot be offered LT.

2.2 Referral for wait-listing for LT: In general, when the disease affects the lungs to such an extent that further no treatments help, no other therapeutic options remain – end stage disease ensues. In such instances, organ transplantation is a therapeutic option if,

(i) there are no absolute contra-indications,

(ii) the anticipated survival without a transplant is less than 50% in 2 years

(iii) greater than 80% chance of surviving 5 years from a medical perspective provided the grafted lung function is good

(iv) greater than 80% chance of surviving 90 days after LT.

3. INDICATIONS AND CONTRA-INDICATIONS FOR LT

Unlike other organs – where end stage failure from **any cause** forms an indication for transplantation, – in case of LT there are disease specific objective criteria for LT.

3.1. Disease specific indications for LT [1]:

3.1.1. Indications for LT in ILD:

- Decline in FVC >10% during 6-month follow-up or DLco >15% in 6 months
- Desaturation <88% or distance <250 m on 6-min walk test or >50 m decline in 6-min walk test over 6 months
- Pulmonary hypertension on catheterization or echocardiography with clinical deterioration
- Hospitalization due to respiratory decline, pneumothorax, or acute exacerbation

3.1.2. Indications for LT in COPD:

- Timing of listing (presence of one criterion is sufficient) BODE index ≥7 FEV1
- ≤15%-20% predicted
- Three or more severe exacerbations during the preceding year
- One Severe Exacerbation with Acute Hypercapnic Respiratory Failure
- Moderate-to-severe pulmonary hypertension

3.1.3. Indications for LT in IPAH:

- NYHA functional Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids
- Cardiac index of <2 l/min/m2
- Mean right atrial pressure of >15 mmHg
- 6-min walk test of <350 m
- Development of significant haemoptysis, pericardial effusion, or signs of progressive

3.1.4. Indications for LT in cystic fibrosis/bronchiectasis:

- Chronic respiratory failure
- With hypoxia alone (PaO2 <60 mmHg)
- With hypercapnia (PaCO2 >50 mmHg)
- Long-term non-invasive ventilation therapy
- Pulmonary hypertension
- Frequent hospitalization
- Rapid lung function decline WHO Functional Class IV

3.2. Contraindications for LT:

3.2.1.1. Absolute contraindications

- Malignancy - active current malignancy
- Untreatable atherosclerotic disease
- Acute medical problems e.g., sepsis, myocardial infarction, liver failure
- Chronic virulent uncontrollable infection
- Active tubercular infection
- Significant chest or spinal deformity
- Significant obesity (BMI ≥35 kg/m2)
- Current nonadherence to medication Psychiatric issues No good support system Substance abuse

3.2.1.2. Relative contraindications

- Age >65
- BMI 30-34 kg/m2
- Severe malnutrition
- Severe osteoporosis
- Previous chest surgery
- Mechanical ventilation or ECLS
- Colonization with virulent organisms Hepatitis B/C
- Diabetes with end-organ damage

4. DECISION MAKING PROCESS WHILE CONSIDERING OPTION OF LUNG TRANSPLANTATION:

This is largely based on objective clinical criteria and comprises of 2 main analyses.

4.1. Risk-benefit analysis: Possible risks in the operation versus anticipated benefits from the operation. If this analysis leans towards more of benefit, then LT is considered. If on the other hand, the risks are prohibitive, then LT is not advised.

4.2. Risks with LT versus risks without LT: The anticipated risks with LT are weighed against possible risks if the patient did not have LT. If the risks with LT are significantly less, then LT is advised.

5. RECIPIENT FACTORS:

5.1. Work up Specific for LT are listed below in detail.

- **Respiratory System:** This is fully evaluated to confirm that end stage has reached and that there are no other non-transplant options available. Investigations include PFT, ABG, CT Chest with contrast, 6 MWT, lung biopsy (in appropriate cases), V-Q scan.
- **CVS:** Echocardiogram, ECG, Coronary angiogram in appropriate cases, Right heart catheterisation
- **Oesophageal assessment:** OGD, pH and impedance manometry, fluoroscopy to assess for GERD.
- **ENT:** To look for and assess sinuses – especially in cases of CF. Adequate drainage and toileting prior to LT is needed in these patients.
- **Frailty and muscle weakness:** This needs to be assessed and optimised as much as can be done.

5.2. Workup common to all transplantation:

- Blood group, tissue typing and panel reactive antibodies(PRA)
- Comprehensive Infectious disease screening
- Whole body PET scan to rule out malignancy
- Dexa scan: to rule out osteoporosis and possible fracture risk.
- Endocrine system: Assessment of diabetes (Hba1c), thyroid function, adrenal assessments, vitamin D levels
- Hepatic system: USG abdomen, fibro scan (if needed) , liver function tests
- Renal system: Biochemical urine and blood parameters, USG, CT of the renal system.

5.3. Waitlisting, deterioration, and mortality on WL – MV/ ECMO bridge to LT:

Once evaluated and candidacy for LT has been established, the patient is wait-listed. The patient is in touch with the transplant team. Any deterioration is brought to the notice of the transplant unit. End stage lung disease – often develop increasing oxygen requirements. They require admission with increasing oxygen supplementation – titrating to HFNC, NIV and at time s, if required MV. Often, gas exchange is not improved with MV, in which case ECMO may be required.

While using MV or ECMO as a bridge to LT may be a lifesaving therapy, the outcomes and associated risks of LT done using MV or ECMO as a bridge is inferior to LT performed in patients without MV or ECMO.

Mortality while awaiting organ transplant does occur, especially in cases of lungs where we rely only on deceased donors for organs – unlike the liver and kidneys. More so, using the standard criteria for selection for donor lungs – only 17 to 20 % of lungs offered for donation are useable. By using extended criteria, this may increase up to only 35 % of lungs being usable.

The COVID 19 pandemic has had significant effects on the donation rates and has added to the challenges of LT.

6. DONOR FACTORS:

6.1. DONOR EVALUATION:

6.1.1. Characteristics of an ideal donor:

6.1.2. Standard Criteria [2,3]:

- Age less than 55 years
- ABO compatible
- Size matched
- Ventilated for a short duration
- No history of chest trauma or previous chest surgeries, no aspiration
- Non-smoker or less than 20 pack-years
- Normal CXR and CT scan of lungs (which is now mandatory in view of COVID 19)
- Normal bronchoscopy with no or minimal secretions (negative grams stain)
- paO2 400 on 100 % FiO2.

6.1.3. Extended criteria [4,5]:

- Age more than 55 up to 75 years
- Prolonged ventilation
- paO2 less than 300 on FiO2 of 100%, but above 200
- Chest injury with pneumothorax and ICD
- Consolidation on CT Scan
- Gram stain positive for organisms
- Fever, leucocytosis

6.2. TYPES OF DONOR ORGANS:

- Good organ: who fulfils the standard criteria – usable if the blood group and size matches
- Bad organ: Not usable
- Marginal donor: Who does not fulfil the standard criteria, still not as bad as bad organ

6.3. DECISION MAKING in the choice of donor organs:

The decision to use a good organ or decline a bad organ is easy and straightforward.

The challenge in decision making is only with regards to the marginal organ.

6.3.1. Scenario 1: If the recipient is very stable, then the marginal organ may be declined for him (the ever present dilemma being -one doesn't know when and if a next organ will be available and will this patient be stable until then?)

6.3.2. Scenario 2: If the recipient is critical either on the ventilator or ECMO, then consideration of a marginal organ becomes a little easier. Given that the recipient is on ECMO or ventilator and is critically unwell, a marginal organ may be chosen since the options are limited and one doesn't know if he will survive till the next organ (if and when available) is offered.

6.4. SIZE MATCHING OF DONOR ORGANS:

Size matching is quite important since small lungs in a large cavity (COPD) may leave a residual air space with a propensity of recurrent collections. Similarly, a large organ may be tight fit in a small chest cavity causing difficulty in closure or compressive atelectasis.

While chest volumes and total lung capacity (TLC) the recipient can be calculated beforehand, it cannot be done so for the donor. Hence predicted TLC can be looked form charts derived based on height and sex. The ratio of the predicted TLC of the donor to that of the recipient is calculated and ratio between 0.8 to 1.2 is deemed acceptable.

Large lungs, if have to be used due to the recipient condition, can be handled by non-anatomical stapling of the protruding parts or by an anatomical resection – middle lobectomy on the right and ligulectomy on the left side.

7. LUNG TRANSPLANTATION SURGERY:

7.1. Types of LT:

7.1.1. Single Lung Transplantation (SLT):

As the name implies, only one diseased lung is removed and transplanted. The poorer functioning lung of the two is transplanted. While SLT have short term benefits such as lesser perioperative mortality and morbidity and adequate functional relief, the long-term benefits deteriorate over time when compared to DLT.

It is nowadays done in patients who are elderly above the age of 65, where the lesser perioperative risks are more relevant than the anticipated long term benefits – in view of their advanced age. Furthermore, the age-related physiological reductions in functional reserve among other organ make SLT more attractive than DLT in elderly patients – given the risk-benefit analysis.

SLT is contra-indicated in infectious pathologies such as cystic fibrosis and bronchiectasis. It is also not preferable in IPAH – where there will be a residual high PVR in the remaining native lung with resultant diversion of all the right ventricular outflow -preferentially into the "low-PVR" new lung. This causes flooding and an increased incidence of PGD. However, some units have described SLT in IPAH.

Thus, end stage lung disease due to ILD or COPD in elderly patients form the majority of patients in whom SLT is done.

7.1.2. Double Lung Transplantation (DLT):

DLT is ideally the treatment of end stage lung disease due to all causes. In view of the increased duration of the operation – the perioperative risks are higher than SLT, however this initial bump is more than offset by improved long term outcomes following DLT.

7.1.3. Heart and lung transplantation (HLT):

When there are patients with end stage combined heart and lung failure, HLT is considered. The common scenario includes – Eisenmenger syndrome, ischaemic cardiomyopathy with irreversible pulmonary hypertension, IPAH with severe RV and LV dysfunction, ILD with severe biventricular failure.

There is a higher incidence of HLT India when compared to the West. This is an unique situation which merits explanation. This variation in practice is due to the late presentation of patients in India – where both heart and lung are involved.

Earlier referral for either isolated lung or heart transplantation in the West – has brought down the incidence of HLT.

8. DRUG THERAPY SPECIFIC TO LUNG | TRANSPLANTATION:

8.1. IMMUNOSUPPRESSION:

8.1.1. Induction therapy: Currently we use,

- **IL2 receptor antagonist:** basiliximab 20 mg IV on Day 0 (soon after anaesthesia) and Day 4.
- **Steroid:** Methylprednisolone 500 mg IV after anaesthesia and 250 mg just prior to release of the clamp of each lung.

8.1.2. Maintenance therapy: Triple therapy consisting of

- **Calcineurin inhibitor:** Tacrolimus aiming for levels between 12 to 15
- **Antiproliferative:** Mycophenolate
- **Steroids**: Prednisolone on a rapidly tapering regimen to 0.2 mg/kg body weight

8.1.2. PROPHYLACTIC ANTIMICROBIAL THERAPY:

- **Co-trimoxazole:** as a prophylaxis against pneumocystis and toxoplasma infections
- **Ganciclovir:** as a prophylaxis against viral infections such as Cytomegalovirus
- **Voriconazole:** as a prophylaxis against Fungal infections – such as aspergillus

9. COMPLICATIONS:

9.1. EARLY COMPLICATIONS:

Only those complications SPECIFIC to LT are discussed here. General immediate complications such as bleeding, AKI which occur post-op are not discussed here.

9.1.1. Hyperacute rejection:

This is a very rare occurrence– given that patients are well

worked up pre-operatively. May occur in sensitised individuals despite therapy (discussed later).

9.1.2. Primary Graft Dysfunction (PGD):

PGD refers to a deterioration in lung function – which is not due to rejection, fluid overload or other such causes. It is thought to be a "reimplantation" response" and usually manifests within 72 hours of LT. It may be graded based on PF ratio, CXR findings into Grade 0,1,2 and 3 (Table 1). PGD usually responds to ventilatory adjustments, Nitric oxide therapy and judicious fluid management. In about 20% of cases, Grade 3 PGD which is severe, occurs and may require a brief period of ECMO to meet the oxygen demands of the body until such time the grafted lung recovers.

Table – 1: 2016 International Society of Heart Lung Transplantation definition of Primary Graft Dysfunction [6].

PGD Grade	Pulmonary edema on CXR	PaO2/FiO2 Ratio
Grade 0	No	Any
Grade 1	Yes	>300
Grade 2	Yes	200 – 300
Grade 3	Yes	< 200

PF Ratio: is PaO2 in mm Hg divided by FiO2 used as a decimal number (range from 0.2 to 1.0)

9.1.3. Gastroparesis and Paralytic ileus:

This occurs not uncommonly after LT and most often responds to conservative measures. Vagal neuropraxia which occurs during dissection of posterior hilum, electrolyte imbalance – specially potassium, opioid use are all thought to contribute. A period of rest to bowel with frequent aspirations, IV supplementation and prokinetics often suffice.

9.1.4. Air leaks, pneumothorax, pleural effusions:

Air leaks are often alveolar and often settle spontaneously, provided high ventilatory pressures are not required. Pneumothoraces, when small and well drained by chest tubes usually settle spontaneously. Sometimes, pleural effusions tend to occur after the drains have been removed and may need percutaneous aspirations.

Significant air leak with loss of tidal volumes in ventilator and collapsed lungs mandate an immediate bronchoscopy to assess the bronchial anastomosis. Any obvious bronchial dehiscence, though very rare, in early post-operative period with air leak and lung collapse needs surgical repair. This can be challenging because bronchus is posterior and access may be difficult. This emphasises the need for a check bronchoscopy prior to chest closure to ensure adequate patent and barostatic anastomosis.

9.2. SHORT TERM COMPLICATIONS:

9.2.1. Acute Rejection:

Acute rejection can occur as early 3 to 4 weeks after transplant. They can be either acute cellular rejection (ACR) or antibody mediated rejection (AMR). They manifest by worsening symptoms of breathlessness, sputum, desaturation with increasing oxygen requirements and opacities of CXR. Lab test, bronchoscopy and BAL for Gram stain and culture are needed to rule in or rule out infection. CT Scan of chest and trans bronchial lung biopsy (TBLB) would be needed for diagnosis. Donor specific antibodies (DSA) and C4d staining in the biopsy will help diagnose AMR.

ACR would require pulse steroid therapy – intravenously. AMR, would require plasmapheresis, pulsed steroids, rituximab and IV globulins.

9.2.2. Infections:

Infections are common and prophylactic antimicrobials are given for the first 6 months to a year. In view of the immunosuppression, opportunistic infections (OI) are common and a high degree of suspicion is needed to diagnose these. Close liaison with the infectious disease expert is mandatory in diagnosing and managing these patients.

9.2.3. Airway Complications [7]:

Airway complications ranges from 5 to 20 % of cases and could be ischaemia, stenosis or dehiscence. Most often mucosal ischaemia settle spontaneously. Percutaneous bronchoscopy interventions may be needed for stenosis and dehiscence. The intervention may range from simple balloon dilatation to injection of mitomycin, deployment of stents. A consensus statement by ISHLT

9.2.4. Side Effects of Drugs / Toxicity:

Important side effects of the drugs used after LT include, but not limited to, the following – which may requires dose alteration or temporary cessation of the drug.

- **Tacrolimus:** Nephrotoxicity, neurotoxicity, rise in Hba1c.
- **Mycophenolate:** bone marrow suppression with cytopenias – most commonly leucopenia
- **Steroids:** Fluid and salt retention, weight gain, hypertension, hyperglycaemia, increased susceptibility to infections
- **Ganciclovir:** Bone marrow suppression
- **Voriconazole:** Hepatic dysfunction
- **Septran:** Fixed drug eruption, hyperkalaemia

9.3. LATE COMPLICATIONS:

9.3.1. Chronic Rejection – Chronic Lung Allograft Dysfunction (CLAD):

This manifest as worsening breathlessness and decline in FEV1. About 50% of patients develop CLAD within 5 years of LT. They could be either **obstructive type** (Bronchiolitis Obliterans Syndrome -**BOS** or Neutrophilic Responsive Allograft Dysfunction **NRAD**) or **restrictive type** (Restrictive Allograft Syndrome – **RAS**).

CLAD does not respond to increased immunosuppression. Patients with NRAD respond to low dose Azithromycin. Other options include extracorporeal photopheresis, total lymphoid irradiation or re-transplantation.

9.3.2. New Onset Diabetes after transplantation (NODAT):

This is a common and serious complication which occurs from 2% to 50% of patients following all solid organ transplantation. Steroids, tacrolimus play a role in the development of NODAT. They can cause cardiovascular complications which can result in considerable morbidity and at time mortality. Hence, close watch should be kept and NODAT should be treated aggressively.

9.3.2. Malignancies:

Malignancies are the second most common cause of death after 5 to 10 years post LT. Prolonged immunosuppression can lead to malignancies. LT patients require more immunosuppression and hence have higher degree of malignancy. The most common cancers in LT patients are non-melanomatous skin cancers, followed by lung cancers and post-transplant lymphoproliferative disease (PTLD)[8]

10. SURVIVAL FOLLOWING LT:

10.1. WESTERN LITERATURE:

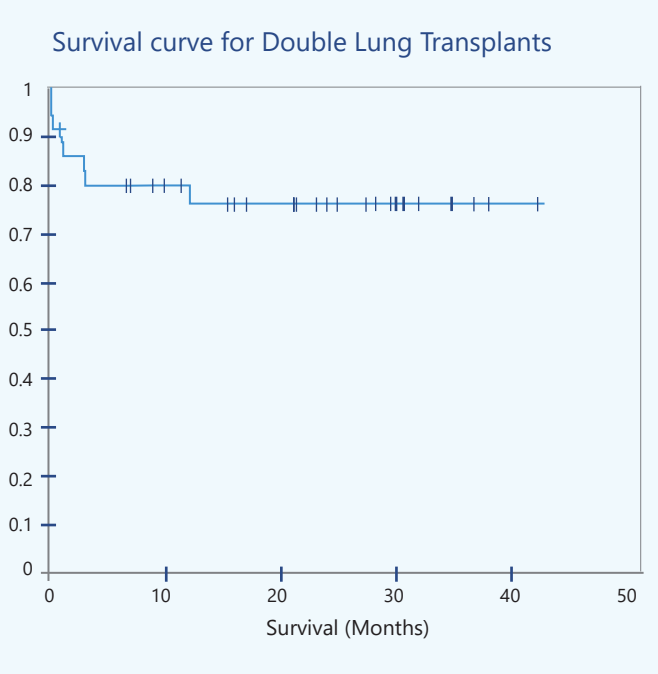
The current 1- and 5-year survival following LT is 85 % and 59% respectively. The median survival following LT differs based on the disease for which LT was done as listed below.

DISEASE	MEDIAN SURVIVAL (years)
Cystic Fibrosis	8.9
COPD with Alpha 1 antitrypsin deficiency	6.7
COPD without Alpha 1 anti-trypsin deficiency	5.6
ILD	4.8

10.2. OUR RESULTS:

Till date, we have performed 58 isolated LTs out of which 51 were DLT and 7 were SLT. In addition, we have performed 30 combined HLTs which also includes 1 patient who underwent combined heart -lung and kidney transplantation. **Our 3-year survival following DLT is 76.2%.**

Analysis of overall survival for Double Lung Transplants has shown a 3-year survival of 76.2 % (Fig 1).



11. SPECIAL SCENARIOS IN LT SPECIFIC TO INDIA :

11.1. Tuberculosis (TB):

India is a TB endemic country. Impact of TB in recipient selection and donor assessment is considerable. In the donor, due to time constraints, TB cannot be categorically excluded. However, in the recipient, patients can be fully evaluated for TB. Those patients with active TB need full treatment prior to listing. Patients with positive Mantoux, but no disease are considered to have latent tuberculous infection (LTBI). They will need prophylactic chemotherapy with INH. Post LT, a high degree of suspicion is required. Proven TB will need cautious chemotherapy looking out for drug interaction.

11.2. Muscle weakness and frailty:

This is a major issue and a lot of patients with ESLD get physically deconditioned and start limiting their physical activities due to hypoxia and eventually become bed bound. This leads to generalised muscle weakness. The worsening lung condition with increasing oxygen requirements makes even mastication a challenge and nutrition suffers. These patients are therefore nutritionally, physically deprived and therefore need nutritional and physical rehabilitation.

LT in a weak and frail patient leads to prolonged ventilation – making them vulnerable to ventilator associated pneumonia (VAP), airways complications if prolonged positive pressure ventilation is required. Such patients often need a slow wean with a tracheostomy.

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A JOURNEY THROUGH HEART TRANSPLANTATION IN INDIA

Dr Jose Chacko Periappuram

Consultant and Head of Department of Cardiothoracic Surgery Lisie Heart Institute, Kochi, Kerala, India. Chairman, Heart Care Foundation

Padmashri Dr Jose Chacko Periappuram FRCS (Glasgow), FRCS (Edinburgh), FRCS (CTh) (UK) performed the first successful Heart Transplant in the state of Kerala, India as well as the first ever successful Heart retransplant in the country. Other achievements include the first Beating heart, Awake Bypass and Total Arterial Revascularization surgeries in the state. He is also the Chairman of " Heart Care Foundation", a charitable trust that financially assists poor heart patients.

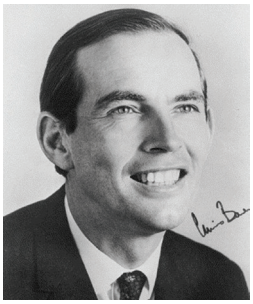
Introduction

Cardiac transplantation is the treatment of choice in patients with end-stage heart disease with significant symptoms and limitation of functional capacity with no medical, interventional, non-transplant surgical and device treatments options left. Also, the recipient should not have any contraindications for transplant and should have reasonable expectancy of life after the transplant to make the procedure worth.

The success story of cardiac transplantation is not won over days or years, but it echoes the progress made in the entire spectrum of medical sciences such as medicine, surgery, immunology pharmacology, infectious diseases, imaging and much more. The initial surgical aspects can be traced to way back in 1890 when Alexis Carrel began experiments with vascular anastomosis followed by animal experiments by Mann and his team at Mayo Clinic, by Demikhov in Russia and by Lower and Shumway's group in the 1930s 50s, and 60s, respectively.

Then came the experience of Xenotransplantation in 1964 of James Hardy who transplanted a chimpanzee's heart to a patient with extensive vascular disease of both legs, who was semi-comatose and in terminal clinical stage. But the animal heart was not able to support the circulation and thus failed. This was followed by the rat race to do the first human cardiac transplantation by many cardiac surgeons including Christiaan Barnard, Richard Lower, Adrian Kantrowitz, and Shumway. The latter three's preparations were delayed due to legal and medical issues related to cardiac death and brain death.

On 3 December 1967, Dr Bernard, performed the world's first successful cardiac transplant on Louis Washkansky at Groote Schuur Hospital Cape Town, South Africa. The heart was harvested from Miss Denise Darvell who met with a road mishap. Adrian Kantrowitz subsequently performed heart transplantation on 6 December 1967, Shumway on 6 January 1968 and Lower in May 1968.



Dr Christiaan Barnard

The initial patient survived for 18 days and died due to a probable rejection. Even though many centres were doing transplants since then, most of the patients succumbed in the postoperative period and 1-year survival was only 11% until late 70s in the very few centres who continued to do the procedure. The surgical aspects associated with the procedure took the focus during the initial days and other clinically important aspects like transplant immunology and infections were not given the deserved importance and this led to increased mortality among those who underwent the procedure leading to the shutdown of many transplant centres across the globe. But, Shumway and his team at Stanford went on with research on many important aspects associated with cardiac transplantation and was instrumental in establishing this fascinating treatment as a medical and surgical specialty.

Indian Scenario

Past

Dr Profulla Kumar Sen became the first surgeon in India to do a heart transplant at KEM Hospital in Mumbai in 1968. He performed the world's 6th heart transplant. Unfortunately, the right heart ballooned within 15 minutes of coming off bypass and the patient died within 3 hours. He attempted another transplant months later but that patient also died within 14 hours with severe pulmonary hypertension. But his work was hampered in those early days of cardiac transplantation by poor results and the absence of laws on brain stem death. There were no further attempts for a long time due to the absence of this law of brain death.3

Dr Profulla Kumar Sen

On 3 August 1994, Dr P Venugopal led a team of doctors in AIIMS in carrying out India's first successful heart transplant. Devi Ram, a 40-year-old heavy industry worker suffering from cardiomyopathy, had been admitted in AIIMS for three months. A 35-year-old lady who had suffered brain haemorrhage was brought into the hospital and her family agreed for organ donation. Devi Ram saw this this is the only way and agreed to heart transplant. "All the conditions were suitable and compatible and so it was decided that the procedure will be carried out...." as Dr. Venugopal recollects.

Dr P Venugopal

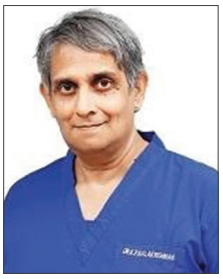
The Transplantation of Human Organ Act (THOA) of India though was passed by the Indian Parliament at that time, it was not signed by the President of India.

Dr.K.M.Cherian is credited with the first heart transplantation after the THOA was passed in 1994 by Indian Parliament. A 36-year-old Hemalatha Soundarrajan was knocked down while crossing the road. She was declared brain dead at his hospital. Her husband was willing to donate her heart. Cherian then contacted many hospitals in Chennai, Cochin, Trivandrum, and even Hyderabad looking for a suitable recipient. Finally, he found the recipient in Chennai General Hospital: Maimoon Beevi, 38 years with dilated cardiomyopathy and had been waiting for a donor heart.

Dr K.M.Cherian

He is also credited with the many firsts including first bilateral lung transplantation, first paediatric heart transplantation, and first heart lung transplantation in India, and so on.

Dr K. R. Balakrishnan has performed many breakthrough surgeries in the field of cardiac transplant like India's first new generation left ventricular assist device (LVAD) in 2012 and the Heart Ware ventricular assist device (HVAD) pump implant in 2013. He has also played an instrumental role in establishing India's First Comprehensive Centre for Heart Failure Management. He is credited with the highest number of heart transplants in India and also has initiated many transplant programs across the country. He may have to be considered as the father of Indian heart transplant program in the 20th century.



Dr K. R. Balakrishnan

The first successful heart re-transplant in India was performed by Dr. Jose Chacko Periappuram in Kerala in 2014 on a patient who developed refractory right ventricular failure 8 months after the initial transplant. The brave man who underwent India's first heart re-transplant is Mr Girish who is still alive and kicking 8 years after the second transplant.

During these COVID times a special mention needs to be made on the efforts of Dr Sandeep Attawar and his team for the impetus given by him in the field of Lung Transplantation.

Stalwarts in the field of heart failure cardiology over the years have been instrumental in growth of the heart transplant programme. Some of them are Dr K K Talwar, Dr R Ravi Kumar, Dr Sandeep Seth, Dr Jo Joseph and many others who are spearheading this niche speciality.

Present

Even though India contributes to around 18% of the total population of the world, the donation rates in India are abysmally low compared to the rest of the world. In Spain, there are around 32 donations per million; in the USA,

25 donations per million; and in the UK, 17 donations per million population; but in India, there are only 0.5 donations per million.

This is obviously lead to a small number of transplantations taking place across the country even though the numbers are increasing slowly and steadily. There were around 350 cardiac transplants until November 2016, but the numbers increased by 239 in 2017, and 285 in 2018. A total of 250 heart transplantations were done in 2019 making 1,140 total heart transplants so far.

Cardiac transplant centres are spread across the entire length and breadth of the country. The southern state of Tamil Nadu leads the list with the greatest number of donations, transplant centres, and transplants. The state accounts for

more than 50% of the total transplants done in the entire country. This is followed by the states of Maharashtra, Karnataka, Andhra Pradesh, Kerala and Delhi.

The distribution of heart transplant in India is as follows in the order of time.

Delhi has performed so far 126 heart transplants, the first one conducted in 1994 by Dr Venugopal. Tamil Nadu has performed so far 590 heart transplants, with the first one in 1996 by Dr KM Cherian. Karnataka has done 118 hearts so far, the first one conducted by Dr Devi Shetty in 1998. Meantime, Kerala has done 48 hearts so far with Dr Jose Chacko Periappuram performing the first one in 2003.

Andhra Pradesh/Telangana 82 hearts (Dr Gokhale 2004), Rajasthan 4 (Dr Chishti 2015), Maharashtra 152 (P K Sen1968), Gujrat 10 (Dhiren Shah 2016), Punjab 5 (Dr Shyam Thingnam 2017), Madhya Pradesh 2 (Dr Sandeep Srivasthava 2017), West Bengal 12 (Mandana 2018). These figures may not be complete and are based on what is available to the authors at the time of writing this article.

The awareness about brain death, organ donation, and organ transplantation are increasing across the country **(Fig.1)**.

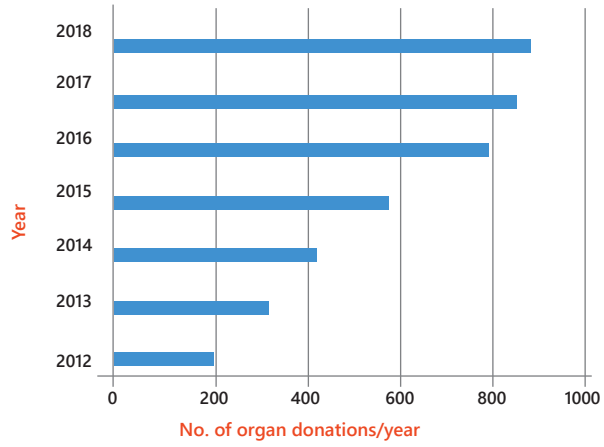


Fig. 1. Deceased multiorgan donations in India from 2012-2018.

The number or multiorgan donations are increasing in India and this has led to a surge or organ transplants for end-stage disease including hearts across the country. But since most of the people do not have access to this life-saving treatment because of multitude or reasons, the underutilization of the donated organs is also a problem in the country **(Fig.2)**.

There are many state level, regional level, and national level coordinating agencies in India helping in procuring, coordinating, and sharing organs across the country. The NOTTO (National Organ and Tissue Transplant Organization) functions as an advisory role for coordinating activities across the national. There are many state level coordinating agencies such as TNOS in Tamil Nadu; JEEVANDAN in Andhra Pradesh and Telangana; ORBO in Delhi; Mohan Foundation, ZCCK in

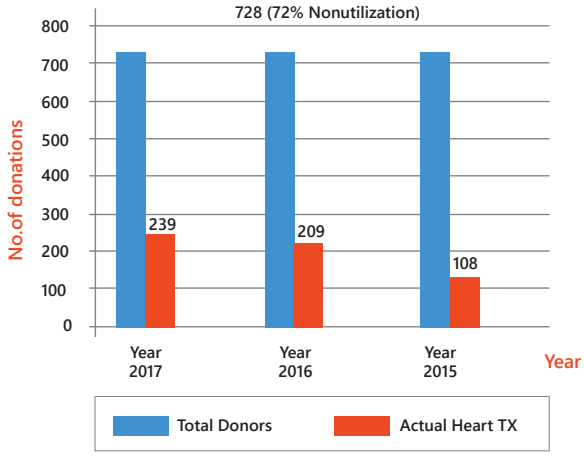


Fig. 2. Donor organ underutilization in India 2015-2017

Karnataka; ZICC in Maharashtra, and KNOS in Kerala. These sorts of systems needed to be created in all states and all the local and regional systems have to be coordinated at the central level for better and optimum donor utilization.

Future

At present, majority of the states do not have a steady recipient list because of the referral bias. Majority of the patients with heart failure (HF) are managed by physicians and cardiologists. So, an important problem is the late referral. Lots of patients are referred late in the clinical course after burning out all available options and after recurrent hospitalizations with HF and this leads to the development of significant pulmonary hypertension making immediate and late clinical outcomes less than optimal. So, physicians and cardiologists need to be educated and motivated for timely referral of these patients for optimum outcomes.

The country needs to augment its donor pool. There should be a national database of the committed donors. The government should take initiatives to link Donor card with Aadhar card for easy retrieval of information. The various stakeholders involved in the process should work faster with efficient interstate allocation, early alert (minimum 12 hours before the planned harvest time), and a national network for air lifting the organs so that organ transportation facilities can be strengthened.

All aspects of donor management have to be streamlined across the country to augment quality of donor management. There is a need for uniform donor management protocol across the country for better optimization of the function of the donated precious organs. Strict protocols should be put in place for better utilization of marginal donors. Transformational opportunities to increase the donation after

cardiac death (DCD) and utilisation of Hepatitis C positive donors would increase the donor pool.

Transplant program in India lack the pyramidal system controlling, and supervising system. Without that, whatever we do, is not going to sustain in progress.

We need to evaluate the National resources, funding and available expertise for organ donation and transplantation. The functioning of regulatory and corporate bodies needs to be evaluated with a view to efficient execution of responsibilities vested on them. Various structures including federal, state, non-governmental organisations and public and private institutions need to co-ordinate the acts. We need to address the issues related to unfair distribution, organ wastage, gaming and poor practices.

Societies and associations need to pull up their socks to create comprehensive registry as mechanisms to audit and police the source and veracity of the data. Meaningful research would be possible only if a comprehensive registry is available.

Collaboration and research at multicentric levels would add good clinical and practical training and research leading to better outcomes. This would help us to succeed training the young surgeons in the field of transplantation. Specialty training and fellowships need to be organised in collaboration of institutions, societies and public and private institutions.

Future proofing of talent is very important in continuity of progress. We need to make a projection of Thoracic organ transplant expertise over the next decade. Knowing the amount of expertise needed to execute the projected work is also to be calculated. We need to prevent the drain of medical manpower as North America and Europe are vast fertile ground for our expertise.

CONCLUSION

Heart transplantation is a well-established modality of treatment for end stage heart disease where no medical, surgical and device therapy options are available and in the absence of contraindications. The therapy is backed by robust experimental and clinical evidences in various aspects like surgical techniques, immunosuppressive therapy, rejection surveillance, short and long term surveillance. Even though India embraced this therapy in the very beginning, the widespread adoption definitely lagged behind owning to a multitude of factors starting from the legal to the financial constraints. Off late the country is making steadfast progress in this amazing field of science and short term and long-term results available as of now appear promising and the scientific community is committed to provide the best of this therapy to the need ones in the country.

There is an urgent need for Co-ordinated work to save organs and thereby preserving lives. Future is good for India provided we move in the right direction.

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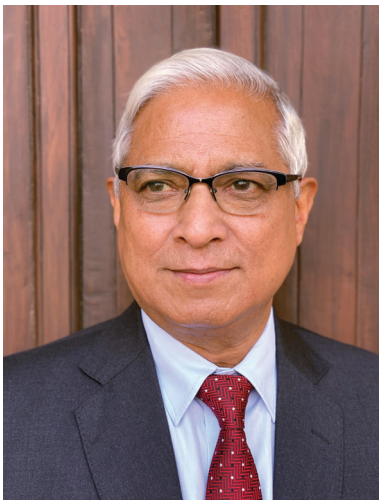
SGLT2 INHIBITORS IN CARDIOVASCULAR DISEASES



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Clinical Trials:
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Recent years have witnessed exciting new treatment modalities in the management of patients with HF. After ARBs, there was a long period of hiatus in the pharmacological management of heart failure leading many cardiologists to wonder if we had reached the end of neurohormonal modulation. All this changed with the publication of the results of PARADIGM1, which demonstrated remarkable benefits in HFrEF when given over and above the currently available therapies. There has been a major shift in therapies; while till now all the benefits were seen in therapies which modulated neurohormonal systems, newer therapies have emerged dealing with completely different metabolic pathways. Among the new entrants, undoubtedly SGLT-2 I have come to occupy the number one position. Serendipity is to be credited for many advances in medicine and the story of SGLT-2 I is no different, as the results of the first CV outcomes trial namely EMPA-Reg2 were largely unexpected. After some of the anti-diabetic drugs demonstrated CV harm, the subsequent trials were required to demonstrate CV safety. However, it came as a pleasant surprise for the researchers, when EMPA-Reg trial demonstrated a remarkable benefit in pre- specified end points driven mainly by the reduction in HF hospitalizations in patients with Diabetes and established cardiovascular disease and started a lot of research with different drugs in this class.

SGLT2 Inhibitors had been in use as anti-diabetic drugs for some time. They primarily act by inhibiting the SGLT-2, which is present in the proximal convoluted tubules of the kidney and is responsible for re-absorption of glucose and sodium. This results in loss of glucose and sodium in urine accompanied by osmotic diuresis. There is also an accompanying weight loss of 3-4 Kg and a drop of 3-4 mm Hg.in most people (Fig.1).

Due to their unique mechanism of action, which is preventing the re-absorption of only filtered glucose, they do not result in hypoglycemia even in non-diabetic patients, unless being administrated with some of the other anti-diabetic drugs that are known to cause hypoglycemia. Though these mechanisms were initially thought be responsible for their benefits, it is now evident that these are not the primary reasons of their benefits.

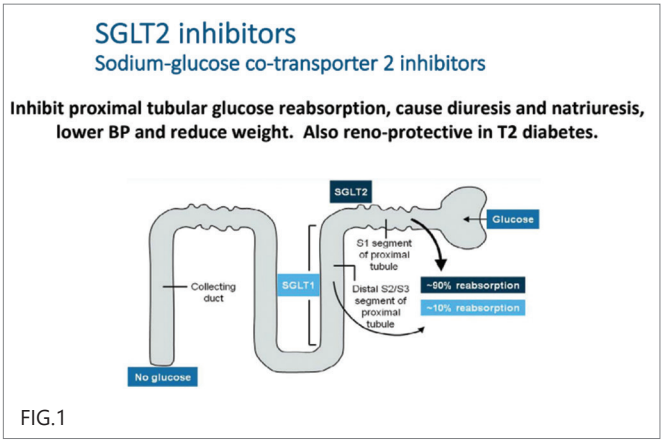

FIG.1

Major SGLT2 trials in prevention of cardiovascular events and what have they shown:

Several trials were launched after EMPA-Reg to explore the role of these drugs in CV and renal outcomes in diabetic patients, but with different characteristics. They explored the role of SGLT2 inhibitors in reduction of cardiovascular

endpoints in patients with Diabetes, either with established heart disease or the presence of multiple CV risk factors. This is important as several patients with CVD have renal dysfunction which plays a critical role in their disease progression and prognosis. These trials demonstrated a remarkable homogeneity in their results which reinforces the role of this group of drugs in the management of diabetic patients with established CAD or the presence of multiple risk factors. At present, we have data for cardiovascular outcomes for 4 major drugs in this class, namely, Empagliflozin, Dapagliflozin, Canagliflozin and Ertugliflozin, of which the first 3 are available in India. There is another drug in this class, Remogliflozin, which though available in India, does not have robust data on CV outcomes, but is much cheaper.

A) Empagliflozin:

Empa-Reg outcomes trial [2]

This was the first trial to show a significant benefit in CV outcomes with SGLT2 inhibitors. The goal of the trial was to assess the cardiovascular (CV) safety of empagliflozin, a sodium–glucose cotransporter 2 (SGLT-2) inhibitor, in patients with type 2 diabetes mellitus (DM2) and established CV disease

The results were: (Fig.2)

- All-cause mortality reduced (3.8% vs. 5.1%), p < 0.01
- Congestive heart failure (CHF) hospitalization reduced similarly in patients with or without CHF at baseline (2.7% vs. 4.1%, p = 0.002)
- CHF hospitalization or CV death reduced (: 5.7% vs. 8.5%), p < 0.001

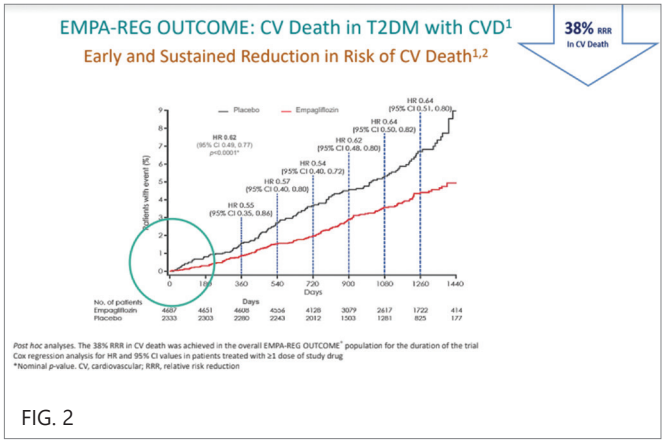

FIG. 2

This trial showed the superiority of empagliflozin in reducing CV events, mortality and HHF in patients with DM2 and established CVD and also a significant benefit on renal outcomes both in patients with and without HF at baseline., it demonstrated a salutary effect on renal outcomes too, including the need to initiate renal replacement therapy.

B) Dapagliflozin:

1-DECLARE TIMI -58 [3]

Declare TIMI-58 enrolled a different population of patients with Diabetes and either established CVD (40.6%) or multiple risk factors for ASCVD (59.4%).The majority of patients did not have a history of HF. The primary endpoint of MACE and mortality was similar in both groups but there was a significantly lower rate of CV death or HHF along with reduction in adverse renal events in those with and without ASCVD, HF or CKD at baseline. (Fig.3, 4)

Primary endpoints

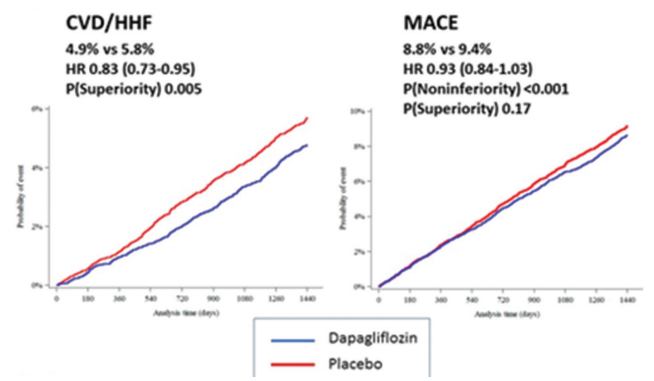

FIG. 3

Secondary endpoints

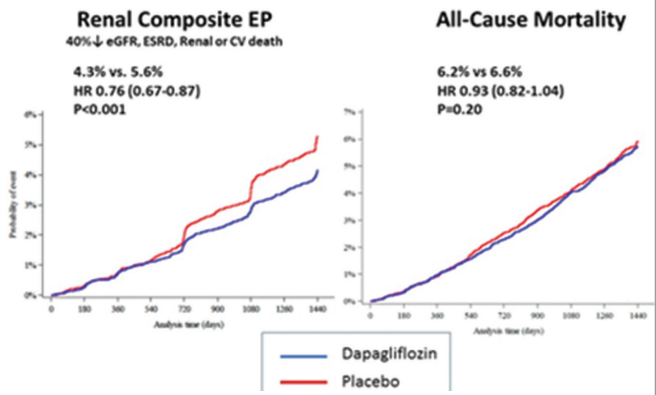

FIG. 4

C) Canagliflozin: (Fig 5)

1-CANVAS [4]

The CANVAS Program combined data from two trials comparing Canagliflozin and placebo involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal. This risk was

never replicated in any other trial, raising the question whether it was a chance occurrence.

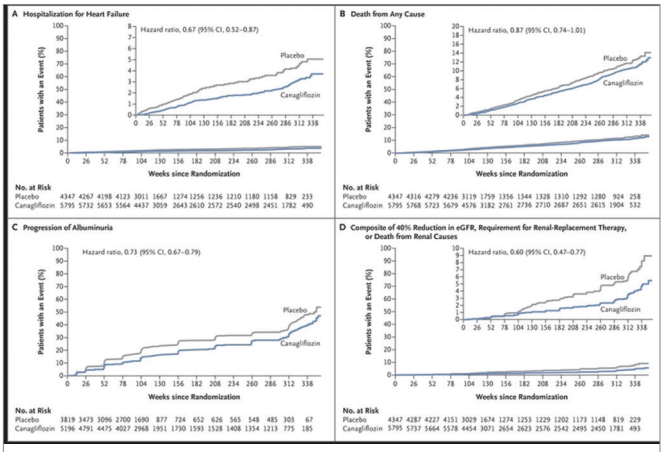

FIG. 5

D) Ertugliflozin:

VERTIS CV Trial [5]

This trial investigated the role of Ertugliflozin in patients with T2DM and established ASCVD involving the coronary, cerebrovascular, and/or peripheral arterial systems (Fig 6,7). The results were somewhat different from the other SGLT-2 inhibitor trials. Ertugliflozin added to guideline-directed secondary prevention therapies was non-inferior versus placebo for MACE. The key secondary composite endpoint of CV death or HHF did not differ between groups, nor did CV death, but there was a 30% lower risk of HHF. The overall pattern of the effects on endpoints of HHF and renal outcomes was in line with those seen in other large trials of SGLT2 inhibitors. The effects of ertugliflozin on the primary end points were less than those demonstrated in other major trials with Dapagliflozin and Empagliflozin. It is unclear if this represents a difference in patient populations between the trials, or a true biological difference in the drug efficacy. (Fig. 6,7)

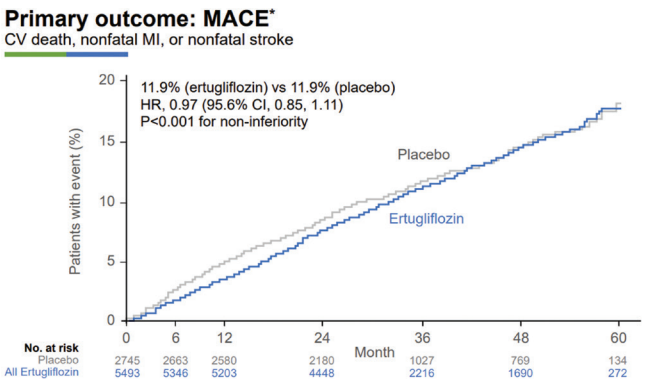

FIG. 6

HHF

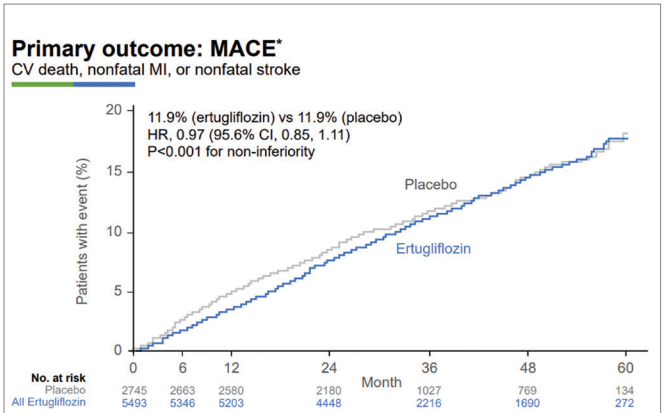

FIG. 7

E) Remogliflozin:

This is another drug in the same class. A few studies are available which demonstrate its efficacy in reduction of blood glucose comparable to the other SGLT2 inhibitors. However, no major CV outcome trials have been performed and therefore its effect on reduction of CV enter is not known. It is however much cheaper than the other SGLT2 inhibitors.

A brief summary of the effects of major CV outcome trials in prevention of CV outcomes is given below. Fig 8

As all these trials had different populations, one should not

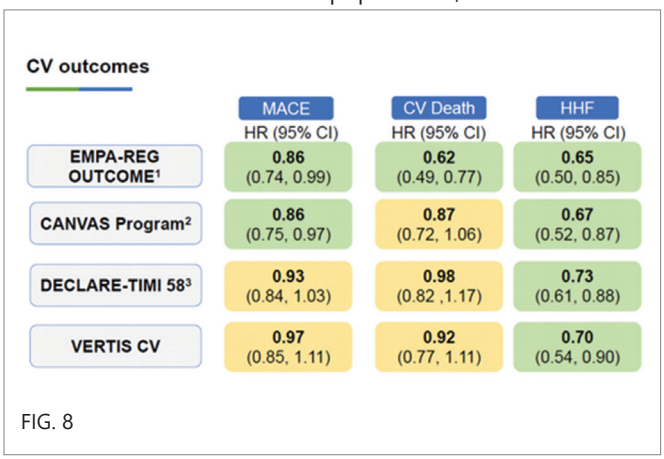

FIG. 8

draw any comparative conclusions about their relative efficacy. It appears, however, that their primary benefit is a consistent reduction in HHF in patients with multiple risk factors or established cardiovascular disease. This benefit is seen in both diabetics and non-diabetics (Fig. 9), regardless of the baseline treatment with other disease modifying agents and other co-morbid conditions. Variability in mortality could be explained by inclusion of different patient populations and trial design.

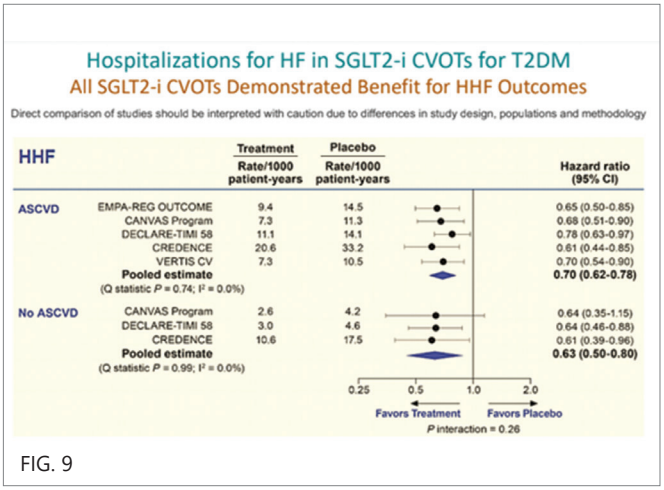

FIG. 9

SGLT2 Inhibitors as a treatment for patients with established HF :

Having conclusively established the role of SGLT2 Inhibitors in reduction in HHF, mortality and in renal endpoints based on several trials, researchers moved on to investigate whether these agents could actually be used to treat patients with established HF, both HFrEF and HFpEF. As these drugs do not cause hypoglycemia, the trials also explored their benefit in non-diabetic patients. The concern about higher incidence of DKA was still present and was marked as an area of special interest in the subsequent trials. Two major trials for HFrEF that reported in quick succession are DAPA-HF and EMPEROR-Reduced. Their results are briefly summarized below:

1- DAPA-HF [6]

This trial conclusively proved that Dapagliflozin used on top of an excellent background standard of care therapy was safe and resulted in a statistically significant and clinically meaningful reduction in HF events and CV mortality. The drug was equally effective in patients with and without diabetes with no significant hypoglycemia in either group. Only a small number of patients were on ARNI as it had been launched shortly before the trial got under way, and the benefits observed in these patients were similar. There was a consistent benefit irrespective of baseline NT-ProBNP levels, SBP, BMI, GFR and background therapies. (Fig 10,11)

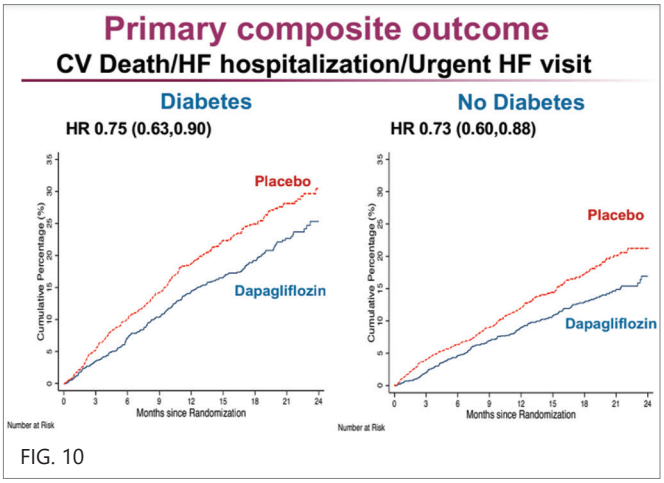

FIG. 10

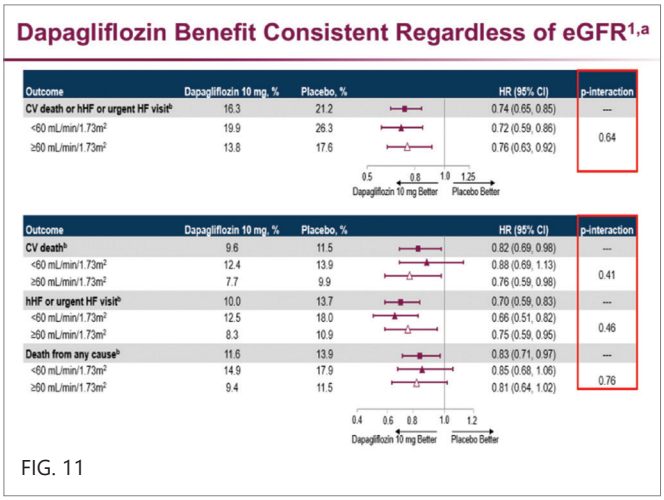

FIG. 11

2- EMPEROR-Reduced [7]

The results of this trial were presented in August 2020. This trial enrolled 3730 patients with HF and reduced ejection fraction and studied the effects of adding Empagliflozin to the standard of care in CV outcomes. Half the patients were non diabetic and on an average had more severe heart failure than those in DAPA-HF Trial. Mean ejection fraction was 27%, mean NT Pro BNP was 1907 and over 70% patients had LVEF 30% or less. There was an impressive reduction in HHF, both first and repeat, and the decline in renal functions was significantly less in the empagliflozin group. The benefits were seen equally in both diabetics and non-diabetics. The mortality reduction, however, was modest at 8%. (Fig 12,13,14)

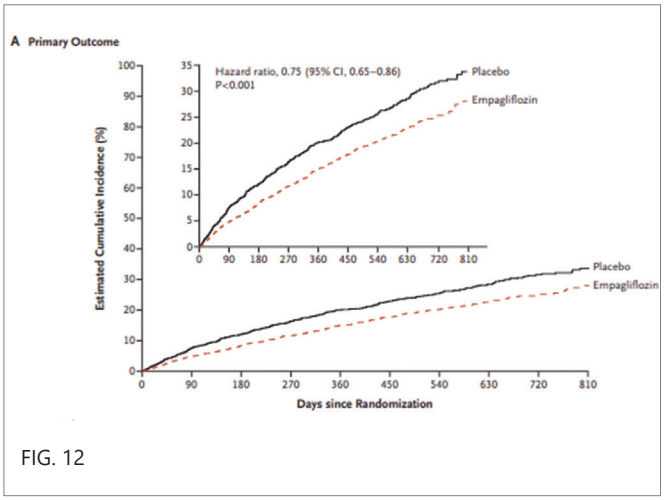

FIG. 12

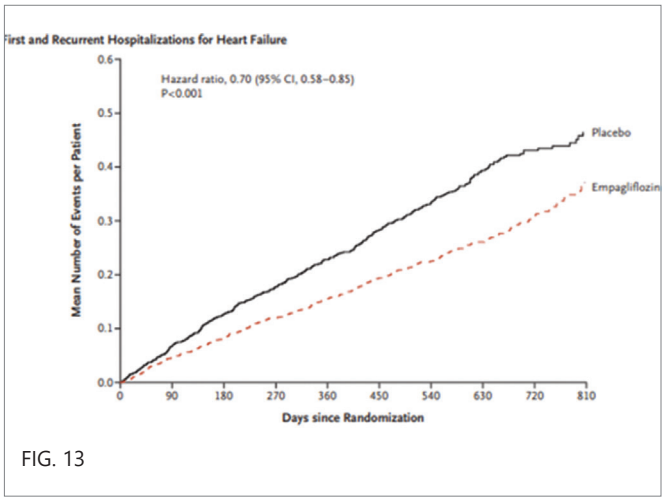

FIG. 13

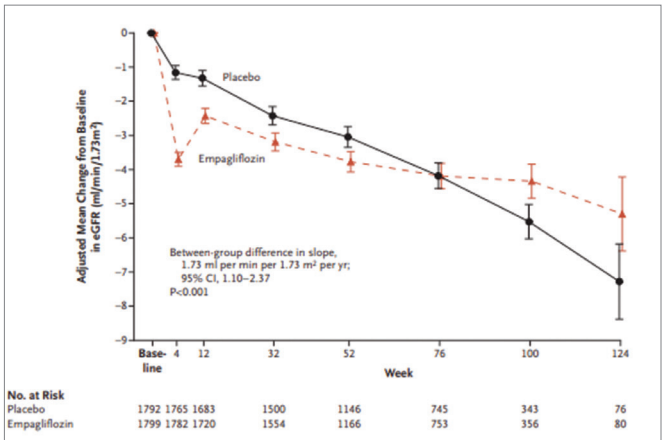

FIG. 14

Sotagliflozin:

This drug is different as it is an SGLT-1 and 2 inhibitor. SGLT-1 is present in the gut and its inhibition prevents absorption of glucose from the gut. Its side effects include GI disturbances. Two trials were done with this drug: SOLOIST8 and SCORED9. SOLOIST enrolled patients with hospitalization due to worsening HF and SCORED looked at endpoints in diabetic kidney disease. Both trials were stopped during COVID due to loss of funding, but they yielded important information.

SOLOIST:

This is the only trial so far with acute heart failure. Its results were in line with the other SGLT2-I trials. The drug was started before discharge from the hospital or soon after.

It showed a very significant 33% reduction in the primary end point of death, HHF and urgent HF visits. Fig.15

SOLOIST Result.

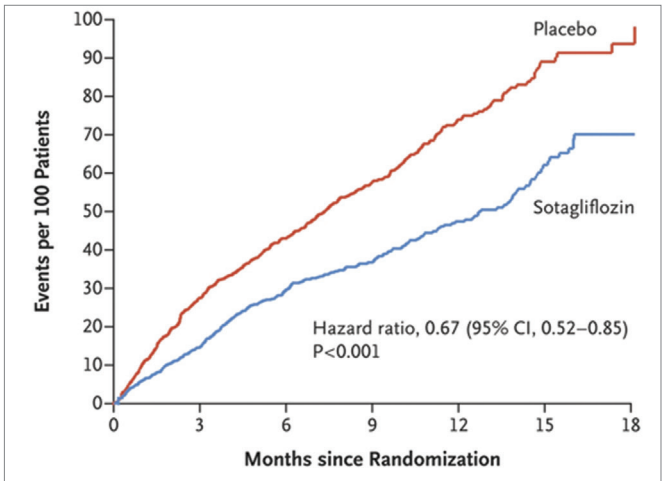

FIG. 15

SCORED:

In this trial, 10,584 patients with type 2 diabetes and CKD were randomized to receive either sotagliflozin or placebo.

Results showed the cohort of patients receiving sotagliflozin had a 26% reduction in the number of cardiovascular deaths, hospitalizations for HF or urgent visits for HF. Additionally, a 23% decrease in myocardial infarction and stroke was observed, which was likely to be due to the SGLT1 effect. (Fig.16)

SCORED Results.

EMPEROR-Preserved [10]

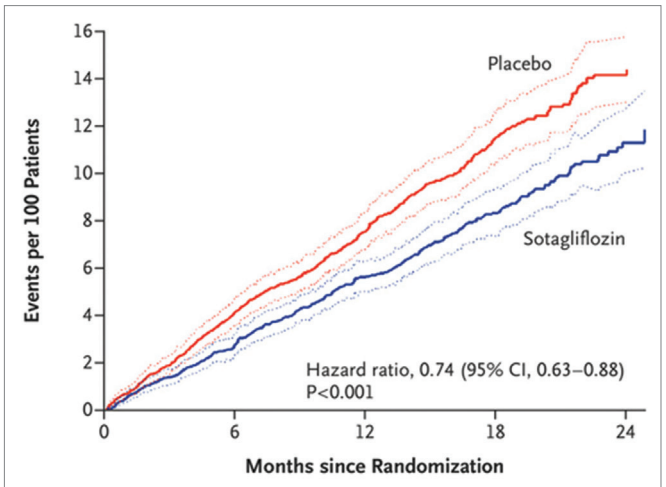

FIG. 16

While there are a large number of effective disease modifying therapies available for HFrEF, there was no proven therapy for HFpEF except diuretics to reduce congestion. EMPEROR-Preserved was published in 2021 and established the role of Empagliflozin in significantly reducing the combined end point of HHF and CV mortality, driven mainly by a reduction

in HHF. This benefit was consistently seen across all pre-specified subgroups, both in patients with and without diabetes and across a broad range of renal functions. There was no effect on mortality and in renal end points, possibly due to the relatively shorter duration of the trial. (Fig.17).

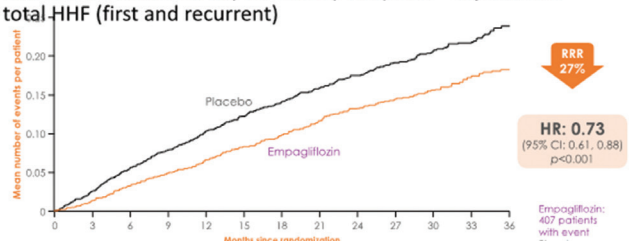

FIG. 17

RENAL OUTCOMES:

A significant number of patients with heart failure have renal dysfunction, either due to HF or due to concomitant renal disease. It worsens the prognosis and also creates difficulties in utilizing some of the disease modifying drugs, specially neurohormonal modulators. Exploratory endpoints from the EMPA-REG OUTCOME and CANVAS trial showed decreased albuminuria, while the CANVAS and DECLARE TIMI-58 trial also showed better renal outcomes of reduction in worsening of estimated glomerular filtration rate (eGFR), initiation of renal-replacement therapy, and CKD related death (7-9). However, these trials were not designed to address the possible reno-protective effects of the SGLT2 inhibitors because the participants enrolled were at a relatively low risk for progression to kidney failure.

CREDENCE Trial: [11]

The goal of the trial was to assess the effect of canagliflozin on renal outcomes among patients with type 2 diabetes mellitus (DM2) and chronic kidney disease (CKD). Patients with Type-2 DM, albuminuria and GFR between 30-60 and on stable doses of ACEI/ARB were enrolled. The trial was stopped early due to overwhelming benefit. Canagliflozin reduced the risk of the primary outcome of ESKD, doubling of serum creatinine, or renal or CV death by 30% ,P = 0.00001 (Fig18)

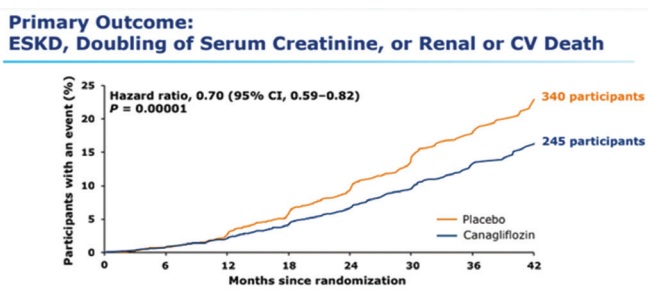

FIG. 18

DAPA-CKD Trial [12]

DAPA CKD Trial was presented in 2020. 4304 patients were enrolled with eGFR between ≥ 25 and ≤ 75 mL/min/1.73 m2; urinary albumin to creatinine ratio between ≥ 200 mg/g and ≤ 5000 mg/g; and were on a stable, maximum tolerated dose of ACE Inhibitor or ARB for at least 4 weeks. 2906 patients had Type II Diabetes.

Dapagliflozin was safe and well tolerated. Neither diabetic ketoacidosis nor severe hypoglycemia were observed in patients with Type II Diabetes.

DAPA-CKD showed that dapagliflozin significantly reduced the risk of worsening of kidney function or death from cardiovascular or kidney disease in patients with chronic kidney disease with and without Type II Diabetes (p =0.000000028). The results highlight the medicine's potential to benefit patients with chronic heart disease who are in need of improved treatment options.(Fig 19, 20).

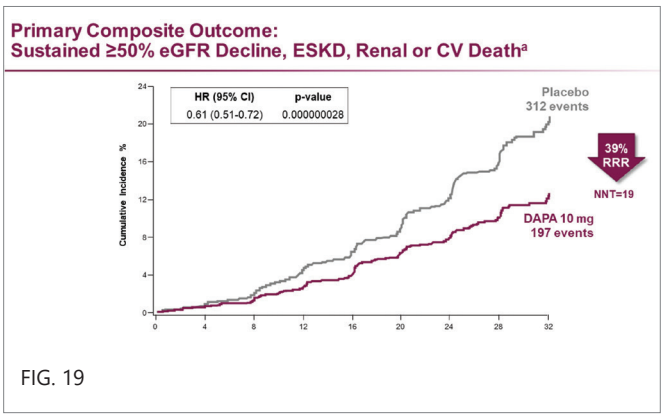

FIG. 19

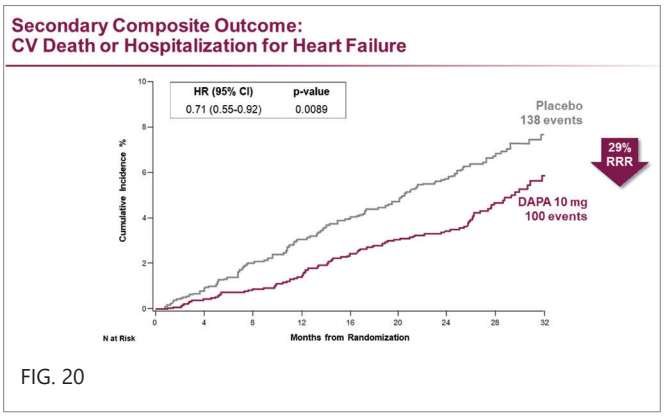

FIG. 20

Mechanism of action

SGLT-2 I have several well documented actions13 Suggested mechanisms include natriuresis and osmotic diuresis; reductions in inflammation, oxidative stress, and arterial stiffness; reductions in blood pressure and body weight; and possible reno protective effects. These effects could produce cardiovascular benefits through a range of cardiac effects, including reduction in left ventricular load, attenuation of cardiac fibrosis and inflammation, and improved myocardial

energy production. Other possible mechanisms include inhibition of sodium-hydrogen exchange, increases in erythropoietin levels, and reduction in myocardial ischemia or reperfusion injury. It is likely that a range of mechanisms underlie the observed cardiovascular benefits of SGLT2 inhibitors; further elucidation of these mechanisms will be answered by ongoing research. (Fig.21)

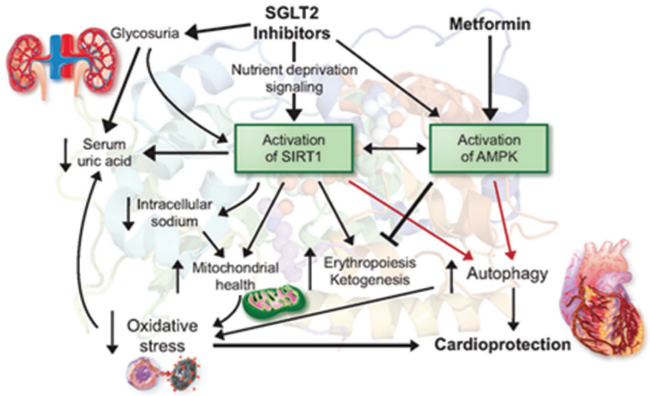

FIG. 21

Proposed framework to explain the mechanism of the cardioprotective effect of SGLT2 inhibitors.

CONCLUSIONS:

With such strong data from large well designed clinical trial appearing in rapid succession, it is safe to say that they have firmly established their place in prevention of HF and improving CV outcomes in carefully selected diabetic patients and have received strong recommendation in various guidelines. Additionally, as a class, SGLT2 inhibitors should be strongly considered in the majority of patients with acute decompensated HF and HF with either reduced or preserved ejection fraction; and with CKD across the full range of proteinuria.

Abbreviations :

ARB :	Angiotensin II receptor blockers
CV :	Cardiovascular
HFrEF :	Heart Failure with reduced ejection fraction
SGLT2 :	Sodium-glucose co-transporator-2
Empa-Reg :	Empagliglozin Cardiovascular Outcome Event
CVD :	Cardiovascular disease
ASCVD :	Atherosclerotic cardiovascular disease
CKD :	Chronic Kidney Disease
CV :	Cardiovascular
T2DM :	Type2 Diabetes Mellitus
EMPA-REG :	Empagliglozin Cardiovascular Outcome Event
CANVAS :	Canagliflozin Cardiovascular Assessment Study
HF :	Heart Failure
MACE :	Major adverse cardiovascular events
NTProBNP :	N-terminal (NT) pro-Brain Natriuretic Peptide
SBP :	Spontaneous bacterial peritonitis
BMI :	Body mass index
eGFR :	Estimated glomerular filtration rate
MI :	Myocardial Infarction
LVEF :	Left ventricular ejection fraction
COVID :	Coronavirus disease
HFpEF :	Heart Failure with Preserved Ejection Fraction

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CMR IN HEART FAILURE

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Cardiac Magnetic Resonance (CMR) imaging is a powerful and versatile imaging modality that provides additional information in patients with suspected or known cases of heart failure (HF) [1]. CMR is the gold standard in ventricular function [2]. Moreover it provides excellent information regarding segment wise myocardial wall motion, myocardial morphology and characterisation, stress myocardial perfusion and viability [3-5]. Newer CMR techniques like T1 mapping and T2* mapping provide additional inputs into the diagnosis and prognosis of various causes of heart failure like amyloidosis [6,7]. Abbasi et al [8] assessed impact of CMR in heart failure patients in term of management and clinical decision making. They found CMR has significant additive impact on management, clinical decision making and diagnosis in 65% patients with heart failure. This impact was observed despite universal use of previous echocardiography in heart failure patients.

A] Assessment of function:

Accurate quantification of right and left ventricular volumes and function is mainstay in management and prognosis of patients with heart failure. CMR is gold standard in assessment of ventricular function [2]. Gradient echo images are used to assess wall motion and ventricular function. Breath hold, retrospective VCG (vectorcardiogram) gated, cine balanced Steady State Free Precession (bSSFP) images are used for this purpose in multi-planar views with standard views being short axis, 2 chamber (2ch) and 4 chamber (4ch) views. Continuous cine stacks in short axis covering entire ventricles (from base to apex) with no slice gap are preferred for ventricular functional assessment. CMR offers excellent myocardium to blood contrast which enables to observe wall motion in great detail. Multi-planar imaging technique involved in CMR is without any geometrical assumptions, hence functional assessment is more accurate even in abnormally shaped LV which occurs in heart failure [1].

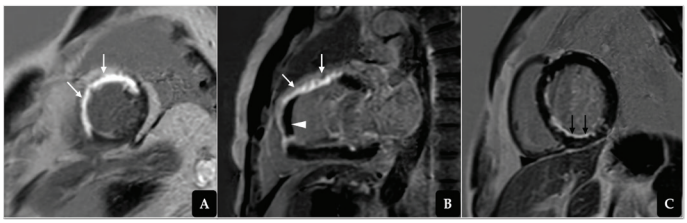
Endocardial and epicardial borders are traced and ventricular functional parameters including end diastolic volume (EDV), end systolic volume (ESV), ejection fraction (EF) and LV myocardial mass are calculated. CMR shows excellent reproducibility in quantification of these functional parameters which is helpful in serial assessment and therapeutic monitoring [9]. With newer techniques, good quality free-breathing cine images are possible even in patients with poor breath hold [10]. In patients with arrhythmia, diagnostic cine images can be obtained using prospective gating, arrhythmia rejection protocols or real time imaging [11].

B] Role of CMR in ischemic heart disease:

Apart from accurate estimation of LV and RV function which is crucial in management of ischemic heart disease (IHD), CMR plays a key role due to its excellent myocardial characterisation. In CMR, Late gadolinium enhancement (LGE) sequences have higher sensitivity in detection of infarction, extent of infarction and assessment of scar burden [12-14]. Predominant role of CMR in IHD is to assess viability and stress inducible ischemia.

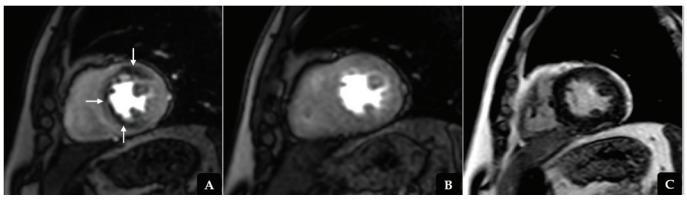
Viability assessment is performed by evaluating regional

wall motion abnormalities and extent of myocardial infarction. Subendocardial layer is the first affected part of myocardium in infarction, where scar formation begins. Depending on severity and duration of impaired blood flow, the scar extends transmurally towards epicardium. Thickness of myocardium infarcted is inversely proportional to degree of functional recovery of myocardium. Hypokinesia with myocardial infarction involving more than 50% of thickness has low probability of functional recovery and subendocardial infarction involving less than 25% thickness has great potential for functional recovery. It is also shown that myocardium with transmural infarction involving >75% thickness is unlikely to improve after revascularisation [15] ***(figure 1).***



CMR myocardial viability results show excellent comparison and is at par with PET (positron emission tomography) findings [16]. Also CMR is proven to have higher sensitivity and specificity in detection of infarcted myocardium compared to SPECT (single photon emission computed tomography) [17].

CMR perfusion imaging in stress and rest environment allows detection of stress inducible ischemia and peri-infarct ischemia. Pharmacological vasodilator stress agents like Adenosine is commonly used to assess stress inducible ischemia. First pass perfusion technique is used with administration of gadolinium based contrast agent. First pass perfusion is assessed after stress induction and also in rest conditions. Presence of perfusion defects on stress imaging with normal rest perfusion (reversible defect) indicates stress inducible ischemia ***(figure 2).***



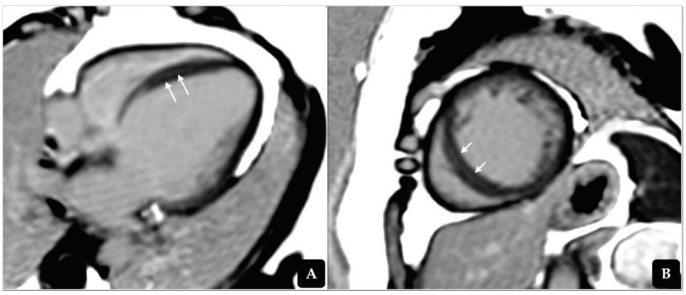
Infarcted tissue shows perfusion defect in rest as well as stress imaging, referred as fixed defect. Ischemia burden more than 10-15% is considered as a significant coronary artery disease and revascularisation will benefit the patient [18,19]. Stress perfusion imaging are further correlated with LGE images to assess viability as well as peri-infarct ischemia. Detection of myocardial ischemia on stress CMR is similar or is at least not inferior to other non-invasive modalities like positron emission tomography (PET) or single photon emission computed tomography (SPECT) [20-22]. Moreover, single stress CMR study along with LGE images provides comprehensive assessment of myocardium evaluating viability as well as stress inducible ischemia and/or peri-infarct ischemia.

CMR is also an excellent modality for detecting LV thrombus and reperfusion injuries. LV thrombus is common phenomenon in chronic myocardial infarction especially with akinetic or dyskinetic segments. Thrombus is seen as filling defect in the LV cavity on bSSFP cine images with no enhancement on LGE images. Reperfusion injuries include mainly microvascular obstruction (MVO) and intra-myocardial hematoma (IMH). MVOs are areas within infarction where complete lack of perfusion exists even after restoration of blood flow, also known as 'no reflow' phenomenon [23,24]. Early gadolinium enhancement (EGE) at 3-5 minutes with high nulling inversion time and LGE images should acquire where MVO appear dark areas within hyper-enhancing infarction [25]. IMH can be easily identified as hypo intense areas within the infarction on T2* imaging. T2* mapping is more sensitive to IMH than other CMR sequences [26]. Presence of MVO or IMH are poor prognostic markers in IHD.

C] CMR in non-ischemic cardiomyopathy:

Determination of cardiac structure and myocardial involvement is essential in classifying the heart failure and also to determine underlying aetiology like, dilated cardiomyopathy, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, myocarditis etc.

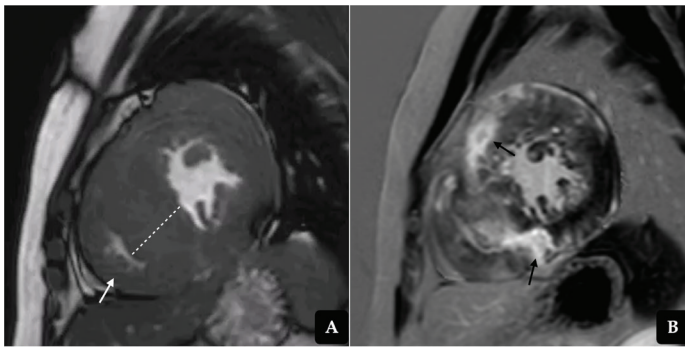
Dilated cardiomyopathy (DCM) is characterised by dilatation of LV with systolic dysfunction in absence of significant coronary artery disease or any other obvious underlying cause [27]. CMR helps to rule out other causes of dilated LV like myocarditis, infarction or infiltration. Primary DCM is diagnosis of exclusion. CMR provides accurate estimation of LV function which is essential in management of DCM. Also it determines RV failure and accurate quantification of RV function. Involvement of RV in DCM is associated with poor prognosis in DCM [28]. Replacement fibrosis in DCM is seen as mid myocardial enhancement on LGE images ***(figure 3).***



This mid wall fibrosis is independent prognostic fibrosis

in DCM which is seen in almost 30% patients of DCM [29]. Presence of septal mid wall fibrosis on LGE image is associated with higher risk for sudden cardiac death (SCD) in DCM patients. SCD risk is highest with concomitant septal and free-wall LGE [30]. Newer T1 mapping and ECV calculation methods in CMR offers risk stratification in cases of DCM. ECV is is found to increase in approximately 58% of DCM patients therefore, ECV estimation offers prognostication in heart failure outcomes incremental to LGE and T1 mapping [31].

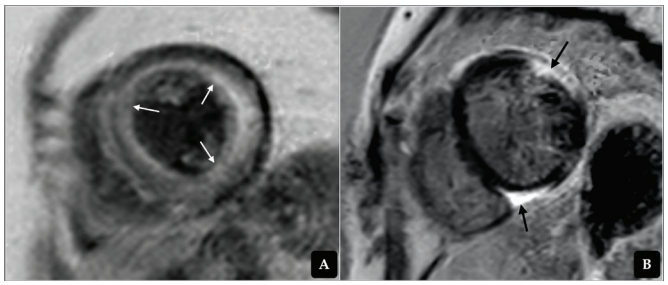
Hypertrophic cardiomyopathy (HCM) is most common genetic cardiomyopathy and is characterised by asymmetrical hypertrophy of LV, myocyte disarray and interstitial plus replacement fibrosis. CMR is excellent modality to assess suspected or diagnosed cases of HCM. CMR can effectively differentiate between different types of HCM like asymmetrical septal HCM, apical HCM and focal HCM [32]. CMR also can effectively assess systolic motion of mitral valve (SAM), LVOT obstruction or mid cavity obstruction. It also allows to detect RV hypertrophy which is present in about 1/3rd of HCM cases [33]. Interstitial and replacement fibrosis observed in HCM very distinct and characterised by patchy mid wall enhancement on LGE images. Percentage of fibrosis can be quantified on LGE sequences as a proportion of fibrosis to the myocardial mass. There is significant association between LGE and cardiovascular all cause mortality in HCM and also a trend towards increased SCD was observed [34]. T1 mapping shows increased native T1 values in about 30% HCM patients with absent LGE [35]. Combined use of LGE, T1 mappings and global ECV calculation can improve selection of candidates for implantable cardioverter defibrillator (ICD) placement [36]. CMR also helps in prognostication in HCM patients where poor prognostic indicators include LV hypertrophy measuring >30 mm in thickness, extensive patchy fibrosis in hypertrophied segments, presence of SAM and severe LVOT obstruction and mid ventricular obstruction with apical aneurysm ***(figure 4).***



CMR also differentiate SHCM from other causes of LV hypertrophy like hypertensive cardiomyopathy, infiltrative cardiomyopathy like amyloidosis and Fabry's disease.

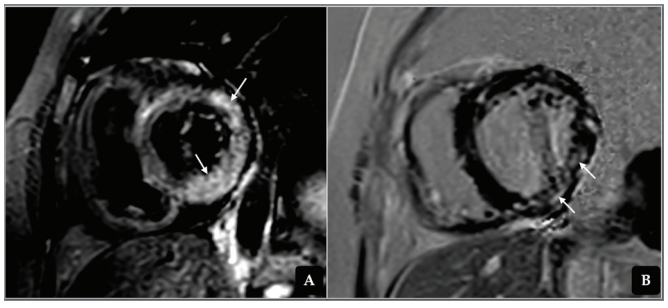
Infiltrative cardiomyopathy is a broad spectrum abnormality consisting amyloidosis, sarcoidosis, Fabry's disease etc.

CMR provides differentiation between types of infiltrative cardiomyopathy due to excellent myocardial characterisation ***(figure 5).***



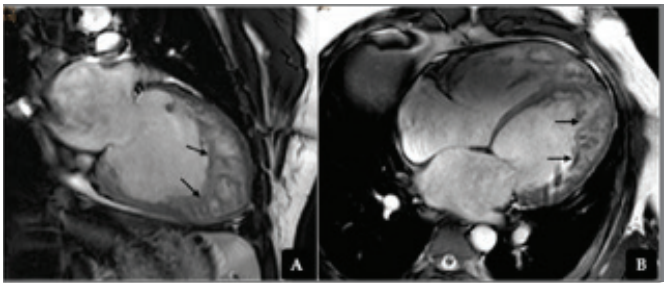
Amyloidosis is characterised by fibril deposition in the myocardium. CMR shows concentric symmetrical hypertrophy of LV with biatrial dilatation and inter-atrial septal thickening. Hypokinesia of LV is noted with pronounced diastolic dysfunction. LGE shows characteristic pattern of concentric subendocardial LGE with dark blood pool giving rise to 'zebra pattern' [37]. CMR also can differentiate between light chain amyloid (AL) and transthyretin related amyloidosis (ATTR), where transmural pattern of LGE is common in ATTR type [38]. CMR also allows to assess involvement of RV in amyloidosis. Noncontrast T1 mapping has high diagnostic accuracy for detecting cardiac AL amyloidosis, which correlates well with markers of systolic and diastolic dysfunction, and is potentially more sensitive for detecting early disease than LGE imaging [39]. Fabry's disease is x linked disorder of sphingolipid metabolism causing LV hypertrophy. CMR shows concentric LV hypertrophy with district and characteristic lateral wall enhancement in LGE images [1]. Sarcoidosis is an idiopathic granulomatous disease which can involve any organ system including heart. CMR features shows patchy of diffuse LGE predominantly in lateral wall [1]. Patients with the presence of LGE are at increased risk of death from any cause and arrhythmogenic events, even if their cardiac function is normal or near normal [40].

Myocarditis is the acute inflammation of the myocardium. Patients with acute heart failure and normal coronaries, myocarditis is suspected. STIR (short tau inversion recovery) sequence on CMR helps to detect acute myocardial edema/ inflammation as bright signals within the myocardium. LGE may or may nor show any enhancement corresponding to acute myocardial edema ***(figure 6).***



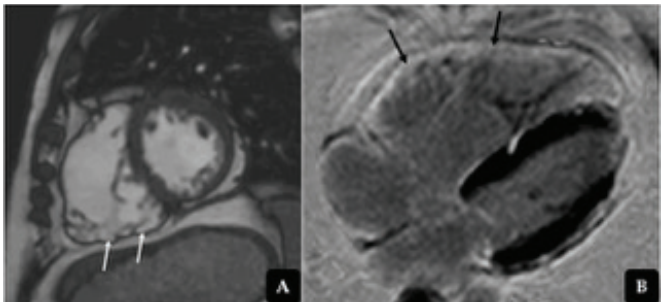
CMR helps in diagnosis and guiding biopsy increasing yield of invasive procedures [41].

LV non-compaction (LVNC) is a specific cardiomyopathy with hypertrabeculation of LV forming a layer of non-competed myocardium at endocardial surface of LV cavity. It has been demonstrated that CMR can reliably detect LV trabeculations more clearly than echocardiography [42]. There are many studies demonstrating different cut off for non-competed to compacted myocardium (NC:C) ratios in end diastole and end systole phases [43]. The criteria for the diagnosis by CMR - NC:C ratio greater than 2.3 during the diastole has a sensitivity of 86% and specificity of 99% [44] ***(figure 7).***



Another method to diagnose this entity is a trabeculated left ventricular mass above 20% of total mass with a sensitivity of 91.6% and a specificity of 86.5% is predictive of LVNC [45].

Arrhythmogenic right ventricular dysplasia (ARVD) is idiopathic cardiomyopathy of RV and is a prominent cause of SCD. It is characterised by RV dilatation and RV dyskinesia. RV is difficult to visualise on echocardiography due to near field signal drop out and crescentic structure if RV. On the other hand CMR can provide three dimensional and multi-planar imaging of RV with accurate quantification of RV volumes and ejection fraction (EF). CMR features of ARVD shows dilatation of LV associated with RV wall dyskinesia and/or aneurysmal outpouchings. LGE shows diffuse or patchy enhancement of RV free wall ***(figure 8).***



According to revised task force criteria for diagnosis of ARVD, CMR can fulfil one major or one minor criterion [46]. One major criteria on CMR include RV dyskinesia/akinesia/dyssynchronous RV contraction with indexed RV EDV > 110 ml/m2 (male) and > 100 ml/m2 (female) or RVEF < 40%. CMR also detects contiguous involvement of LV myocardium.

Iron overload cardiomyopathy is manifestation of repetitive blood transfusions in patients with hemoglobinopathies or in primary hemochromatosis. CMR is approved as gold standard to quantify myocardial iron overload. T2* imaging technique is used in qualification of iron overload which is ECG gated, single breath hold sequence [47]. Accurate quantification of myocardial iron provides excellent inputs to start or modify chelation therapy in patients with hemoglobinopathies [48].

D] Heart failure with preserved ejection fraction (HFpEF):

HFpEF consists of approximately 50% of cases of heart failure and contains diverse clinical heterogeneity [49]. These cases usually present with diastolic dysfunction. Echocardiography is traditional modality to diagnose and grade diastolic dysfunction in these cases. However, in last few years CMR showed promising role in HEpEF. Diastolic dysfunction is usually diagnosed by left atrial (LA) dilatation, LV hypertrophy, mitral inflow patten, LV filling curve etc. CMR allows accurate estimation of LA volume with the help of 2ch and 4ch cine views. LA volume is estimated using biplane area length (BAL) technique where LA volume (ml) = (0.85 × A2C × A4C)/L (A2C and A4C are the LA areas on the 2ch and 4 ch views, and L is the shorter length of the LA, from either the 2ch or 4ch). It is shown that CMR BAL technique is equally accurate with CMR Simpson's volumetric assessment and echocardiography BAL technique is less accurate as compared to CMR volumetric assessment especially in cases of atrial fibrillation [50]. LA size more than 32 ml/m2 is associated with increased rate of heart failure independent of age, LV hypertrophy, diabetes, hypertension, myocardial infarction of mitral inflow velocities [51]. LV hypertrophy is most common structural abnormality associated with HFpEF. CMR findings are more reproducible than M mode and 2D echocardiography in assessing LV hypertrophy [52]. Phase contrast imaging of CMR is used to calculate transmitral flow pattern with E and A velocities and E/A ratio which can be used in classifying different grade of diastolic dysfunction [53]. Other parameters like flow assessment across pulmonary veins and LV time-volume filling curves on CMR provides further assessment in HFpEF. CMR feature tracking (CMR-FT) is newer technique for evaluation of LV strain. CMR-FT are anatomic elements typically identified along the cavity-myocardial interface due to the high contrast resolution between blood pool and myocardium [54]. Blood-myocardium interface is traced in end diastolic cine images and CMR-FT software automatically tracks it throughout cardiac cycle. Global longitudinal strain is calculated on long axis cine images while global circumferential strain and global radial strains are calculated on short axis cine images [55,56]. CMR-FT is evolving and promising modality in assessment of HFpEF.

Around 10-15% cases of HFpEF belong to restrictive cardiomyopathy (RCM) or constrictive pericarditis (CP) [57].

RCM and CP share similar clinical presentation and many common features in diagnostic imaging tests however, the management of both conditions is extremely different as CP can be treated by pericardiectomy. CMR is excellent modality to differentiate between RCM and CP due to its multi-planar 3 dimensional imaging capabilities. Endomyocardial fibrosis (EMF) is most common cause of RCM [58]. EMF on CMR is characterised by obliterative apical fibrosis and thrombus. Apical fibrosis is seen as diffuse circumferential enhancement and thrombus is seen as non-enhancing filling defect in the apex on LGE images affecting single or both ventricles [59]. Other causes of RCM like amyloidosis, Fabry disease and iron overload cardiomyopathy are described above in the article. On the other hand, CP is associated with thickened pericardium causing abnormal pericardial compliance which affects relaxation of ventricles. CMR shows diffuse or focal thickening of pericardium with or without post contrast enhancement. Dynamic imaging with CMR can detect the exaggerated respiratory interdependence of the ventricles and abnormal septal bounce [60]. Treatment includes sodium restriction and diuretic agents to reduce edema and hepatic congestion; however, definitive therapy will require surgical pericardiectomy.

E] Cardiac resynchronisation therapy (CRT):

Patients with significant LV dysfunction, a challenge related to management involves determining which patients will benefit from CRT. Echocardiographic measurements are not sufficient to identify those individuals that will benefit from CRT. Cine CMR helps to detect areas of global or regional LV dyssynchrony. With use of LGE images of CMR, identification of scarred myocardium provides important information as to whether myocardial segments will improve contractility or develop synchronous contraction when a pacing lead is placed in close juxtaposition. As, if pacing leads are placed in regions with scarred myocardium, it will not facilitate the development of synchronous contraction [61].

CONCLUSIONS:

CMR is excellent modality in evaluation of suspected or known cases of heart failure. CMR provides valuable information in ischemic heart disease in terms of viability and detection of stress inducible ischemia. CMR is also unique in differentiating between the various causes of LV dysfunction. CMR information helps in assessing prognosis and also deciding management in various cardiomyopathies. CMR also allows to assess risk stratification in patients undergoing cardiac resynchronisation therapy. Newer imaging techniques like CMR-FT helps to study strain patterns in different cardiac diseases.

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THE YEAR IN CARDIAC SCIENCES 2021 – HEART FAILURE

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Introduction

In the year 2021, the universal definition and classification of heart failure (HF) was published that defines HF as a clinical syndrome with symptoms and/or signs caused by a cardiac abnormality and corroborated by elevated natriuretic peptide levels or objective evidence of cardiogenic congestion. This definition and the classification of HF with reduced ejection fraction (HFrEF), mildly reduced, and HF with preserved ejection fraction (HFpEF) is consistent with the 2021 ESC Guidelines on HF. Among several other new recommendations, these guidelines give a Class I indication for the use of the sodium–glucose co-transporter T2) inhibitors dapagliflozin and empagliflozin in HFrEF patients. As the first evidence-based treatment for HFpEF,

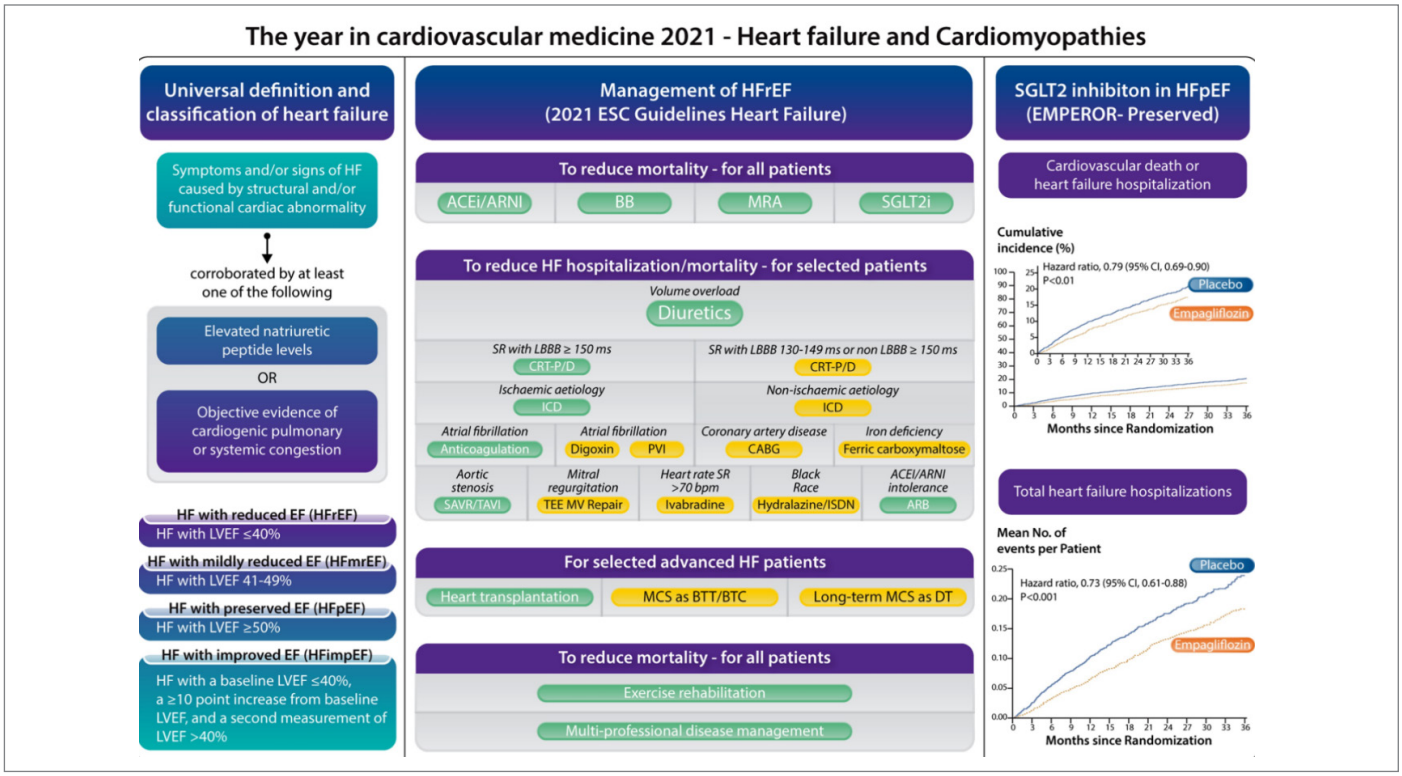


Figure 1: Summary of the universal definition and EF classification of heart failure; management of HFrEF according to 2021 ESC guidelines for heart failure and results of the EMPEROR-preserved trial.

in the EMPEROR-Preserved trial, empagliflozin reduced the composite endpoint of cardiovascular death and HF hospitalizations. Several reports in 2021 have provided novel and detailed analyses of device and medical therapy in HF, especially regarding sacubitril/valsartan, SGLT2 inhibitors, mineralocorticoid receptor antagonists, ferric carboxymaltose, soluble guanylate cyclase activators, and cardiac myosin activators. In patients hospitalized with COVID-19, acute HF and myocardial injury is quite frequent, whereas myocarditis and long-term damage to the heart are rather uncommon.

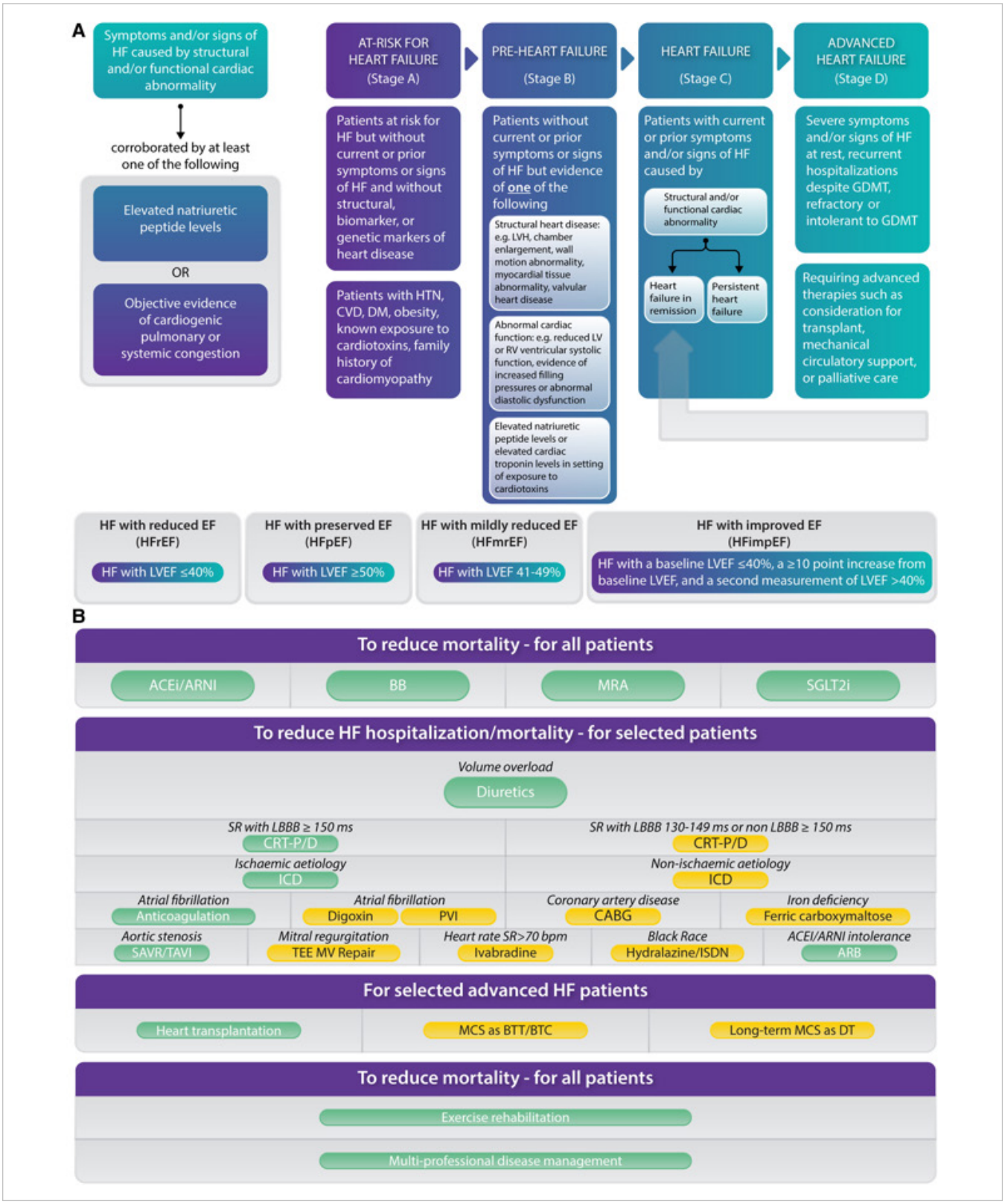


Figure 2: (A)Universal definition of heart failure (upper left panel) and new classification of heart failure according to left ventricular ejection fraction (lower panel) and stages of heart failure (upper right panel). (B) Overview of the management of pharmacological treatment of heart failure with reduced ejection fraction according to 2021 ESC Guidelines on Heart Failure.

This article is a summary of important progress that has en made in 2021 regarding the diagnosis and treatment of HF with a special focus on articles published in 2021 in the European Heart Journal and the European Journal of Heart Failure (Figure 1).

Definition and classification of heart failure

With the recognition of the need for standardization of an HF definition, the Universal Definition and Classification of Heart Failure was developed, which defined HF as a clinical syndrome with current or prior symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide (NP) levels or objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities (Figure 2). It also provided revised definitions for stages of HF, categorized as 'At-Risk for HF' (former Stage A) for patients at risk for HF but without current or prior symptoms or signs of HF and without structural cardiac changes or elevated biomarkers of heart disease; Pre-HF (former Stage B) for patients without current or prior symptoms or signs of HF but evidence of structural heart disease, abnormal cardiac function, elevated NP levels or elevated cardiac troponin levels; 'Heart Failure' (former Stage C for symptomatic patients, 'Advanced HF' (former Stage D) for patients with severe symptoms and/or signs of HF (Figure 2). Ejection fraction categories were classified as HFrEF: left ventricular (LV) EF ≤40% (Figure 2); HF with mildly reduced EF (HFmrEF): LVEF 41–49%; HFpEF: LVEF >50%; and HF with improved EF (HFimpEF): HF with a baseline LVEF ≤40%, a ≥10 point increase from baseline LVEF, and a second measurement of LVEF >40%. The EF categories used in the recent 2021 ESC HF Guidelines were consistent with these classifications.. In the Universal Definition of HF, there was also an emphasis on trajectories of HF and to use 'persistent HF' instead of 'stable HF' for patients with ongoing symptoms/signs and 'HF in remission' instead of 'recovered HF' for patients with resolution of symptoms and signs of HF or with the resolution of previous structural/functional heart disease (Figure 2).

Epidemiology

The HF Atlas survey reports a wide-ranging incidence of HF and HF hospitalizations across Europe with considerable heterogeneity in the resources for management and the data quality providing data to allow the development of strategies to improve inequalities. Exposure to ambient air pollutants increases the risk of HF in a dose-dependent fashion, and there was a particularly high risk of HF among persons with genetic higher susceptibility to HF (Figure 3). Air pollution probably should be considered in risk scores to predict HF.

A recent European registry report demonstrated that dilated cardiomyopathy (DCM), not skeletal myopathy, is the major determinant of prognosis in patients with dystrophin gene mutations. Finally, cancer and HF occur more commonly together that predicted by risk models, and a recent study suggests that statins reduce the risk of both and have a greater risk reduction with more prolonged use.

Diagnostics and risk stratification

For HFrEF, the main diagnostic criterion remains LVEF ≤40%. However, there is more controversy in the other categories, HFmrEF and HFpEF. Pieske et al. formulated, on behalf of the ESC, new diagnostic criteria, including echo parameters, NPs, and if a definitive diagnosis cannot be made, to turn to stress testing and/or invasive haemodynamics.

There is increasing appreciation that classical diagnostics fall short in complex multifactorial diseases with various aetiologies and precipitants, and several studies have addressed whether an agnostic approach, where large data sets are queried by computer algorithms, may be superior in making a specific diagnosis. Such techniques are referred to as machine learning (ML) and artificial intelligence (AI). Peyster et al. used an automated image analysis to detect rejection after heart transplantation and described a 'Computer-Assisted Cardiac Histologic Evaluation (CACHE)-Grader' pipeline that was non-inferior to the rejection grading provided by independent pathologists. Another field of research for which AI provides an attractive tool is the categorization of patients who received a general diagnosis of HF. Verdonschot et al. studied 795 consecutive DCM patients with data on aetiology and co-morbidities, imaging studies and endomyocardial biopsies, and identified four distinct phenogroups. Woolley et al. using an algorithm based on 363 biomarkers to phenotype, 429 patients with HFpEF identified four clusters with different clinical parameters and important differences in prognosis.

Artificial intelligence/machine learning might be particularly useful for a diagnosis of HF. Kwon et al. evaluated data from 34103 patients who underwent echocardiography and electrocardiogram (ECG) and created an ML algorithm that could detect HFpEF. Segar et al. employed ML models to aid in predicting race-specific risk for incident HF.

In the near future, we will be faced with many more potential utility of AI/ML models, as there is a clear need for individualized approaches and decision-making. It will be essential, however, to provide recommendations as to what input is (minimally) required for models, and the models must be prospectively tested in independent settings. Furthermore, treatment decisions based on the models must be tested in a randomized blinded fashion.

Imaging and biomarkers

A state-of-the-art diagnosis of HF remains challenging. The ESC guidelines recommend using an array of signs and symptoms, supplemented with imaging and biomarkers studies. The imaging primarily relies on echocardiography and CMR, and NPs and high sensitivity troponins are the preferred

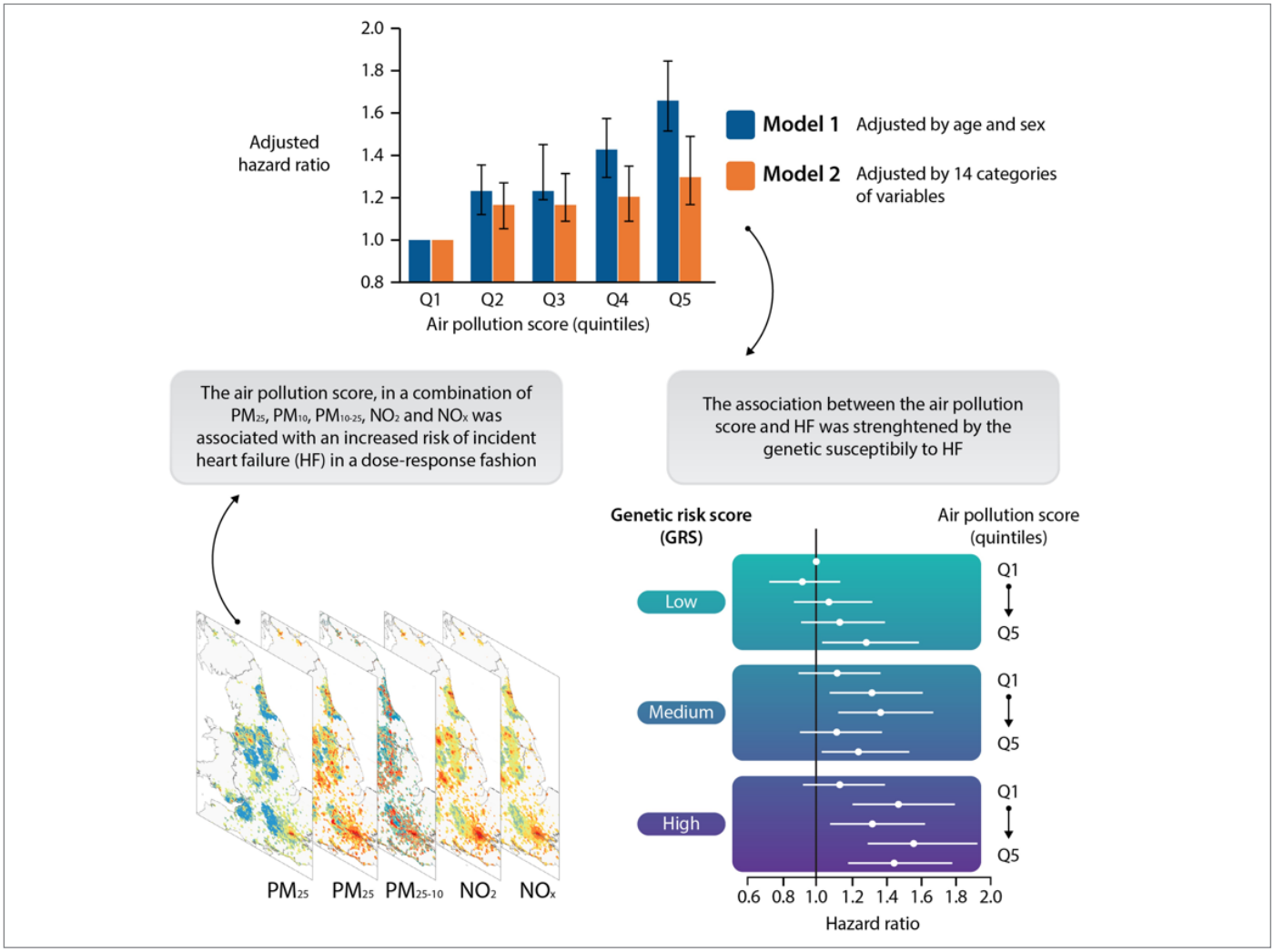
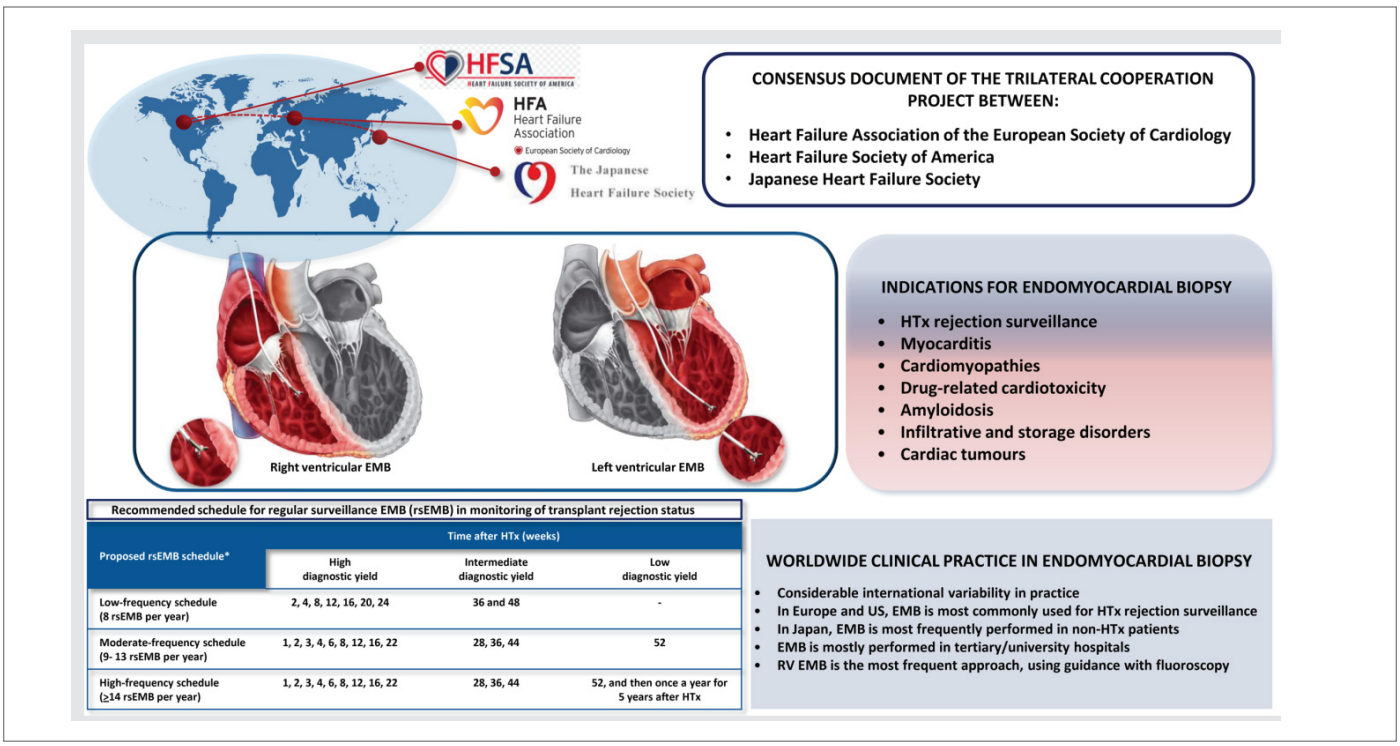


Figure 3: Long-term joint exposure to various air pollutants, including PM2.5, PM10, PM2.5–10, NO2, and NOx is associated with an elevated risk of incident heart failure in an additive manner. Persons with genetic higher susceptibility to heart failure displayed a particularly high risk of heart failure.



biomarkers. However, sophisticated classification of patients in various categories using imaging and biomarkers may enhance adequate phenotyping, and imaging of non-cardiac tissues such as fat may have relevance to HF phenotyping, too. Furthermore, next-generation genetic analyses has been shown to have a consequence for prognosis and diagnosis of HF. In addition, a recent article highlighted the indications of endomyocardial biopsies.(Figure 4)

Specific situations

Acute heart failure

The 2021 ESC guidelines did not significantly change recommendations for acute HF, although the use of opioids was downgraded to a Class III recommendation. Evidence continues to accrue supporting the use of urinary sodium in assessing outcomes in acute HF.

Cardiogenic shock

Mortality remains high in cardiogenic shock, and randomized trials assessing therapies remain rare but a single-centre trial randomized patients with cardiogenic shock to either milrinone or dobutamine and showed no differences in any of the primary or secondary outcomes. In the follow-up of the IMPRESS trial in cardiogenic shock, there was no difference in mortality comparing intra-aortic balloon pumps vs. the Impella device at 5 years. A biomarker composite outperformed other risk scores for cardiogenic shock using 4 biomarkers [Cystatin C, Lactate, interleukin-6, and N-terminal pro brain natriuretic peptide (NT-proBNP)]. A recent consensus statement outlines important suggestions for optimizing cardiogenic shock trials.

Ventricular assist devices and heart transplantation

A single entry registry confirms that HeartMate III (HMIII) outcomes are better than historical controls confirming randomized trials. The stroke rate with HMIII is less than with the Heartware ventricular assist device (HVAD)—one of several reasons the HVAD has been withdrawn from use. Disappointingly, left ventricular assist devices (LVAD) use does not reduce myocardial fibrosis nor does a new risk score improve the prediction of right ventricular failure post-LVAD, but on the bright side, elderly patients have benefits in quality of life and exercise capacity with LVADs. There is substantial inter-observer variability in the diagnosis of cellular rejection in myocardial biopsies but automated computation image analysis may allow improved standardization as described in the section on Diagnostics and Imaging. Non-invasive prediction of rejection in cardiac transplant recipients has been elusive, but studies using peripheral blood cell-free DNA show promising early results.

Pregnancy/patients with peripartum cardiomyopathy

Women with a known cardiomyopathy or at risk for HF planning pregnancy, or presenting with HF during or after pregnancy are in need of individualized pre-, during, and post-pregnancy assessment and counselling.

Patients with peripartum cardiomyopathy are at risk for detrimental outcomes but often do recover from HFrEF. Recent publications investigated the value of ECG abnormalities for predicting echocardiographic results and the role of hypertensive disorders during pregnancy.

Hypertrophic cardiomyopathy/amyloidosis

In the health status analysis of EXPLORER-HCM, mavacamten markedly improved the health status of patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM) compared with placebo. Gaps in evidence for risk stratification for sudden cardiac death in HCM were summarized by Pelliccia et al. In a study by Marston et al. using Sarcomeric Human Cardiomyopathy Registry, patients with childhood-onset HCM were reported more likely to have sarcomeric disease, carry a higher risk of life-threatening ventricular arrhythmias, and have a greater need for advanced HF therapies. In the German Cardiac Society position statement, Yilmaz et al. outline a diagnostic algorithm to detect cardiac amyloidosis, to accurately determine its extent, and to reliably identify the underlying subtype of amyloidosis, thereby enabling subsequent targeted treatment.

Cancer

Heart failure often complicates the treatment of cancer, and a recent paper proposes definitions of cardiovascular (CV) toxicities. Classically, chemotherapy and radiotherapy have been identified as risk factors, but in the recent decade, immunotherapy with immune checkpoint inhibitors (ICIs) is becoming the mainstay of cancer treatment. However, ICIs also carry a risk for CV side effects. D'Souza et al. reported on this risk in a Danish registry and show that ICI is associated with a 1.8% 1-year risk for (peri-)myocarditis, and with an almost 10% risk for any CV complication. Given the increasing use of ICI, this issue will require clinical guidance and further study, as ICIs have an impact on several cells and tissues. There are initial reports providing guidance as to treat ICI-induced myocarditis.

This field extends the increasing awareness that incident cancer is more common in patients with prevalent HF, and that cancer and HF may be connected more closely than anticipated before. In support of this, Ren et al. demonstrated that the use of statins reduces incident cancer. Finally, a special article by Zannad et al. discusses aspects of cancer research that may be applicable to HF research, with the aim of streamlining the clinical trial process and decreasing the time and cost required to bring safe, effective, treatments to HF patients.

Pharmacotherapies

New algorithm of the 2021 ESC Guidelines on heart failure for the pharmacological treatment of heart failure with reduced ejection fraction

The 2021 ESC Guidelines on HF provide a Class I recommendation for pharmacological treatment of all HFrEF patients with a combination of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor–neprilysin inhibitor (ARNI), a beta-blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium–glucose co-transporter 2 (SGLT2) inhibitor (dapagliflozin or\and empagliflozin) (Figure 2B)The guideline still recommends the use of ARNI as a replacement for ACE inhibitor; however, an ARNI may also be considered as a first-line therapy instead of an ACE inhibitor. It is recommended that these four disease-modifying drugs are initiated within a short time frame. Potential advantages of another algorithm for the sequencing of these drugs have been suggested by McMurray and Packer with beta-blockade and SGLT2 inhibition as first-line therapies. However, albeit appealing from a pathophysiological standpoint such a new sequence is not yet evidence-based.

A recent consensus document of the HFA of the ESC identified nine patient profiles that may be relevant for treatment implementation in patients with HFrEF taking into account heart rate, atrial fibrillation, symptomatic low blood pressure, estimated glomerular filtration rate, or hyperkalaemia. Using such a personalized approach may lead to a better and more comprehensive therapy for each individual patient.

Angiotensin-converting enzyme inhibition

While ACE inhibitors are a standard for the prevention and treatment of HF for many years, the impact of these drugs as preventive therapy for HF in patients with Duchenne muscular dystrophy was unclear. A large French registry showed that prophylactic treatment of patients without LV dysfunction with an ACE inhibitor was able to prevent the transition to HF and improve survival in Duchenne muscular dystrophy.

Angiotensin receptor–neprilysin inhibitors (PARAGON, PARADIGM, PARALLAX, PARADISE-MI, LIFE)

In an analysis of the PARADIGM-HF trial, initiation of sacubitril/valsartan, even when titrated to target dose, did not lead to greater discontinuation or down-titration of other guideline-directed medical therapies and was associated with fewer discontinuations of MRA. In real-world patients with HFrEF, sacubitril/valsartan was effective, safe, and well tolerated. Sacubitril–valsartan was found to be useful in treating resistant hypertension in HFpEF in the PARAGON-HF trial when compared with valsartan. In the PROVE-HF trial, in patients with HFrEF, 32% improved their EF to >35% by 6 months and 62% to >35% by 12 months after initiation of sacubitril/valsartan therapy. In patients with asymptomatic LV systolic dysfunction late after myocardial infarction, treatment with sacubitril/valsartan did not have a significant reverse remodelling effect compared with valsartan. In the PARADISE-MI trial, sacubitril/valsartan did not significantly reduce the rate of CV death, HF hospitalization, or outpatient HF requiring treatment in patients with LVEF ≤40% and/or pulmonary congestion following acute myocardial infarction, compared with ramipril (results presented at the ACC). In the Sacubitril/Valsartan in Patients with Advanced Heart Failure with Reduced Ejection Fraction in the Advanced Heart Failure (LIFE-HF) trial, which enrolled NYHA Class IV patients and LVEF ≤35%, sacubitril/valsartan did not improve the clinical composite endpoints (presented at ACC 2021). PARALLAX trial will determine if sacubitril/valsartan improves NT-proBNP levels, exercise capacity, quality of life, and symptom burden in HF patients with EF >40%.

In the new 2021 ESC Guidelines on HF, sacubitril/valsartan is recommended as a replacement for an ACE inhibitor in patients with HFrEF as a Class I recommendation. Initiation of sacubitril/valsartan in ACE inhibitor naive patients with HFrEF on the other hand is suggested as a Class IIb recommendation.

Sodium–glucose co-transporter 2 inhibitors (EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, SOLOIST)

Sodium–glucose co-transporter 2 inhibitors are rapidly becoming the panacea for the entire spectrum of cardiometabolic and renal disease. In trials in type 2 diabetes mellitus (T2DM), a beneficial effect was observed for CV endpoints in general, while the effects on incident HF were overwhelmingly positive. These effects were validated in patients with prevalent HFrEF, first in DAPA-HF and a year later in the EMPEROR-Reduced trial. Numerous subanalyses from these trials were published in 2021.

First, besides the striking effects on hard endpoints, it is more and more recognized that functional status and symptoms are important to patients with HFrEF. Both in DAPA-HF and EMPEROR-Reduced, these were improved, although a smaller dedicated trial with empagliflozin did not improve functional status. Further, a series of subanalyses showed no interaction of SGLT2 inhibitors with common HF drugs, such as MRAs, and most importantly, also not with sacubitril/valsartan. Furthermore, the equal effects of the drugs were ascertained by analysing the effects across countries and ethnicities. Another striking observation was that dapagliflozin was associated with a lower incidence of new-onset diabetes. Collectively, to date, we have not seen any analysis suggesting a differential or lesser effect of SGLT2 inhibitors in HFrEF. We therefore must start to learn how to employ these drugs practically.

Different from HFrEF, the efficacy of SGLT2 inhibitors in HFpEF remained to be proven. However, the EMPEROR-Preserved study presented during ESC 2021 demonstrated that empagliflozin reduced the primary combined endpoint of CV death and HF hospitalization in almost 6000 patients with HFpEF (Figure 5). These data are extremely important and provide hope for millions of HFpEF patients for whom there were no evidence-based therapies. Over a median follow-up

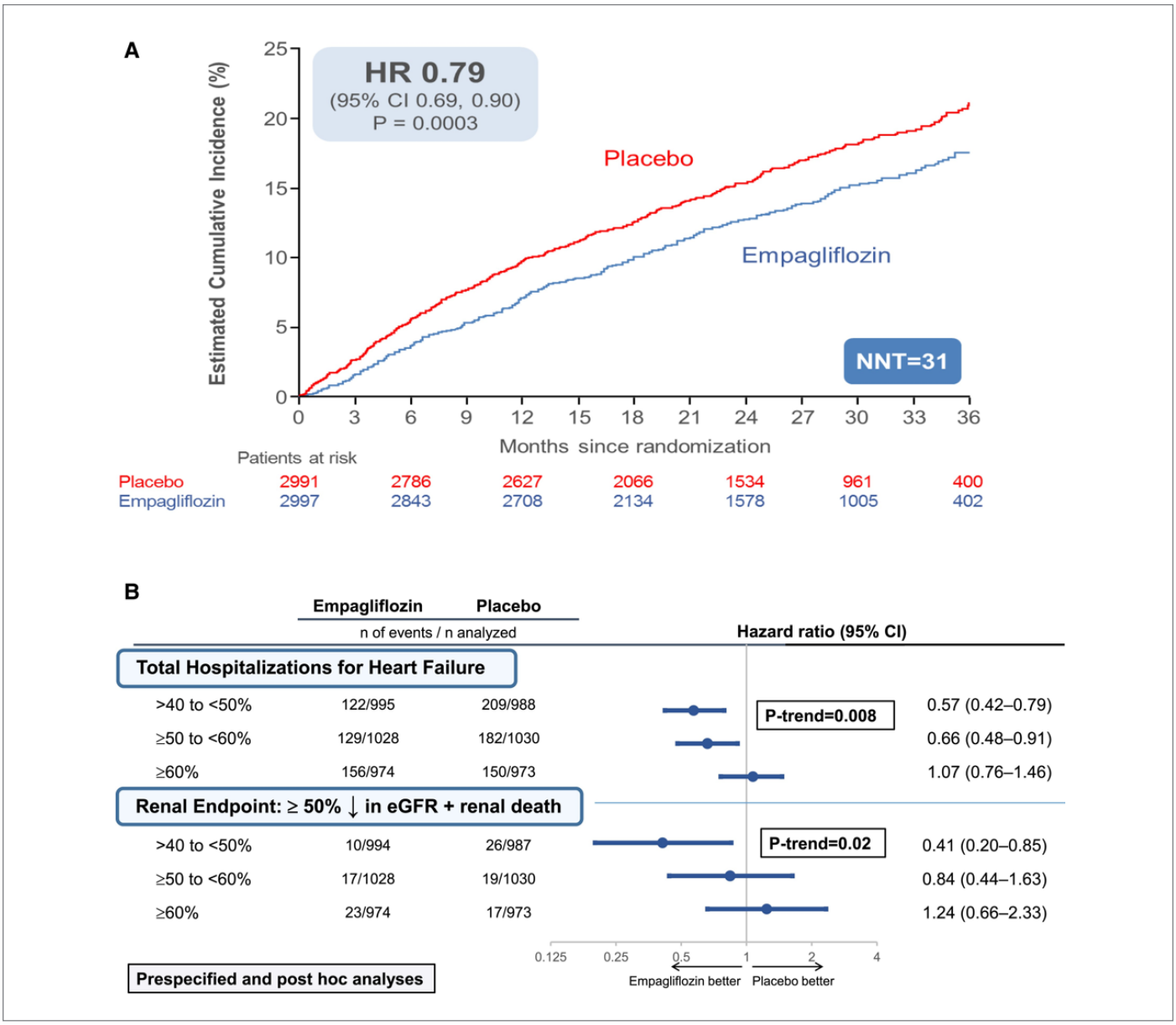


Figure 5: SGLT2 inhibition (EMPEROR-Preserved). (A) EMPEROR-Preserved enrolled 5988 patients with heart failure with preserved ejection fraction and followed them up for a mean of 26 months. The primary endpoint (a composite of cardiovascular death or heart failure hospitalization) was reduced by 21%, translating in a number needed to treat of 31. (B) In a pooled analysis of the EMPEROR-Reduced and -Preserved trials, it was observed that in the higher left ventricular ejection fraction range, the relative benefit of the SGLT2 inhibitor empagliflozin may be attenuated. In the figure, the effects of empagliflozin HF hospitalization and renal outcomes are visualized for the left ventricular ejection fraction 40–50, 50–60, and >60% categories. There is a significant trend towards lesser efficacy in the higher left ventricular ejection fraction categories.

of 26 months, the primary outcome event occurred in 13.8% of the patients in the empagliflozin group and in 17.1% in the placebo group [hazard ratio (HR): 0.79; 95% confidence interval (CI): 0.69–0.90; P < 0.001]. Empagliflozin was very effective in reducing HF hospitalization, but all-cause mortality was not reduced. The effects of empagliflozin were consistent in patients with or without diabetes. Shortly, the result of the second mortality trial in HFpEF with the SGLT2 inhibitor dapagliflozin, DELIVER, will be presented. Sodium–glucose co-transporter 2 inhibitors were also evaluated in patients with acute HF or immediately after acutely decompensated HF. The SOLOIST trial, with the mixed SGLT 1/2 inhibitor sotagliflozin, enrolled 1244 patients with T2DM and recent worsening HF and showed a beneficial effect of the study drug, initiated before or shortly after discharge, with regard to a significantly lower total number of CV deaths and HF hospitalizations and urgent visits for HF. The ongoing EMPULSE trial will provide more data in the acute HF arena.

Sodium–glucose co-transporter 2 inhibitors do not stop to amaze us in renal disease. After the publication of the hallmark trials CREDENCE and DAPA-CKD, in 2021, the SCORED trial came out, demonstrating in patients with T2DM and chronic kidney disease, allocated to sotagliflozin or placebo, a reduction of 37% in the primary endpoint of CV death and HF events (HR: 0.74; 95% CI: 0.63–0.88; P < 0.001). However, sotagliflozin was associated with adverse events such as diarrhoea, genital mycotic infections, volume depletion, and diabetic ketoacidosis.

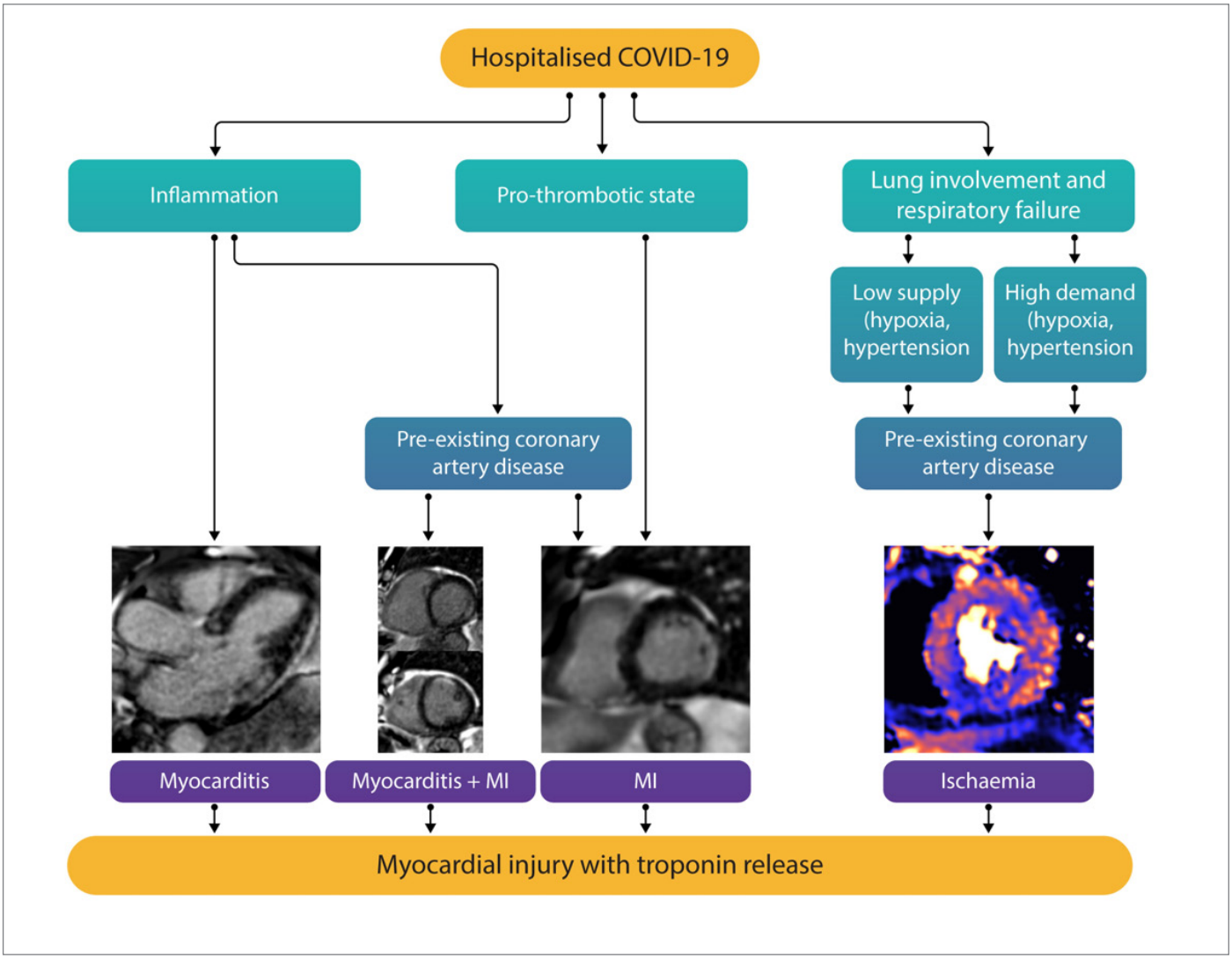


Figure 6: Myocardial injury in recovered COVID-19 patients assessed by cardiovascular magnetic resonance. Myocarditis-like injury can be encountered, with limited extent and minimal functional consequence.

in patients hospitalized with COVID-19 (DARE-19 trial). Myocarditis emerged as a rare complication of COVID-19 mRNA vaccinations, especially in young men.

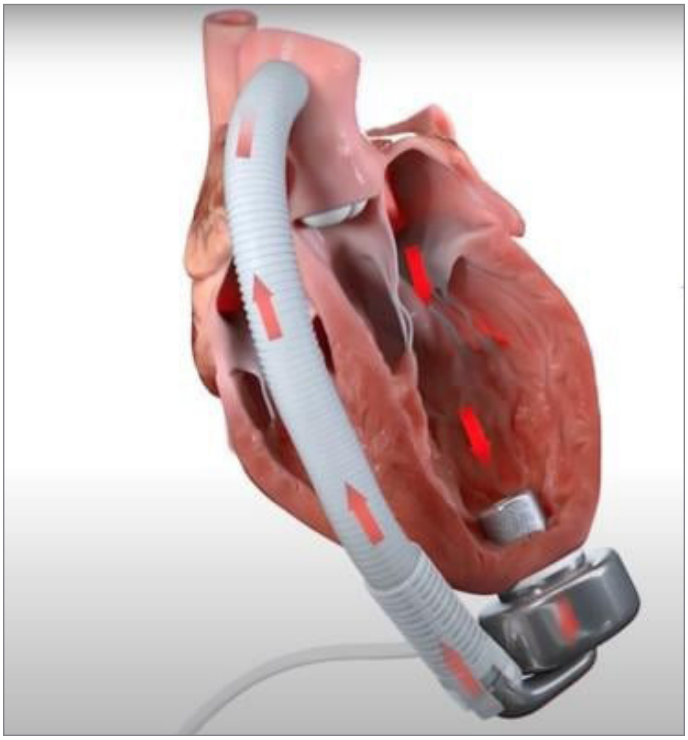
Benefit–risk assessment for COVID-19 vaccination was favourable for all age and sex groups; and almost all patients with myocarditis had resolution of symptoms and signs. Long-term complications of SARS-CoV-2 infection include persistent sinus tachycardia, postural orthostatic tachycardia syndrome, atrial arrhythmia, and cardiomyopathy. Among athletes recovering from COVID-19, several CMR studies reported varying rates and degrees of cardiac abnormalities suggestive of myocarditis. Screening by troponin, ECG, echocardiography, and additional CMR and/or stress echocardiography if abnormal, resulted in only 0.6% of the athletes being restricted to return to sports, and none had cardiac events. Though myocardial injury is common in COVID-19, and SARS-CoV-2 RNA can be detected in the heart, myocarditis is an uncommon pathologic diagnosis occurring in 4.5% of highly selected cases undergoing autopsy or endomyocardial biopsy. During convalescence after severe COVID-19 infection with troponin elevation, myocarditis-like injury can be detected by CMR, however, with limited extent and minimal functional consequence (Figure 6).

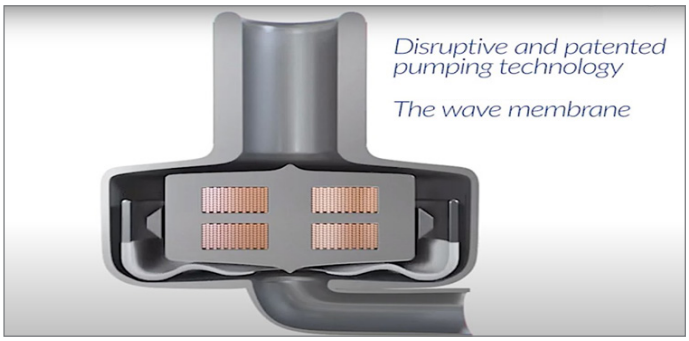
Innovative New Pulsatile LVAD Wins 2021 HealthTech Award

October 20, 2021 – CorWave, a French medtech company developing a next-generation heart pump, won the 2021 HealthTech Award in the Medtech category this week for its left ventricular assist device (LVAD) membrane pump technology. Rather than conventional rotary pumps, this LVAD uses electromagnetic pulses to causes a membrane to move up and down, creating pulsatile pumping action more similar to the native heart.

CorWave received the Medtech Award, which recognizes a medical device or diagnostic company that has distinguished itself over the past two years by making big advances in areas such as R&D, operational development, or financing.

CorWave also made major progress in R&D, completing an unprecedented in vivo preclinical study in which its heart pump successfully operated in pulsatile mode, synchronizing with the native heart without the aid of sensors, for 90 days. On the operational development front, CorWave bolstered its team with the recruitment of two seasoned international professionals who bring over three decades of experience in the heart pump field. They will lead the key operational functions of the company as it transitions to clinical device production and clinical trial phase.





CorWave is a French company that develops innovative cardiac assist devices for heart failure patients. CorWave's wave membrane is a breakthrough technology that differs from today's commercially available LVADs by its physiological operation, including the ability to mimic a pulse and blood flow rates similar to those of a healthy heart. Ultimately, CorWave's membrane pump technology is expected to reduce the complications associated with current devices and improve the management of heart failure patients. CorWave was founded in 2012 by start-up studio MD Start and is funded by renowned investors including Bpifrance, EIC Fund, Financière Arbevel, M&L Healthcare, Novo Holdings, Seventure, Sofinnova Partners and Ysios. The company has secured €80 million in equity and non-dilutive financing and employs over fifty people.

Conclusions:

In the year 2021, the universal definition and classification of heart failure (HF) was published that defines HF as a clinical syndrome with symptoms and/or signs caused by a cardiac abnormality and corroborated by elevated natriuretic peptide levels or objective evidence of cardiogenic congestion. This definition and the classification of HF with reduced ejection fraction (HFrEF), mildly reduced, and HF with preserved ejection fraction (HFpEF) is consistent with the 2021 ESC Guidelines on HF. Among several other new recommendations, these guidelines give a Class I indication for the use of the sodium–glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin in HFrEF patients. As the first evidence-based treatment for HFpEF, in the EMPEROR-Preserved trial, empagliflozin reduced the composite endpoint of cardiovascular death and HF hospitalizations. Several reports in 2021 have provided novel and detailed analyses of device and medical therapy in HF, especially regarding sacubitril/valsartan, SGLT2 inhibitors, mineralocorticoid receptor antagonists, ferric carboxymaltose, soluble guanylate cyclase activators, and cardiac myosin activators. In patients hospitalized with COVID-19, acute HF and myocardial injury is quite frequent, whereas myocarditis and long-term damage to the heart are rather uncommon.

TRIVANDRUM HEART FAILURE REGISTRY

Dr S Harikrishnan
MD, DM, FACC, FRCP,
FIACS, FAMS
Professor of Cardiology
SCTIMST, Trivandrum.

Dr S Harikrishnan is currently Professor at the Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, Kerala. After Graduation from Medical College, Trivandrum, he completed post-doctoral DM training in cardiology from SCTIMST in 1998. Subsequently he got Commonwealth Fellowship in Interventional Cardiology and had training in Leeds University, UK. He also had training in public health at Emory University, USA through the PH -LEADER program.

Dr Harikrishnan is primarily an interventional cardiologist but his main research interest is in heart failure. After establishing the first heart failure cohort in India, – the Trivandrum HF cohort which has completed 7 years of follow-up, he is now leading the National HF registry which is the largest in the country and has enrolled 10800 patients. He has also lead the largest pulmonary hypertension registry - the PROKERALA registry.

In 2019, Dr Harikrishnan was awarded one of the ten National Centers of Excellence in Clinical Research (CARE), established nationwide by Indian Council of Medical Research (ICMR) which includes the first HF Biobank in India. He has got more than 100 publications in International peer reviewed Journals with high impact with more than 25000 citations and an h-index of 37.

He has edited three books, which includes a unique monograph on Balloon Mitral Valvotomy, and another titled – WA RACE AGAINST TIME – describing the epidemic of cardiovascular diseases in developing economies and Manual of Heart Failure Management. He is also the founder editor of the International peer-reviewed journal - Pulmonary Circulation.

He is the fellow of the National Academy of Medical Sciences, American College of Cardiology, International Academy of Cardiovascular Sciences and Royal college of Physicians, London.

Cardiovascular diseases (CVD) has overtaken communicable diseases as the leading cause of mortality in low-income and middle-income country (LMIC) countries like India towards the fag end of the last millennium itself.

Heart failure (HF), which is the culminating stage of most of the advanced heart diseases is emerging as a major public health problem in LMIC.

HF is a disease with high mortality and also morbidity. With one-year mortality of 30% and 5-year reported mortality of 50%, the outcomes are worse than the estimates for common cancers of breast and the colon.

HF is a condition which requires resource intensive therapy in the acute phase and also will need lifelong therapy in most of the affected people. (1). So it can further compromise the health systems in LMIC which are already stressed.

In this background, we will discuss the epidemiological data of HF from India. The real data on incidence and prevalence of HF from India are scarce(2). There are also a few estimates and projections of burden of heart failure based on risk factor data (3)(4)(5). There is only a small community study on the prevalence(5) of HF from India. The rest of the data are from a few registries(6)(2)(7)(8).

HF Burden is on the rise?

We will try to answer this question first. We know the prevalence of HF increases with age. As the population in India is ageing, naturally the HF burden is likely to rise. (3). The most important reason for rising prevalence of HF is the increasing prevalence of atherosclerotic vascular diseases and their risk factors (9). The third factor is the persisting burden of conditions like rheumatic heart disease (RHD), chronic obstructive pulmonary disease (COPD) and untreated congenital heart disease (CHD) which add to the HF burden. Based on all these facts which can influence the burden of HF relevant in Indian context, we can predict that the burden likely to increase in India in the next few decades.

The Trivandrum HF registry

The Trivandrum HF registry (THFR) is a prospective heart failure registry set-up in 2013 supported by Indian Council of Medical Research (ICMR), in Trivandrum district, the southern-most part of Kerala. The study had two arms – urban arm, the Trivandrum city area and in a Rural arm - sub-urban rural area called Athiyannoor, about 25 kilometres from the city. The population in this area was nearly 10 lakhs , contributed by Trivandrum city urban area of 9,57,000 (area 215 Sq Km) and 1,66,549 in the rural area of 60 sq. km(2).

All the 12 hospitals in the urban area and the 5 of 5 eligible hospitals in the rural area who were catering to patients with heart failure joined the registry and recruited patients for a period of one year (2013). All the participating hospitals enrolled consecutive patients who were admitted with HF satisfying the ESC 2012 criteria(10).

Optimal treatment was defined by various guidelines as a combination of beta blockers(BB), angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), and aldosterone receptor blockers in HF patients with

reduced ejection fraction (HFrEF).

The THFR registry was subsequently converted to a cohort with the support of ICMR and now being followed-up at regular intervals. Seven years of follow-up is completed and we have published the five years follow-up data in 2021.

What did we find in THFR?

THFR recruited 1205 patients in the one-year period. Females formed only 30% of the cohort, while the sex ratio is almost equal in the western data. Mean age of the patients in THFR was 61.2 +/- 13.7 years. Indian patients with HF in the Trivandrum HF registry were younger by 10 years compared to the data from US and Europe. (Figure 1). The proportion of patients above 85 years was 4% in THFR while it was 25% in ADHERE registry from US. We can see from the data that in India, HF affects a much younger, predominantly male population.

The most common aetiology of HF in THFR was ischaemic heart disease (IHD) (71%), followed by dilated cardiomyopathy (DCM) contributing to 17%. (Table 2). This was the same among men and women. ADHERE registry data also shows predominance of IHD, but the proportion was slightly less (63% vs 71%).

While rheumatic heart disease (RHD) contributed 8% of the HF burden in THFR, it was not contributing significantly to the burden in the US population. Women reported a higher prevalence of RHD (11.6%) Vs men (6.2%). This shows that even now in India diseases of the ester era like RHD are contributing to the burden of HF.

The patients were classified into different groups based on ejection fraction (EF). (11) Heart failure with preserved ejection fraction (HFpEF: defined as EF>50%) constituted 236 (19.6) % of the population. Heart Failure with mid-range Ejection Fraction (HFmrEF: defined as EF 40%-49%) constituted 217 (18%) of the population and heart failure with reduced ejection fraction (HFrEF: defined as EF<40%) was the highest proportion, which constituted 752 patients (62.4%).

The median hospital stay was 6 days and the in-hospital mortality was 8.5%. The 90-day mortality was 18%. Compared to the western registries, ADHERE (12) and OPTIMISE-HF (13), THFR showed that hospital stay was longer, and in-hospital and 90-day mortality rates, both were higher. Despite the youngish population, the HF mortality was higher in THFR as compared to data from the west. The possible reasons could be the relatively higher prevalence of comorbidities and comparatively lower ejection fraction in this THFR cohort.

'Guideline-based' medical treatment was defined as the combination of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and aldosterone receptor blockers in patients with HFrEF. Only a fourth (25%) of the patients with LV systolic dysfunction received optimal treatment at discharge. There were no gender differences in prescription of guideline-directed medical treatment status at discharge (25.3% in men compared with 22.9% in women).

Patients who did not receive guideline-based therapy experienced higher mortality than those who received guideline-based therapy($p < 0.001$)(2). Only one-fourth of the total study population received guideline-based medical treatment, which indicates gross underutilisation of evidence based therapies.

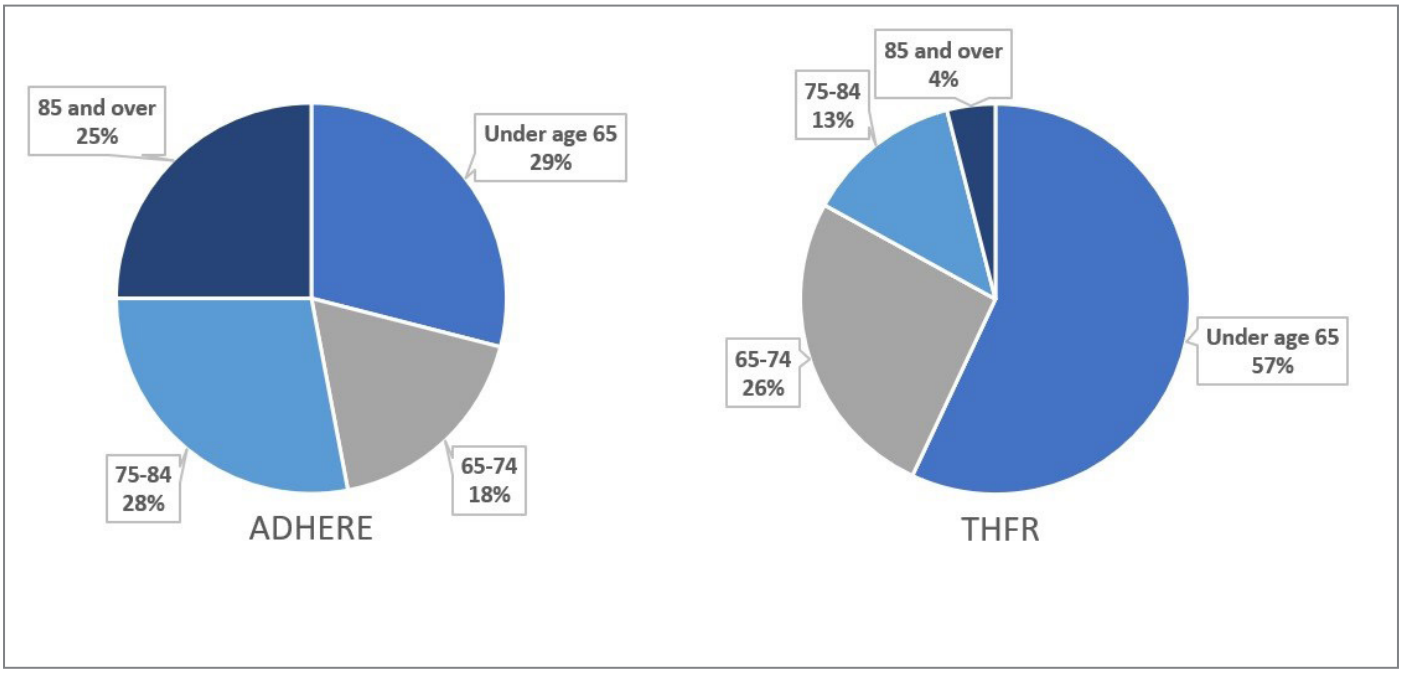


Figure 1: Age distribution – Comparison of Trivandrum Heart Failure Registry (Right) with the ADHERE registry of US (left).

Table 1: Baseline characteristics of patients in THFRy.

Variables	Total (N=1205)
Age mean (SD)	61.23 (13.68)
Women, n (%)	371 (30.79)
Etiology, n (%)	
Coronary heart disease	866 (71.87)
Dilated cardiomyopathy	156 (12.95)
Hypertrophic cardiomyopathy	27 (2.24)
Rheumatic heart disease	95 (7.88)
Diastolic heart failure	11 (0.91)
Miscellaneous	50 (4.15)
Tobacco use, n (%)	
Current use	188 (15.60)
Past use	301 (24.98)
Alcohol use, n (%)	
Current use	234 19.42)
Past use	21 (1.74)
History of hypertension, n (%)	696 (57.76)
History of diabetes, n (%)	662 (54.94)
Atrial arrythmia, n (%)	177 (14.69)
History of stroke, n (%)	75 (6.22)
History of COPD, n (%)	186 (15.44)
History of CKD, n (%)	216 (17.93)
Heart rate>100 beats/minute at admission, n (%)	720 (60.05)
NYHA Class 4 at presentation, n (%)	382 (32.87)
LV ejection fraction<35, n (%)	544 (45.15)

COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; NHYA: New York Heart Association; LV: left ventricular

One year, three-year and five year outcomes

The cumulative all-cause mortality at 1-year was 30.8% (n = 371). The reported all-cause mortality at 1-year of 30.8% is similar to the mortality reported from US and the European data. (14), (15). The cumulative 3 year mortality was 44.8%. and 5 year mortality was 58.8%(16) (Table 3). Predictors of higher mortality were lack of GDT, age, serum creatinine, and NYHA functional class IV.

Table 2: Cumulative all-cause mortality in the Trivandrum Heart Failure Registry cohort

Variable	Number (percentage) Total N=1205
In-hospital mortality	102 (8.5)
Cumulative 30-day mortality	151 (12.5)
Cumulative 90-day mortality	218 (18.1)
Cumulative 1-year mortality	371 (30.8)
Cumulative 2-year mortality	492 (40.8)
Cumulative 3-year mortality	540 (44.8)
Cumulative 5-year mortality	58.8 %

Readmissions and outcomes

The 1-year hospital readmission was 30.2% (n = 333) among the 1,103 participants discharged from the index hospitalization with no gender difference. Those patients who had readmissions had higher mortality at one-year. The impact of readmissions on outcomes was evident at the three-year follow-up also with higher mortality rates among those readmitted. Figure 2 (8).

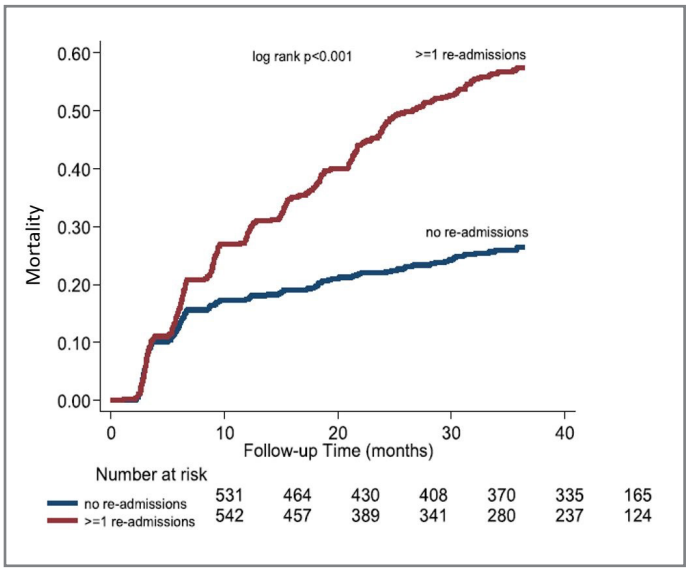


Figure 2: Long-term readmission and mortality rates in the Trivandrum Heart Failure Registry

Key points from the 5-year follow-up of the Trivandrum Heart Failure Registry

1. Higher mortality than the western population for HF patients with both reduced and preserved left ventricular ejection fraction
2. Continuing survival benefit for patients who were initiated on guideline-directed therapy
3. Re-hospitalisations are associated with higher long-term mortality.

In summary, the data from THFR shows that patients hospitalized with HF in India were younger by a decade, more likely to be men and had a higher prevalence of ischemic heart disease. The patients reported longer hospital stay at index admission, and higher in-hospital mortality compared with published data from western registries. Prescription of guideline based therapy was sub-optimal(25%) but found to improve outcomes. Lack of GDT predisposed to readmissions and re-admission was a predictor of mortality.

In view of the suboptimal rates of prescription of guideline-directed therapy, physicians and healthcare administrators should initiate quality improvement measures aimed at focused care which can improve the outcomes of patients with HF in the developing world.

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Please call or write to us:

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manojdurairaj@hotmail.com,
talha.meeran@gmail.com

Designed by Maithili Kulkarni

ABO INCOMPATIBLE HEAR... A YOUNG INFANT

ABO incompatible hea... contraindicated due to... hyper acute rejection o... anti A/anti B blood gro... Children needing heart... have very high waiting... due to paucity of suita... Children with O blood... disproportionately hig... for organs while organ... with less common gro... go waste. Complemen... fully developed in new... they don't produce iso... with absent or very lo... Thus, the factors for a... are not present in infa... children and this fact... incompatible pediatri... We present one ABO... transplant in five-mo...

A four month old boy was t... on ventilator and inotropes... Child was in cardiogenic sh... recordable pulse and bloo... Child was resuscitated wi...

Dr. Mukesh Goel

Senior Consultant, Cardiothoracic Surgery Heart & Lung Transplant Indraprastha Apollo Hospital, New Delhi

Dr Mukesh Goel completed MCh in CTVS from GB Pant ... 2001

HEART FAILURE AND HEART TRANSPLANTATION IN CHILDREN AND FOR CONGENITAL HEART DISEASE: CURRENT SCENARIO

Dr K Ganapathy Subramaniam

Dr K. Ganapathy Subramaniam is senior consultant cardiac surgeon at MGM Healthcare and visiting consultant at Institute of Child Health, Egmore. He finished his M.Ch (Cardiac Surgery) at AIIMS (New Delhi) and Pediatric Cardiac Training at Dr. K. M. Cherian unit at Frontier Lifeline and Sydney, Australia. He looks after the Pediatric and Congenital heart disease program at MGM Healthcare under the leadership of Dr. K. M. Cherian unit at MGM Healthcare and is a part of the Heart and Lung transplant Unit at MGM Healthcare under the leadership of Dr K.R. Balakrishnan.

His areas of interest include complex congenital and neonatal cardiac surgeries, Heart transplantation, Lung transplantation in Pediatric patients and in patients with Congenital heart disease and Mechanical Circulatory support

He has played an active role in setting and helping transplant programs across the country and was involved in the developing transplant program in Pune, Kolkata, Bangalore, Hyderabad, Jaipur and Vijaywada. He works along with Aishwarya Trust to make Pediatric Cardiac Surgery accessible to underprivileged people.

History and Prevalence

Heart transplantation is an accepted modality of treatment for children with heart failure refractory to medical therapy. The first Pediatric transplant for an Ebstein's anomaly was attempted by Adrian Kantrowitz in 1967 on Dec 6 (within 3 days of the first heart transplant) and the child survived for ... Leonard Bailey and his team at Loma Linda ... in much publicized Baby ... Left heart

Selection and Timing of Surgery

Selection of patients and timing of transplantation is cru... but what is even more important is the selection of the donor. Worsening activity levels not improving with me... therapy, feed intolerance, recurrent admissions for heart ... failure symptoms with need for inotropes for stabilizatio... and increasing Brain Natriuretic Peptide (BNP) levels (wh... are usually increased more than 10 times the recommend... upper normal limit at the time of transplantation) can be ... for deciding about timing for transplantation. Worsening ... abdominal pain due to hepatic congestion) is a c... pediatric population.

PRE HEART TRANSPLANT WORK UP AND OUTPATIENT POST OP CARE FOR THE PEDIATRIC HEART TRANSPLANT PATIENT

Dr Swati Garekar is a pediatric cardiologist practising at Fortis hospital Mulund Mumbai.
She completed her MBBS from Seth GS Medical college and KEM Hospital Mumbai after which she did her MD pediatrics at the Children's Hospital of Michigan, Detroit. She went on to complete her 3 year pediatric cardiac fellowship at the same institution. She is interested in echocardiography, fetal echo, 3D printing of hearts, and heart failure/transplants.

RODUCTION:

...ally, around 5000 heart transplants occur around the ... of which 500 are pediatric ones. The number of heart ...ants being performed in India is increasing and is fast ...g a practical option for our patients. This is true f... ...atric world as well. There is ...

required by the family post transplant also needs to be discussed.

3. Judging the severity ...

VALVE SURGERY AND HEART FAILURE

Dr. Chandrasekar Padmanabhan

Chair, Division of cardiothoracic surgery Director, Heart failure and transplantation, GKNM Hospital, Coimbatore

- Fellowship from the Royal Australasian College of Surgeons
- Advanced fellowship from Mayo Clinic , USA
- Member of ACS/ STS/EACTS/ HVS/ASCVTS/SIHFT/INSHLT/SCS/Mayo alumni
- Fellow of IACTS and C S Sadasivan Orator- 2020
- PI for six major trials: STICH/CORONARY/SIRS/BACE/LAAOS/PROMOTE
- Reviewer for IJCTVS/Asian Annals and EACTS- annual meeting .
- Organized live workshops for 20 consecutive years at GKNMH
- More than 25 years of experience in the practice of specialty with more than 10,000 procedures to credit
- Areas of interest: Reconstructive Valve surgery / Aortic surgery /surgery for heart f...

Preamble

...Failure (HF) is very wide and has ...

Valvular Heart Disease (VHD), especially Aortic stenos... aortic regurgitation (AR) and mitral regurgitation (MR... result in heart failure. VHD is acknowledged as a spec... disease and so most heart failure clinical trials exclud...

RIGHT HEART FAILURE IN PULMONARY H...

Dr. Prashant Bobhate

MD (Peds), FNB (Peds Card), FPVRI

Dr. Prashant Bobhate is a Paediatric Cardiologist and Pulmonary Hypertension specialist working as Consultant Paediatric Cardiologist and heading the pulmonary hypertension clinic at Kokilaben Dhirubai Ambani hospital, Mumbai. After completion of MBBS from Lokmanya Tilak Municipal Medical college and MD Paediatrics from Seth GS medical college and KEM hospital Mumbai, he did his Fellowship in Paediatric Cardiology at Fortis Escorts Heart Institute, New Delhi

Right heart failure in pulmonary hypert...

Advanced pharmacological management of PAH ha... the evaluation and management of right ventricular ... failure (RVF). RVD is defined as an abnormal structu... whereas RHF is a clinical syndrome with signs and s...

Normal RV ejection fraction (RVEF) is determined b... venous return), native contractility of the right vent... PVR), and pericardial compliance. Ejection of blood ... resistance pulmonary circulation ensures that the e... normal RV output is much less as compared to the ... sensitive to afterload, and minimal increase in the a... RVEF. (1) Patients in RHF generally exhibit elevated ... atrial pressure >8 mm Hg) and reduced cardiac ind...

Pathophysiology and clinical manifesta...

Although RV failure can be acute or chronic, in pul... chronic secondary to persistently increased afterlo... of myocyte hypertrophy and remodeling is gradua...

Chronic RV Pressur...

↓

Right ventricular dilatation

USE OF SWAN GANZ CATHETER AND HEMODYN... MONITORING IN CONGESTIVE HEART FAILURE

Dr. Bagirath Raghuraman

MD, DNB, DM

Dr. Bagirath Raghuraman is presently working as Senior Consultant interven... Transplant Cardiologist, Program Director, Heart Transplant, at Narayana Ins... Sciences, Narayana Health City, Bangalore. Apart from training in Interventio... management of heart failure and cardiac transplantation at Papworth hospit... United Kingdom. He also underwent training in the use of cardiac assist devi... The Rotenburg Cardiovascular Clinic at Fulda, Germany, he underwent trainin... management of heart failure at the University of Minnesota, Minneapolis, US... this, he underwent training in Balloon pulmonary angioplasty for Chronic thr... hypertension (CTEPH) at the Tokyo Medical University Hospital, Tokyo, Japan...

His area of expertise apart from interventional cardiology has been manage... failure, mechanical circulatory support devices, cardiac resynchronisation the... transplantation.

LUNG TRANSPLANTATION – AN OV...

Dr T. SUNDER

MS (Gen), FRCS(Eng.), FRCS (Cardiothoracic), FCCP (USA)
Director- Lung Transplantation, Apollo Hospitals, Chennai

Dr. T. Sunder currently heads and direct... Hospitals, Chennai. He graduated (1987... and got his Masters in General Surgery ... a brief period in the Department of Card... College, Chennai, he underwent further ... He qualified in Fellowship Examination ... Consultant Cardiothoracic Surgeon in E...

He joined Apollo Hospitals, Chennai in ... lung transplantation programme with his ...

His special areas of interests i... circulatory support, pulmonar... academic interests include bi...

He serves as an Associate Edit... Surgery, which is the official p... & Vascular surgeons.

He is also the Section editor fo... Practice of Cardiovascular Scie...

He is passionate about photogr... photography.

PERIOPERATIVE MANAGEMENT OF HEART TRANSPLANT PATIENTS

Dr. Manoj Kumar Sahu

Dr. Manoj Kumar Sahu is working as an Additional Professor in the Intensive Care for CTVS in all India Institute of Medical Science (AIIMS), New Delhi. He has completed his MD and DNB in Anaesthesiology & Critical Care from Banaras Hindu University, Varanasi and Diplomate National Board of Examinations, New Delhi respectively. He has been a part of the heart transplantation program of the Institute since 2012.

His interest areas are Thoracic organ transplantations, Extracorporeal membrane oxygenation and Pediatric Cardiac Intensive care.

Introduction

Heart transplantation (HTx) is accepted worldwide as a Gold Standard treatment option for End Stage Heart Disease. Heart Transplantation provides a substantial improvement in survival and quality of life. However, transplantation is not without risk, and transplant recipients will suffer some form of complication, which can range from mild to potentially fatal. Bleeding, kidney failure, primary graft dysfunction, allograft rejection, ...

glycosylated hemoglobin (HbA1c)

- Biochemistry- renal & liver function tests, Lipids, Electrolytes, amylase, lipase etc.
- Coagulation parameters – Prothrombin time, International normalisation ratio and activated partial thromboplast in time

A JOURNEY THROUGH HEART TRANSPLANTATION IN INDIA

Dr Jose Chacko Periappuram

Consultant and Head of Department of Cardiothoracic Surgery Lisie Heart Institute, Kochi, Kerala, India. Chairman, Heart Care Foundation

Padmashri Dr Jose Chacko Periappuram FRCS (Glasgow) FRCS (Edinburgh), FRCS (CTh) (UK) performed the first successful Heart Transplant in the state of Kerala, India as well as the first ever successful Heart retransplant i... the country. Other achievements include the first Beating heart, Awake Bypass and Total Arterial Revascularization surgeries in the state. He is also the Chairman of " Heart Care Foundation", a charitable trust that financially assists poor heart patients.

Introduction

Cardiac transplantation is the treatment of choice in patients with end-stage heart disease with significant symptoms and limitation of functional capacity with no medical, interventional, non-transplant surgical and device treatments options left. Also, the recipient ...

On 3 December 1967, Dr Bernard, performed the world... first successful cardiac transplant on Louis Washkansky ... Groote Schuur Hospital Cape Town, South Africa. The h... was harvested from Miss Denise Darvell who met with ... road mishap. Adrian Kantro... subsequently performed h... transplantation on 6 Dece... Chumway on 6 Janu...

THE YEAR IN CARDIAC SCIENCES 2021 – HEART FAILURE

DR Dhaval Naik

MS (Gold Medalist) DNB (CTS) India

- Cardiothoracic & Heart Transplant Surgeon
- Director, ECMO/ELSO Services, CIMS Hospital
- Cardio-Thoracic surgery training (DNB), Apollo Hospitals, Chennai, under Dr. M. R. Girinath
- Advance Fellowship in Cardiac Surgery at Royal Prince Alfred Hospital, Sydney, Australia under Dr. Matthew Bayfield and Dr. Paul Bannon
- Fellow of Minimally Invasive Cardiac Surgery at Herzzentrum, Leipzig, Germany under Dr. Mohr
- Advanced Fellowship in ECMO/ELSO in at Regensburg, Germany under Prof. Alois Philipp & Thomas Muller
- Advanced Fellowship in Heart-Lung Transplantation and Ventricular Assist. Devices in at St. Vincent's Hospital, Sydney, Australia
- First Minimally Invasive Cardiac Surgery Programme in Gujarat
- First ECMO Program in Gujarat
- Pioneer in Heart Transplantation Programme in Gujarat
- Ex. Executive Member, Indian Association of Cardiothoracic Surgeons (IACTS), India
- Treasure , ECMO Society of India
- Member, Research Committee, Abott, Serdia
- Bestowed with an award for "Excellence and Innovation in Cardiothoracic Surgery" by BER group in Singapore

CMR IN HEART FAILURE

Dr Onkar B Auti

DNB, Fellowship in Cardiac imaging, Level 3 certified in CMR (EACVI)

Dr Onkar Auti, is a Consultant Radiologi... Ruby Hall clinic, Pune.

- Specialist in Cross Sectional Cardiac... and children
- Published 10 articles in peer review...
- Author of multiple textbook chapte...
- Multiple national and few internatio...
- Involved in regular academic activit...
- Life member of Indian Radiological ...
- Executive committee member of ...

Cardiac Magnetic Resonance (CMR) im... and versatile imaging modality that pr... information in patients with suspected ... heart failure (HF) [1]. CMR is the gold s... function [2]. Moreover it provides exce... regarding segment wise myocardial wa... morphology and characterisation, stres... perfusion and viability [3–5]. Myocar...

SGLT2 INHIBITORS IN CARDIOVASCULAR DISEASES

Dr V.K. Chopra
DM, FACC, FESC, FHFA, FCSI

Dr V K Chopra
DM, FACC, FESC, FHFA, FCSI
Senior Director – Clinical Cardiology, Heart Failure & Research, Max Super - Speciality Hospital, Saket, New Delhi

- Founder President – Heart Failure Association of India 2013
- 75 papers publications in National and International Journals

Clinical Trials:

National Lead Investigator in TIMI-51, ELIXA, Red-HF, ROCKET-AF, PARAGON-, FOURIER, Odyssey East, SCORED, DAPA-HF, EMPEROR- Reduced, EMPEROR-Preserved, DARE-19, FINE-ARTS, EMPACT-MI, PARADIGM and several others.

Recent years have witnessed exciting new treatment modalities in the management of patients with HF. After ARBs, there was a long period of hiatus in the pharmacological management of heart failure leading many cardiologists to wonder if we had reached the end of neurohormonal modulation. All this changed with the publication of the results of PARADIGM1, which demonstrated remarkable benefits in HFrEF when given over and above the currently available therapies. There has been a major shift in therapies; while till now all the beneficial ... accompanying weight loss of 3-4 Kg and a dro... Hg in most people (Fig.1). Due to their unique ... of action, which is preventing the re-absorpt... filtered glucose, they do not result in hypog... in non-diabetic patients, unless being adm... some of the other anti-diabetic drugs tha... cause hypoglycemia. Though these mec... thought be responsible for their benefit ... that these are not the primary reasons of the...

TRIVANDRUM HEART FAILURE REGISTRY

Dr S Harikrishnan

MD, DM, FACC, FRCP, FIACS, FAMS
Professor of Cardiology SCTIMST, Trivandrum

Dr S Harikrishnan is currently Professor at the Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, Kerala. After Graduation from Medical College, Trivandrum, he completed post-doctoral DM training in cardiology from SCTIMST in 1998. Subsequently he got Commonwealth fellowship in Interventional Cardiology and had training in Leeds University, UK. He also had training in public health at Emory University, USA through the PH -LEADER program.

Dr Harikrishnan is primarily an interventional cardiologist but his main research interest is in heart failure. After establishing the first heart failure cohort in India, – the Trivandrum HF cohort which has completed 7 years of follow-up, he is now leading the National HF registry which is the largest in the country and has enrolled 10800 patients. He has also lead the largest pulmonary hypertension registry - the PROKERALA registry.

In 2019, Dr Harikrishnan was awarded one of the ten National Centers of Excellence in Clinical Research (CARE), established nationwide by Indian Council of Medical Research (ICMR) which includes the first HF Biobank in India. He has got more than 100 publications in international peer reviewed Journals with high impact with more than 25000 citations and an h-index of 37.

He has edited three books, which includes a unique monograph on Balloon Mitral Valvotomy, and another titled – WA RACE AGAINST TIME – describing the epidemic of cardiovascular diseases in developing economies and Manual of Heart Failure Management. He is also the founder editor of the International peer-reviewed journal - Pulmonary Circulation.

He is the fellow of the National Academy of Medical Sciences, American College of Cardiology, International Academy of Cardiovascular Sciences and Royal college of Physicians, London.

Cardiovascular diseases (CVD) has overtaken communicable diseases as the leading cause of mortality in low-income and middle-income country (LMIC) countries like India towards increasing prevalence of atherosclerotic vascular diseases and their risk factors (9). The third factor is the persisting burden of conditions like rheumatic heart disease (RHD), ...

with reduced ejection fraction (HFrEF), mildly reduced, and ...ed ejection fraction (HFpEF) is consistent ...SC Guidelines on HF. Among several other ...idations, these guidelines give a Class I ...he use of the sodium–glucose co-transporter ...dapagliflozin and empagliflozin in HFrEF ...e first evidence-based treatment for HFpEF,

...ure and Cardiomyopathies