

**Heart failure:
A difficult target for device therapy
Clinical and regulatory considerations**

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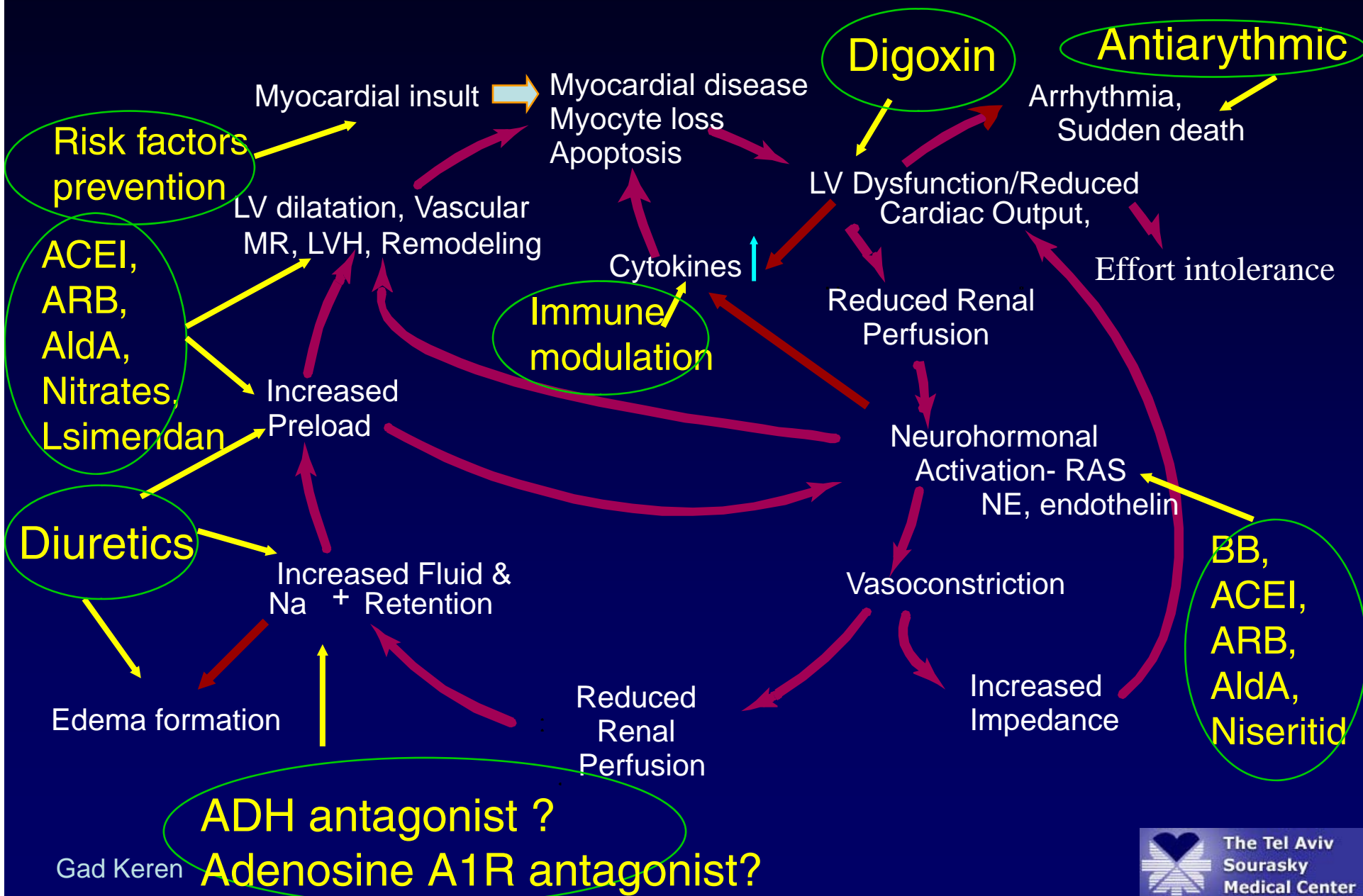
Primary objectives in the management of pts with HF

- **Improve quality of life (health status)**
 - Feel better (symptom questionnaires , NYHA)
 - Exercise more (6mWT, VO₂Max)
 - Prevent hospitalization
- **Increase survival**
- **Prevent disease progression**

Device based therapy

Pharmacotherapy

Pharmacotherapy in Low EF CHF

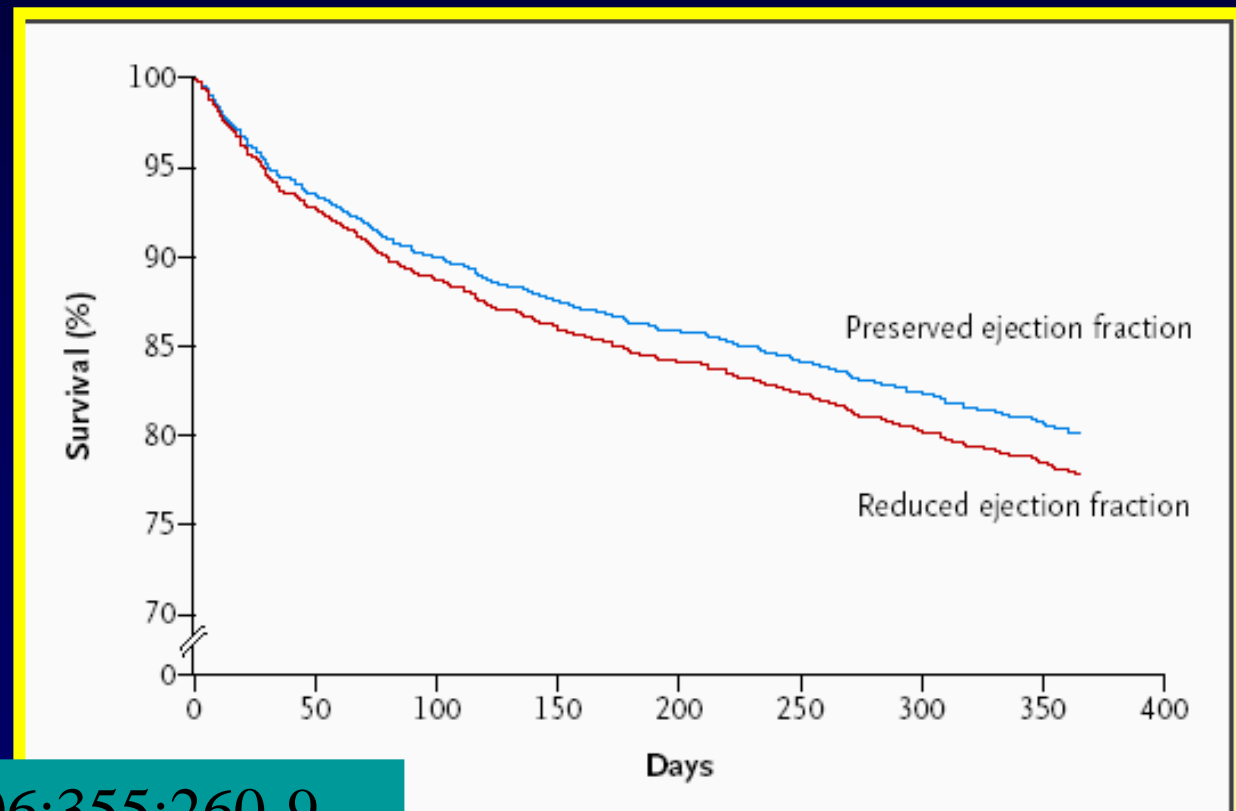


Outcome of population with new onset HF and preserved EF.

- 2802 pts with HF, 103 hospitals in Canada, F/U

- 31% of pts with HF have EF > 50%

- Survival of HF pts with normal EF is similar to low EF

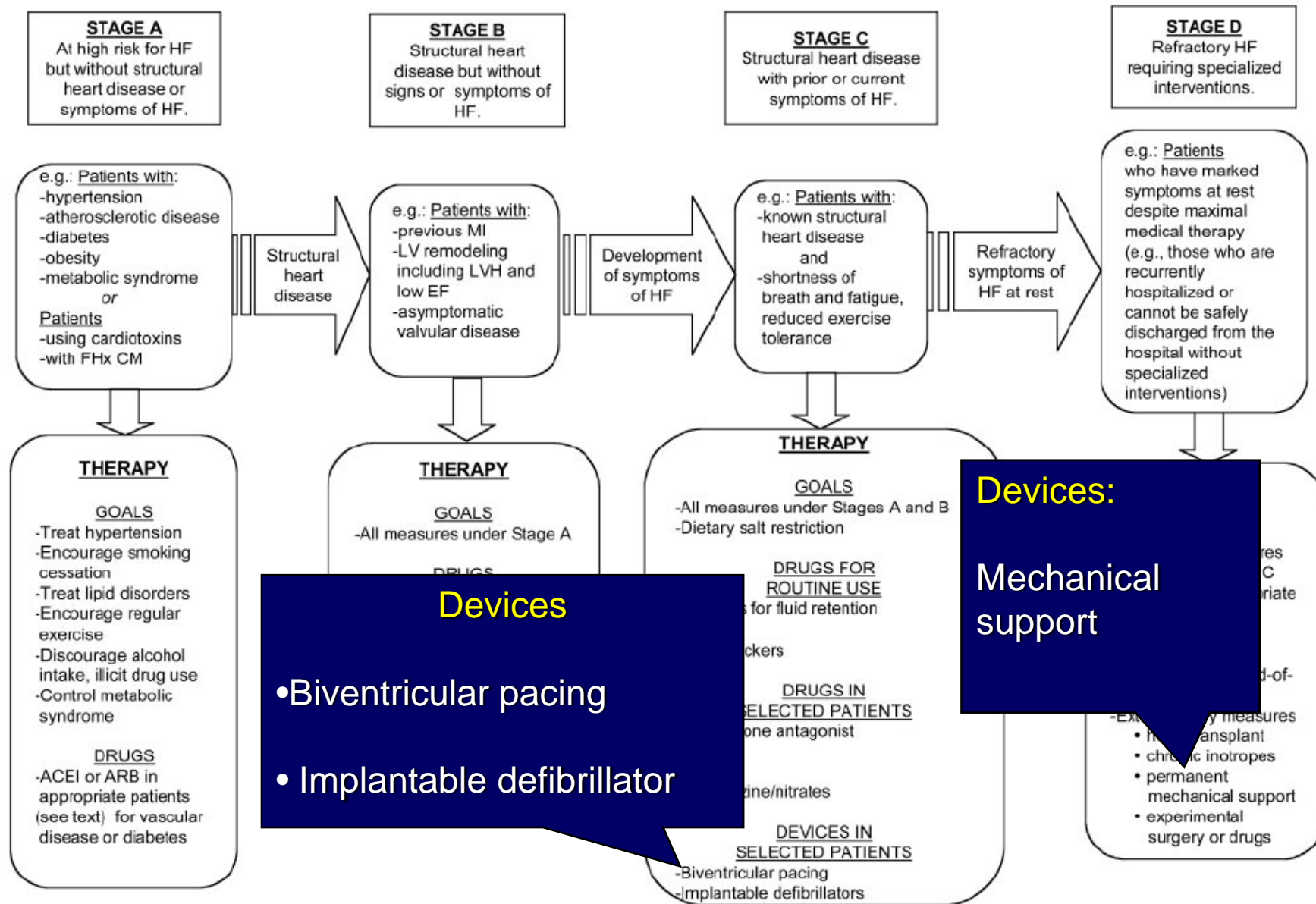


Bhatia R. NEJM 2006;355:260-9

ACC/AHA

At Risk for Heart Failure

Heart Failure



Devices

- Biventricular pacing
- Implantable defibrillator

Devices:

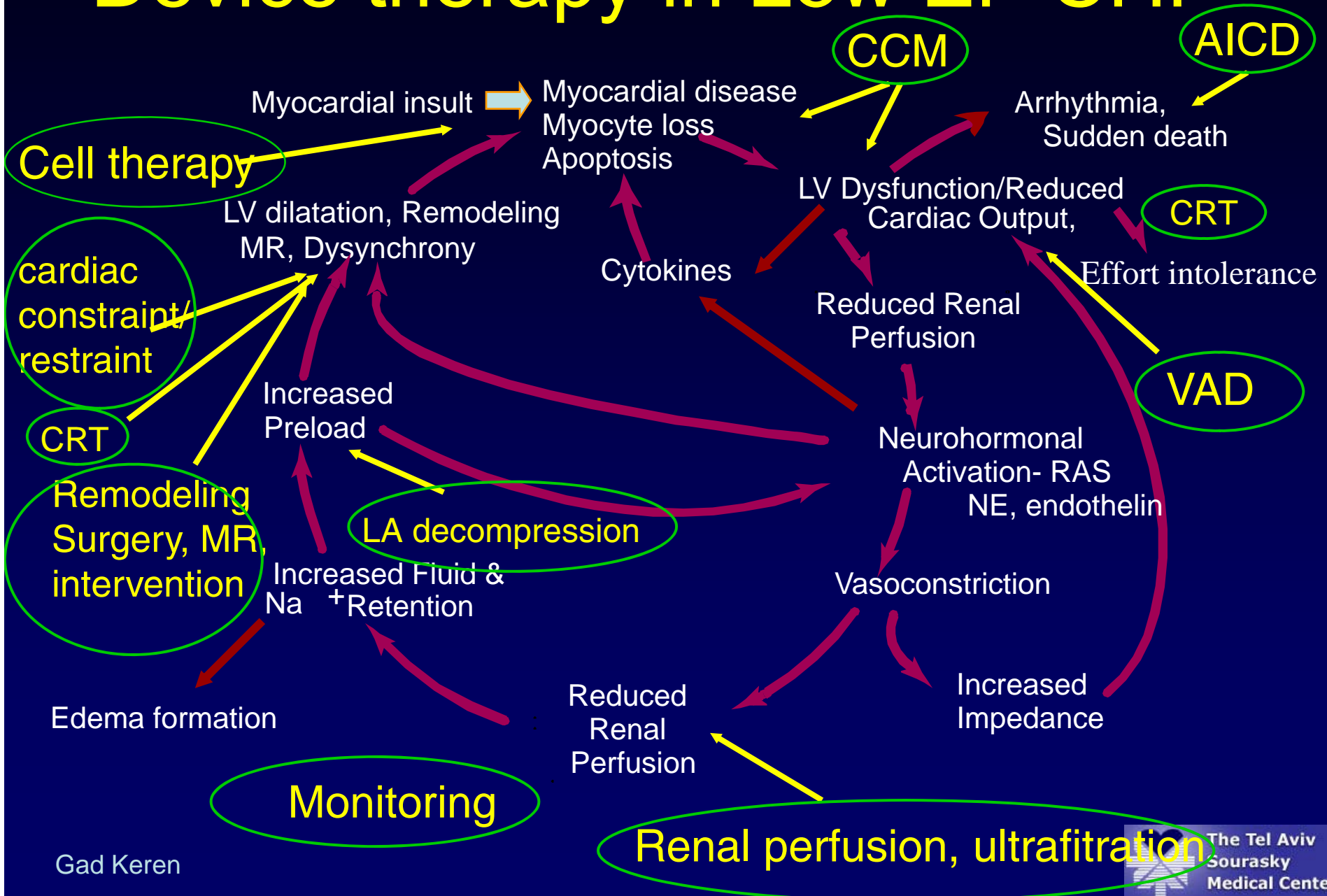
Mechanical support

Stages in the development of HF/recommended therapy by stage. FHx CM indicates family history of cardiomyopathy; ACEI, angiotensin converting enzyme inhibitors; and ARB, angiotensin receptor blocker.

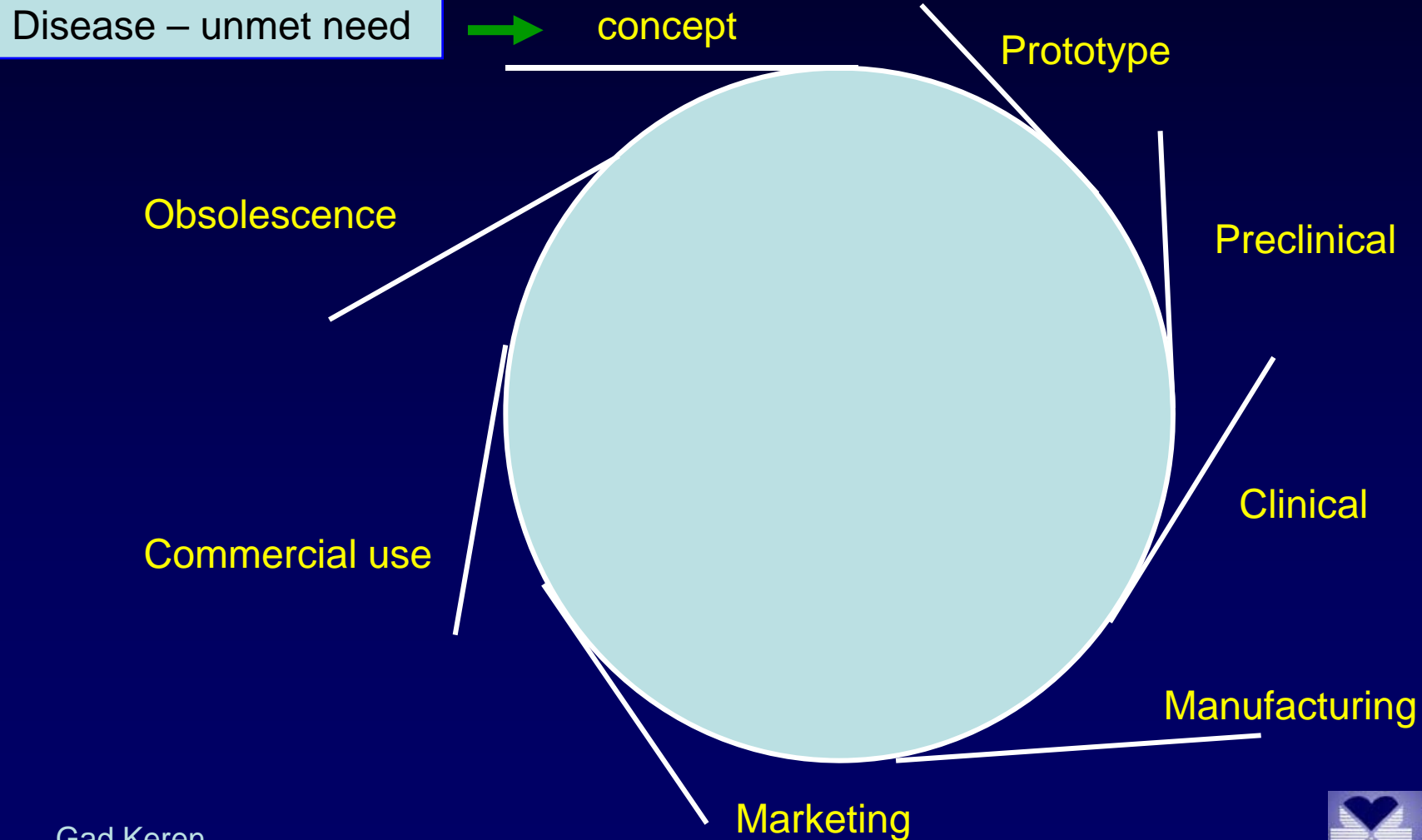
Why device based treatment for HF

- Limitations of pharmacotherapy
- Side effects of drugs
- Heart transplant- limited availability
- Proven efficacy of devices

Device therapy in Low EF CHF



Life cycle of a medical device



Implantable devices for HF expectations

- Diagnose and Monitor HF condition
- Treat rhythm disorders
- Improve mechanical efficiency of the heart
- Replacement of all or part of the heart function (Tx, cell therapy)

Novel HF devices – How do we assess their value?

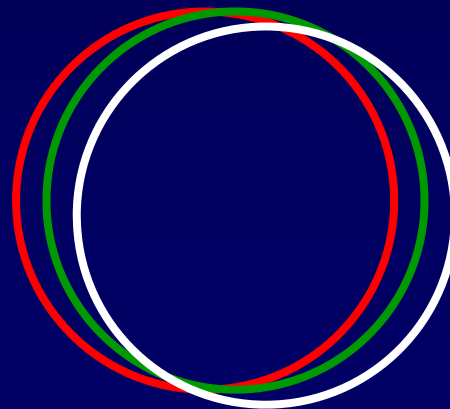
- Understand the mechanism of action
- Optimize physiologic parameters (pressures, flow)
- Improve CO (blood flow).

- Long term mortality benefit
- Improve quality of life

What are the major heart failure therapy (device) endpoints?

- Physiologic end points
- Clinical events
- Mortality

Ideally



Heart failure endpoints

Endpoint	Limitation
Mortality	Requires large sample
Symptoms (QOL/NYHA)	Potential bias
Hospitalizations	(50% not related to HF)
Exercise – (VO ₂ /6mWT)	Long term(12m) vs short term(3m)
Bio-Markers (NE/BNP)	Surrogate
LV volume/dimension	surrogate

Can surrogate markers predict clinical endpoints?

Potential surrogate endpoints in HF

- Cardiac size and LVEF
- Blood pressure
- Filling pressures
- Pulmonary artery pressure
- Cardiac output
- BNP
- Catecholamines

FDA regulation: Subpart H- section 314.510 (1992)

“FDA may grant marketing approval for a new drug on the basis of adequate and well controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic , therapeutic , pathophysiologic, or other evidence to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity”

Potential scenarios for Endpoints



Potential complications of device therapy

- Malfunction
- Infection
- Bleeding and hematoma
- Thrombus formation
- Arrhythmia
- Cardiac rupture
- Pneumothorax

Table IV. Frequency of first ICD complications (n= 539 implants)

Type of complication

Lead fracture	15 (3%)
Infection	14 (3%)
Hematoma	8 (1.5%)
Lead dislodgment	8 (1.5%)
Pneumothorax	6 (1%)
Cardiac perforation	2 (0.4%)
Total complications	62 (12%)

Lead- and device-related complications in the Antiarrhythmia Trial

Jack Kron, MD,^a John Herre, MD,^b Blair Halperin, MD,^a Michael Olarte, MS,^c Qing Yao, PhD,^c et al. College Park, Md, New York, N.Y.

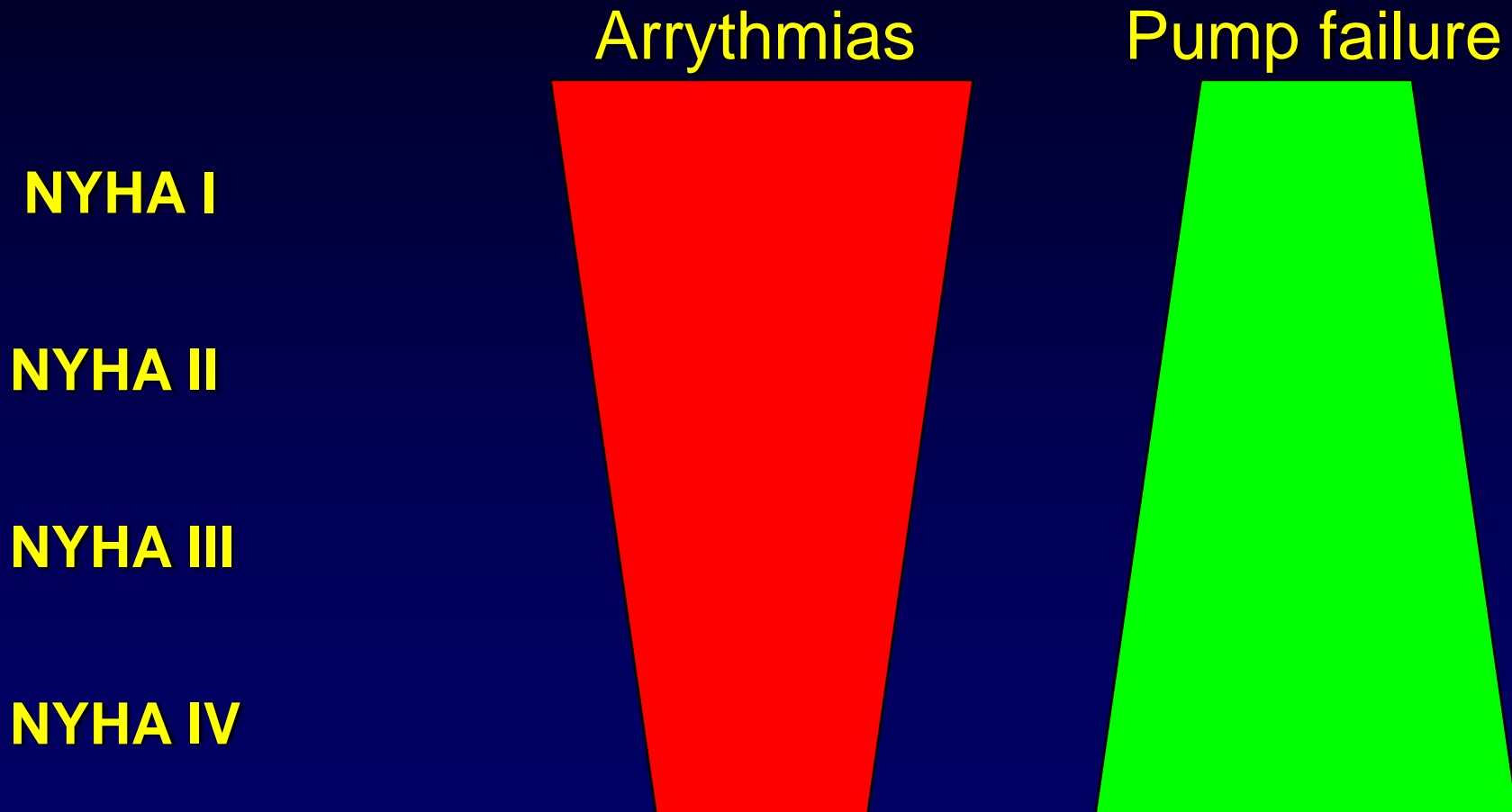
Background Implantation of an implantable cardioverter-defibrillator (ICD) approach has become routine therapy. We identify and prospectively characterize complications of Implantable Defibrillators (AVID).

Methods and Results Complications occurred either as initial treatment assignments or during follow-up. The subclavian route of insertion resulted in 46 of 339 (14%) versus 6 of 135 (4%), $P = .005$, as did the use of a thoracic generator site, 31 of 238 (13%) versus 17 of 291 (6%), $P < .02$. Most dislodgements and infections tended to occur in the 3 months after implantation, whereas lead fractures continued to occur throughout follow-up. Failure to use perioperative antibiotics was a predictor of system infection ($P = .001$).

Conclusions These data suggest that complications of ICDs are common. The continued occurrence of lead fractures suggests the need for routine ICD system surveillance. (Am Heart J 2001;141:12-8.)

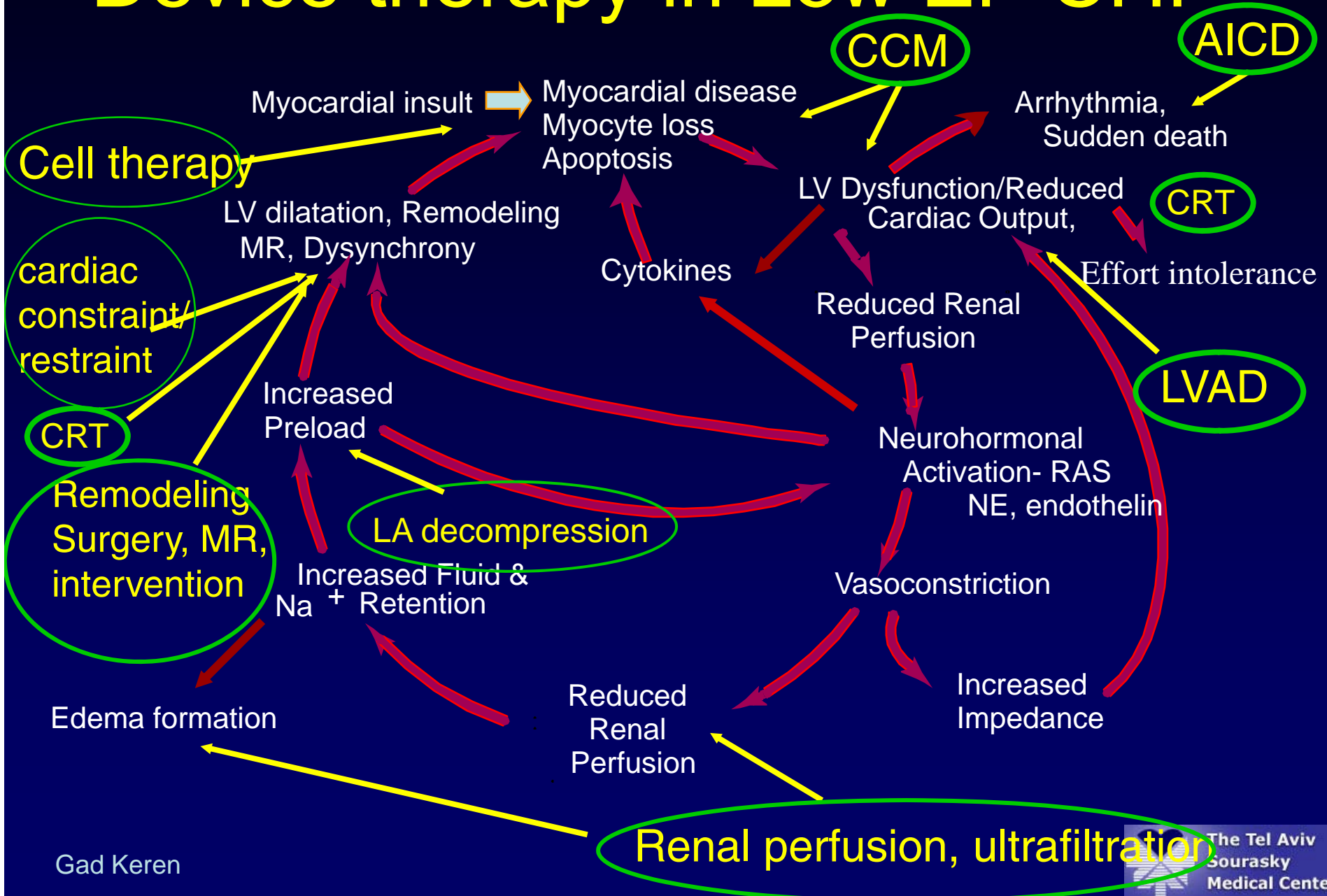
- Inappropriate shocks?!

Mechanism of death in SHF



As functional class deteriorates, death is more commonly not sudden. MERIT-HF Study Group, *Lancet* 1999.

Device therapy in Low EF CHF



Effect of CRT alone or CRT-D in severe HF low EF

- Improve exercise capacity
- Improve quality of life
- Reduce HF hospitalizations
- Reduce mortality

- Cazeau S et al; MUSTIC study ; NEJM 2001;344:873 (67 pts, CRT – pacing on/off)
- Abraham WT et al; MIRACLE study group, NEJM 2002;346:1845 (453 pts, 3-4 HF, CRT vs control)
- Bristow MR et al; COMPANION trial, NEJM 2004;350:2140 (1520 pts, 3-4 HF, Ischemic and non ischemic, CRT, CRTD)
- Cleland JG et al; CARE-HF trial , NEJM 2005;352:1352 (813 pts, 3-4 HF, CRT vs Medical, improve mortality)

- Detect major Co-morbidities and Precipitating Factors
- Non-cardiovascular**
 - Anemia
 - Pulmonary disease
 - Renal dysfunction
 - Thyroid dysfunction
 - Diabetes
 - Cardiovascular**
 - Ischemia/CAD
 - Hypertension
 - Valvular dysfunction
 - Diastolic dysfunction
 - Atrial fibrillation
 - Ventricular dysrhythmia
 - Bradycardia

Symptomatic heart failure + reduced ejection fraction

Diuretic + ACE inhibitor (or ARB)
Titrate to clinical stability

Betablocker

Persisting signs and symptoms?

Yes

No

ADD aldosterone antagonist OR ARB

Persisting symptoms?

Yes

No

QRS duration > 120 msec?

Yes

No

LV ejection fraction < 35%?

Yes

No

Consider: CRT or CRT-D

Consider: digoxin, hydralazine/nitrate LVAD, transplantation

For the and Ch

Consider ICD

No further treatment

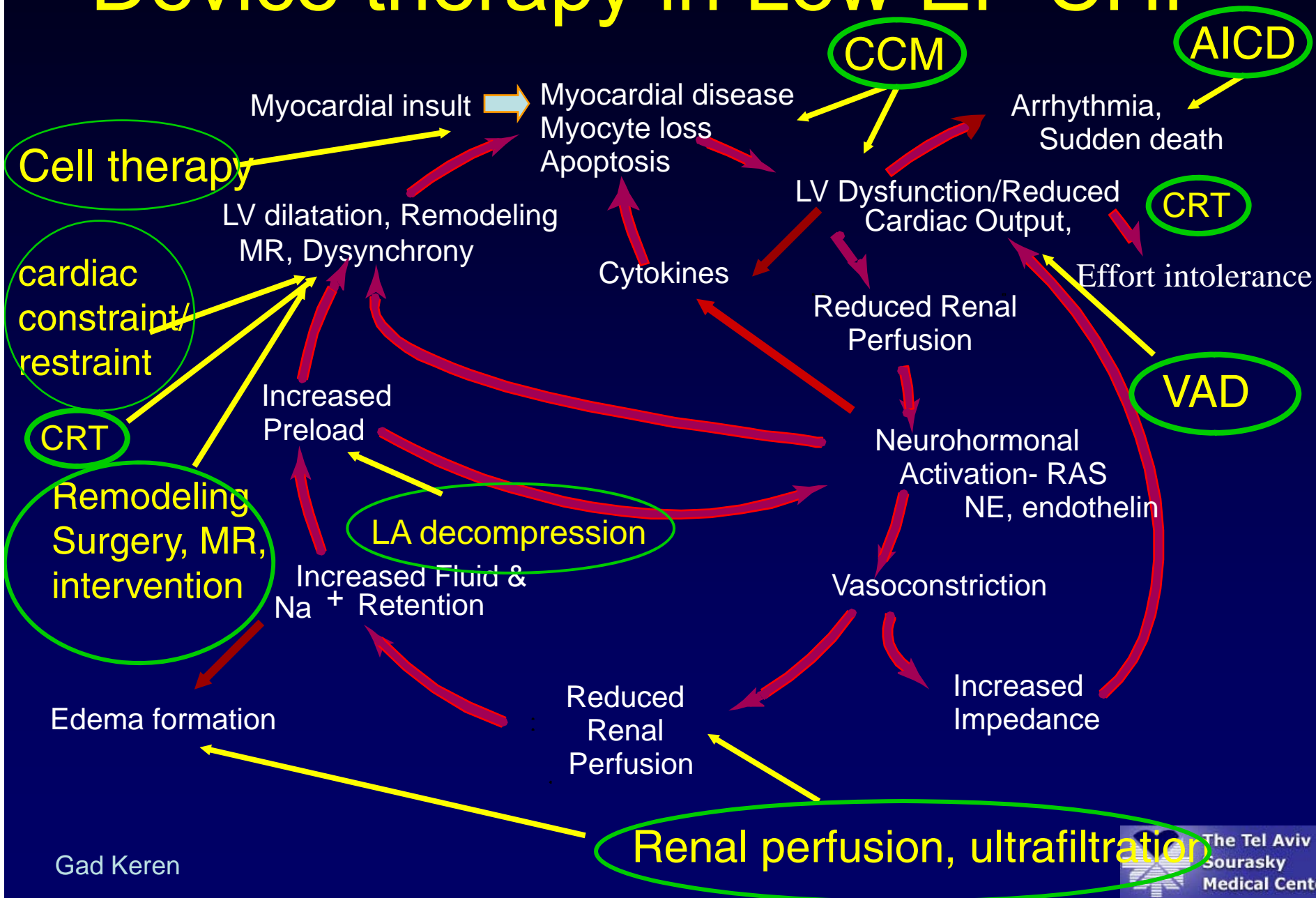
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CRT + D: open issues

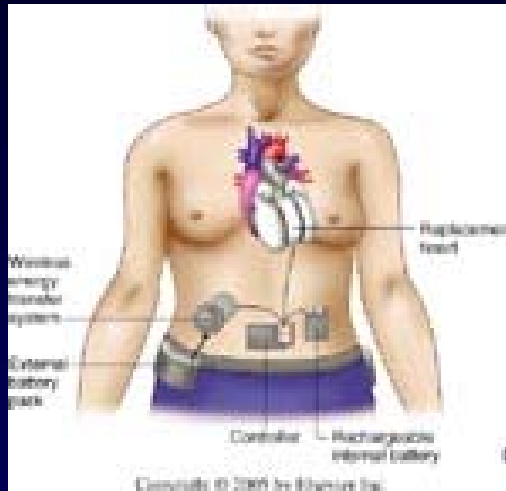
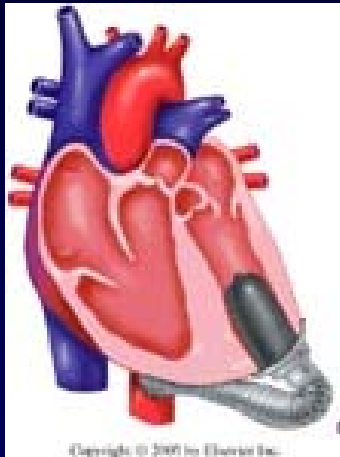
- Recent data suggest that CRT may be beneficial in lower NYHA class pts and this is further explored – (MADIT + CRT)
- The therapeutic potential in narrow QRS HF pts is still explored (Echo-CRT for desynchrony) even though RethinQ showed negative results.

Device therapy in Low EF CHF



Various pumps and LVADs

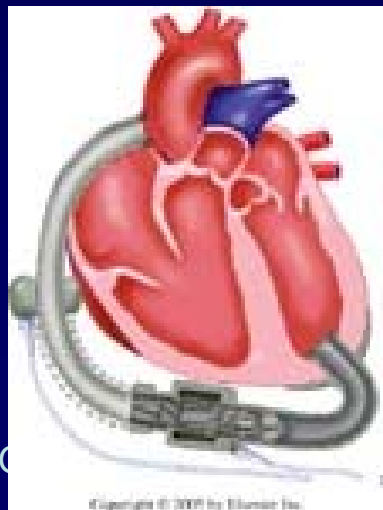
Jarvick 2000



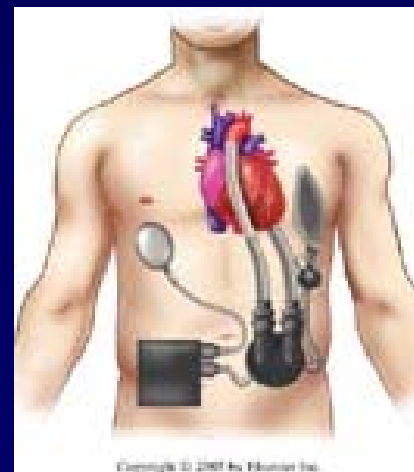
Abiocor – total artificial heart



Heartmate – Thoratec LVAD



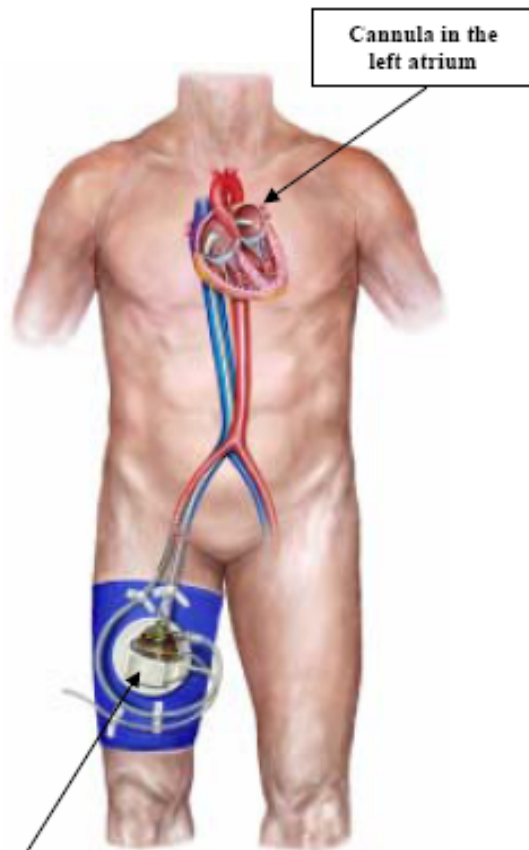
Micromed – DeBakey axial flow pump



Arrow – Lionheart

Percutaneous temporary ventricular assist devices

A

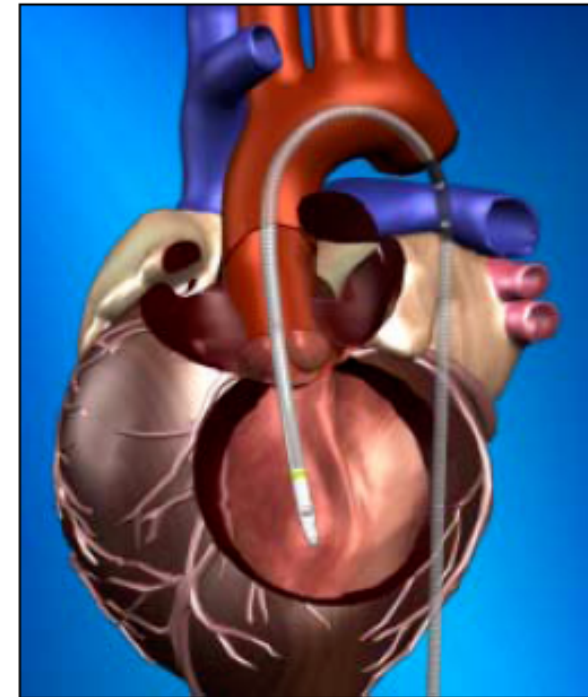


Tandem Heart
pVAD

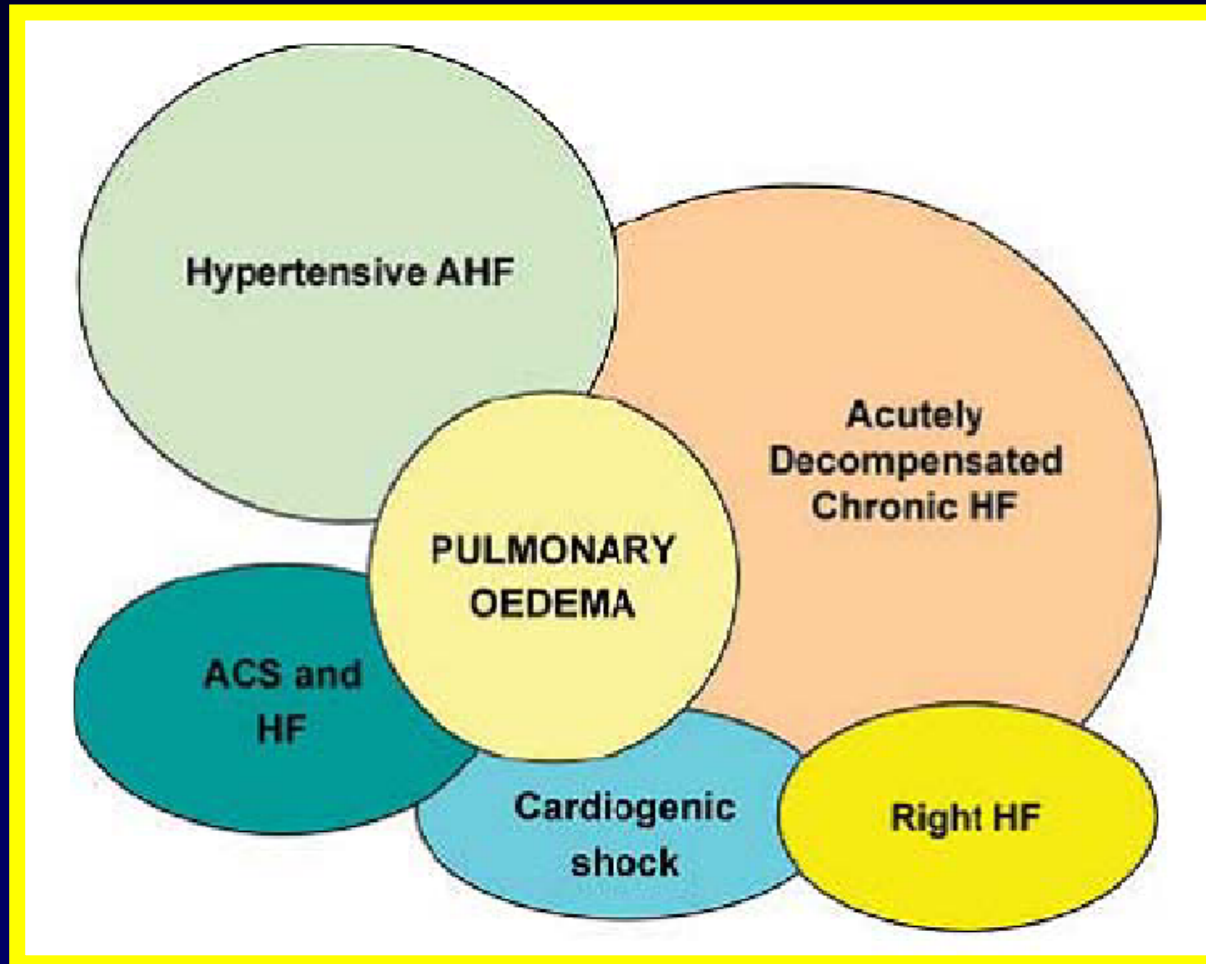
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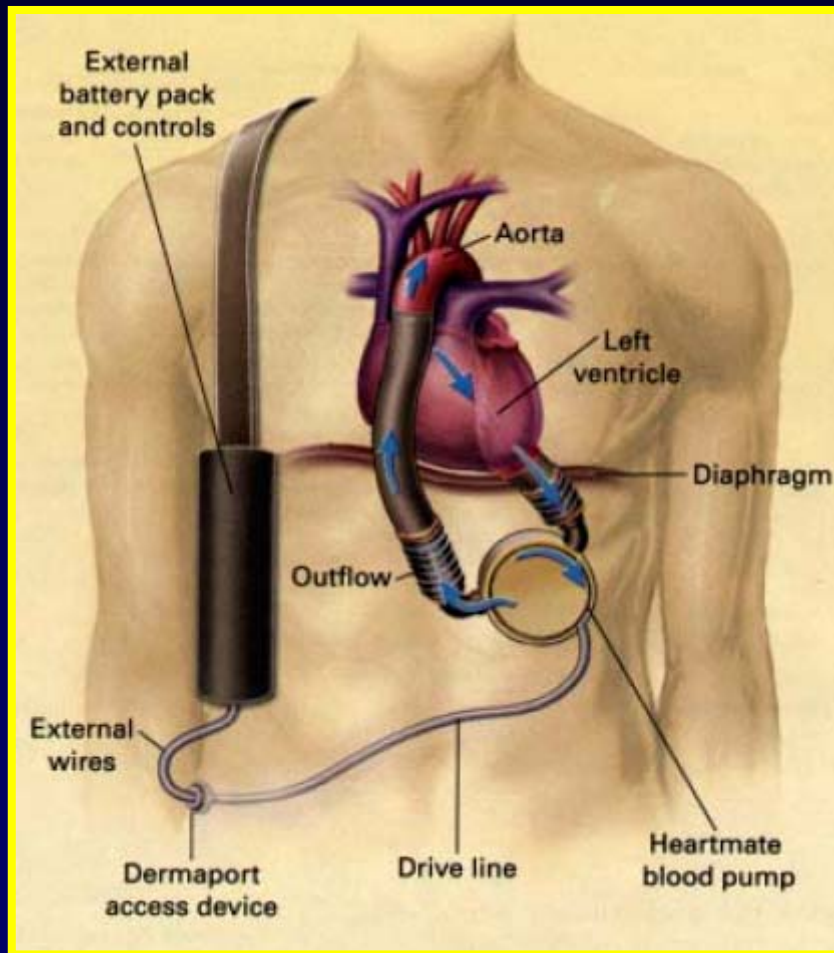
C



Classification of acute HF

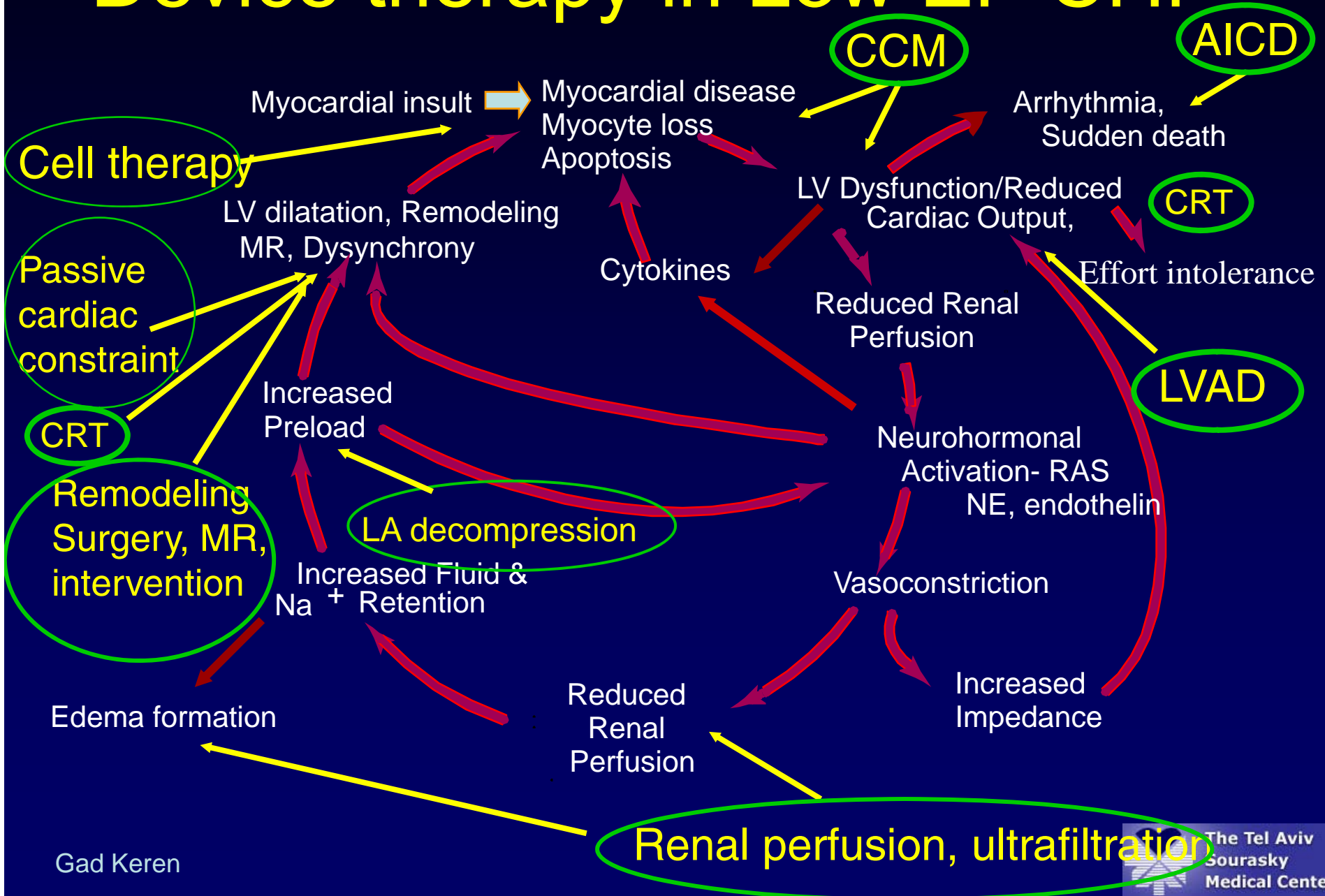


LVAD as a bridge to heart transplantation or destination therapy



- Restore BP and CO (5.0 l/min at rest)
- Improve end organ perfusion
- Improve survival to transplantation
- Provide pressure and volume unloading of the heart.
- In some pts – LV function and clinical improvement

Device therapy in Low EF CHF

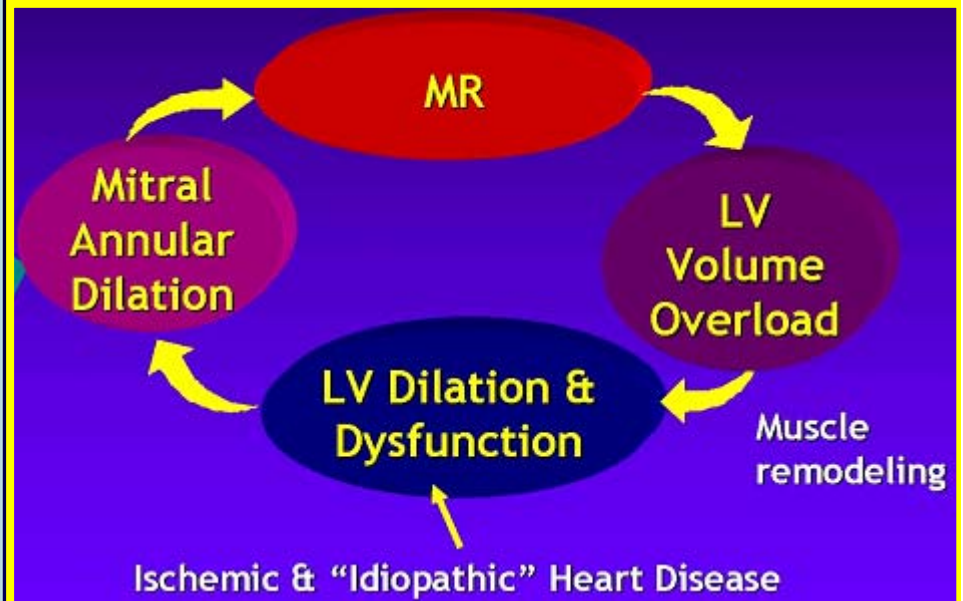
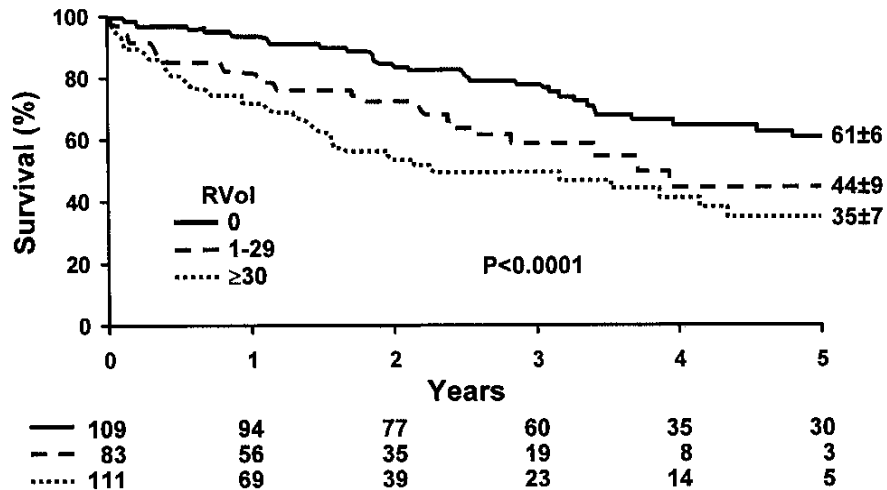
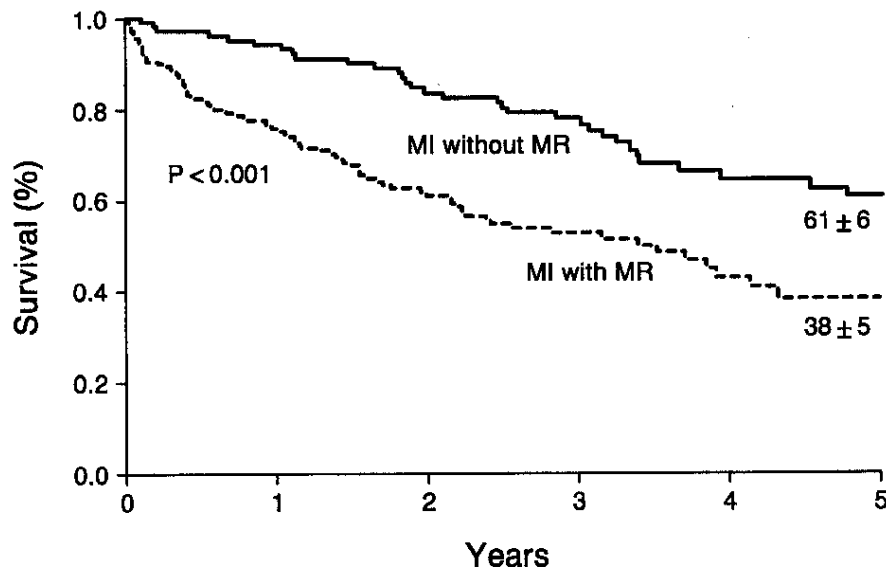


Ultrafiltration

- Efficient removal of excess water and sodium.
- Improved hemodynamic parameters.
- Improved hyponatremia. (Decrease of excess ADH?).
- Decrease PRA and Norepinephrine.
- Improved renal excretion of water and Sodium.
- Shown in RAPID-CHF and UNOLAD trials

Ultrafiltrate Removed (mL)	Weight (kg)			Duration of Therapy (h:mm)	Met Study Endpoints
	Pre	Post	Change		
2415±788	98.8±21	96.5±20	-2.3±2.7	6:30±1:38	100%

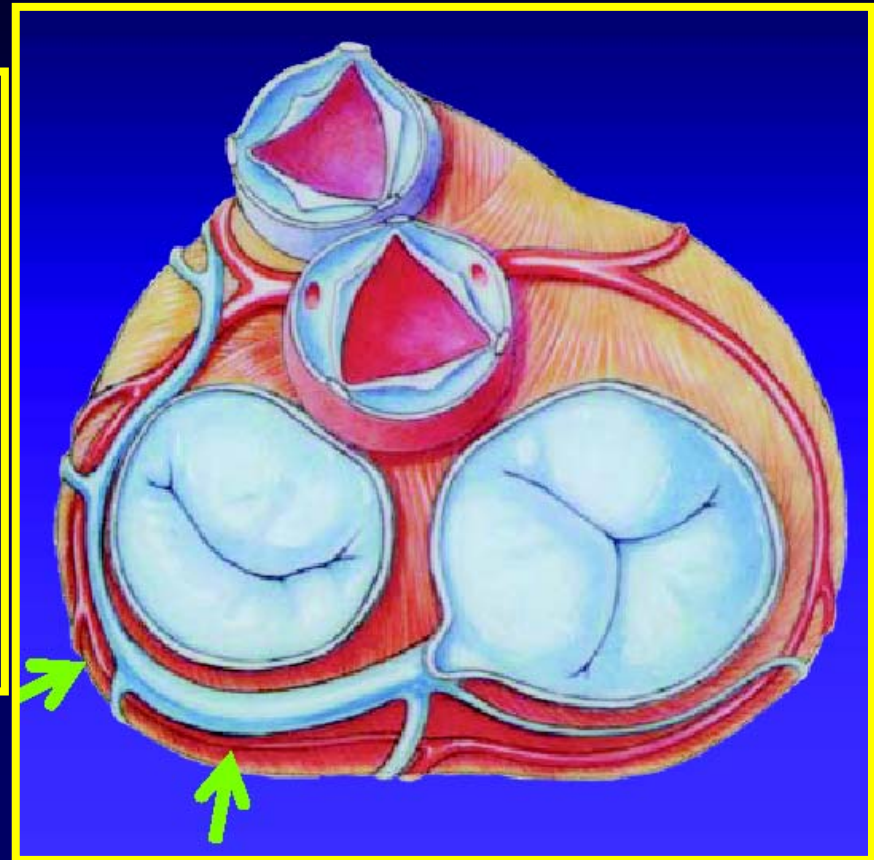
Functional MR



- Medical
- Surgical

Experimental Percutaneous MR repair

- **Annuloplasty approaches**
 - Coronary sinus
 - Transventricular
 - Transatrial
- **Edge to edge approaches**
 - Clip
 - Suture

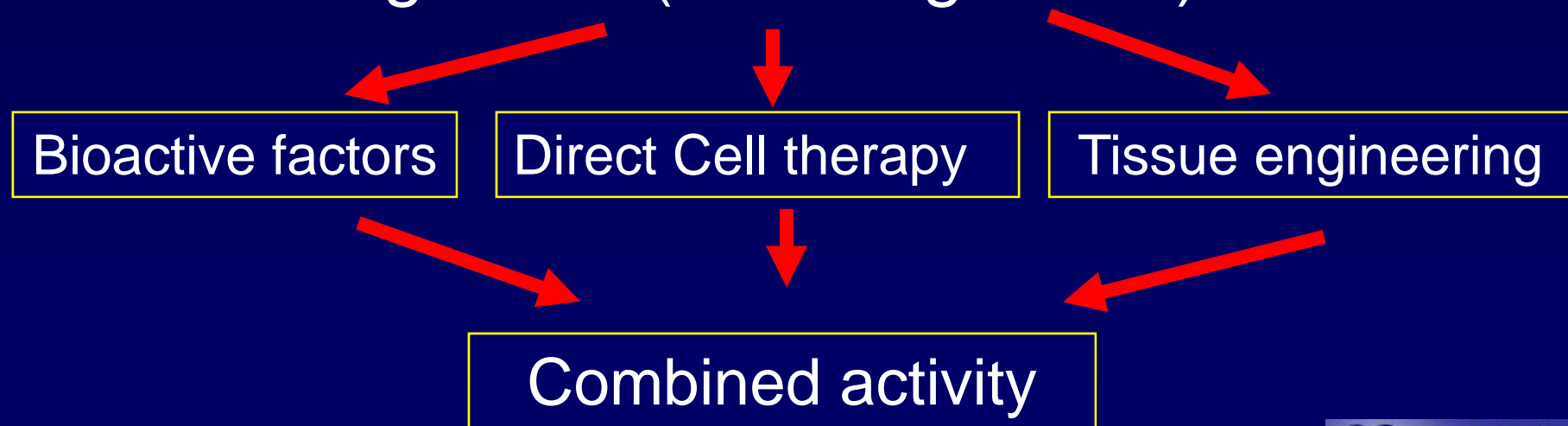


Mirtaclip – EVEREST 1 and 2 – update from TCT 2008

- Recruitment completed
- +3/4 MR, mostly degenerative disease
- MR reduced to < +2 (endpoint)
- % 70 <surgery free at 12 m.
- Improved or stable NYHA Class in most pts
- Significant reverse left ventricular remodeling
- MR reduction was durable in most pts

Goal of cell therapy in the heart

- Increase number / function of contracting cells
- Synchronize contraction with native cardiomyocytes
- Develop an extended vasculature to improve blood supply to ischemic areas or newly functioning areas (vasculogenesis).



Diagnosis Monitoring

Biomarkers,
home based
devices, imaging

CHF

Pharmacotherapy

Myocyte preservation,
improved contraction,
neurohumoral blockade,
kidney preservation,
enhancement of cell
recruitment and engraftment



Device based therapy

Pump function, valve
function, kidney
perfusion, cell and
drug delivery



Cell therapy

Recruitment,
implantation,
engraftment,
functional
enhancement of
potentially
contracting cells,
vasculogenesis

