New Pharmacological Developments In Heart Failure

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Disclosures

• Presenter’s Name: Dr. Diego Delgado

• I have the Relationships with commercial interests:
  – Advisory Board/Speakers Bureau – Novartis
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  – I have received no speaker’s fee for this learning activity
Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization
Learning Objectives

• To review new pharmacological developments in heart failure.

• The understand the clinical use of new heart failure therapies.
Trend in HF

- Reduction in HF mortality (12%)
- Increase aging population
- Higher incidence of cardiac risk factors
- Higher prevalence of HF

Source: Framingham, Olmstec County, Canada (ICES)
Heart Failure Trajectory
1/3 of patients have no follow-up and they have the worst outcomes as soon as 30 days.

<table>
<thead>
<tr>
<th>Consultation within 1 year post HF hospitalization</th>
<th>GP + Spec 42%</th>
<th>Spec 1%</th>
<th>GP 24%</th>
<th>No FU 34%</th>
</tr>
</thead>
</table>

Mortality

- 30-day mortality
- 1-year mortality
Time from First Diagnosis CHF Until Consultation with a Cardiologist

Proportion of Beneficiaries Who Have Not Consulted

Time Since CHF Diagnosis (Days)

Projection of cost in US

Heindereich Circ Heart Failure 2013
Good…. but not perfect

Guideline-Directed Medical Therapy

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Decrease in Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>10</td>
</tr>
<tr>
<td>Angiotensin-receptor blocker</td>
<td>20</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>40</td>
</tr>
<tr>
<td>Mineralocorticoid-receptor blocker</td>
<td>50</td>
</tr>
</tbody>
</table>

Residual risk still exists

HF mortality remains high (50% over 5 years)
Decline In Systolic Function Leads To Activation Of Three Major Neurohormonal Systems

- **Ang**=angiotensin; **AT1R**=angiotensin II type 1 receptor; **HF**=heart failure; **NPs**=natriuretic peptides; **NPRs**=natriuretic peptide receptors; **RAAS**=renin-angiotensin-aldosterone system
Natriuretic Peptides

Natriuretic peptides
+ Bradykinin
+ Adrenomedulin

Vasodilatation
↓ Blood pressure
↓ Sympathetic tone
↓ Aldosterone levels
↓ Fibrosis
↓ Hypertrophy
↑ Natriuresis/diuresis

Neprilysin
• Neutral endopeptidase
• Breaks down vasoactive peptides
• Contributes to hypertension and HF progression

Inactive Peptides

NEP INHIBITORS
NEPRILYSIN Inhibition Must Be Accompanied By Simultaneous RAAS Blockade

NEP metabolizes Ang I and Ang II via several pathways\(^1,2\)

Inhibition of NEP alone is insufficient as it is associated with an increase in Ang II levels, counteracting the potential benefits of NEP inhibition\(^2\)

NEP inhibition must be accompanied by simultaneous RAAS blockade (e.g. AT\(_1\) receptor blockade)\(^2\)

- ACE=angiotensin converting enzyme; AT\(_1\)=angiotensin II type 1; Ang=angiotensin; NEP=neprilysin; RAAS=renin angiotensin aldosterone system
LCZ696

Complex with two active components:

- **Sacubitril**: further metabolized to the neprilysin inhibitor LBQ657

  *Plus*

- **Valsartan**: angiotensin receptor (AT1) blocker
LCZ696 Simultaneously Enhances The Beneficial Effects Of The NP System While Blocking Detrimental Effects Of The RAAS

- ANP=atrial natriuretic peptide; Ang=angiotensin; AT1 = angiotensin II type 1; BNP=B-type natriuretic peptide; cGMP=cyclic guanosine monophosphate; CNP=C-type natriuretic peptide; GTP=guanosine triphosphate; NEP=neprilysin; NP=natriuretic peptide; NPR=natriuretic peptide receptor; RAAS=renin-angiotensin-aldosterone system
Early Experience with LCZ696: HF with Preserved EF (PARAMOUNT Study)

Phase II trial
300 pts with HFP EF

Randomized 1:1 LCZ696 vs valsartan

LCZ696 had greater short-term reduction in NT pro BNP, Left atrial size, improvement in NYHA class
PARADIGM-HF: Study Design

**Single-blind active run-in period**
- Enalapril 10 mg BID*
- LCZ696 100 mg BID†
- LCZ696 200 mg BID‡

**Randomization**
- n=8442

**Double-blind Treatment period**
- LCZ696 200 mg BID‡
- Enalapril 10 mg BID§

**2 Weeks**
**1–2 Weeks**
**2–4 Weeks**

**On top of standard HFrEF therapy (excluding ACEIs and ARBs)**

**Note:** Health Canada approved corresponding doses for LCZ696 are as follows:
- LCZ696 100 mg: 48.6 mg sacubitril / 51.4 mg valsartan
- LCZ696 200 mg: 97.2 mg sacubitril / 102.8 mg valsartan

- *Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; †200 mg TDD; ‡400 mg TDD; §20 mg TDD.
Primary endpoint: Death from CV causes or first hospitalization for HF

Hazard ratio = 0.80 (95% CI: 0.73–0.87) p<0.001

NNT*=21 patients
# Safety

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with SBP &lt;90 mmHg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Elevated serum creatinine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dL</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dL</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Elevated serum potassium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/L</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/L</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Angioedema</strong> (adjudicated by a blinded expert committee)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalized without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>---</td>
</tr>
</tbody>
</table>

Fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an AE.
Angiotensin Neprilysin Inhibition
With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
Heart Rate and Heart Failure
The higher the Heart Rate, the higher the risk of CV death and HF hospitalization

- Patients on optimal contemporary treatment (Shift placebo group)

<table>
<thead>
<tr>
<th>Heart rate at baseline (bpm)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 - &lt;72</td>
<td>1.00</td>
</tr>
<tr>
<td>72 - &lt;75</td>
<td>1.15</td>
</tr>
<tr>
<td>75 - &lt;80</td>
<td>1.33</td>
</tr>
<tr>
<td>80 - &lt;87</td>
<td>1.80</td>
</tr>
<tr>
<td>≥ 87</td>
<td>2.34</td>
</tr>
</tbody>
</table>

Risk increases by 3% per 1-bpm increase
16% per 5-bpm increase
Early benefits: CV mortality and HF hospitalization (primary endpoint)

The curves for ivabradine and placebo begin to diverge at 3 months, and the difference is statistically significant at 6 months.

Swedberg S et al., Lancet 2010, 376, 875-885
Early CV mortality benefits in patients with high HR (≥75bpm)

Cumulative frequency (%)

HR = 0.83 (0.71-0.97)
P = 0.0166

- All-cause mortality: 17% reduction, (p<0.0109)
- HF mortality: 39% reduction, (p<0.0006)

Bohm M et al., Clin Res Cardiol, 2013, 102, 11-22
**Comparison: LCZ696 and Ivabradine**

**Ivabradine- Chronic HF**

- Add on therapy
  - Little evidence for de novo HF
- Need BB titrated first
- Indicated for those in NSR and HR >70 bpm
- Limited by bradycardia
- Not affected by BP, creatinine
- One titration (5 to 7.5) at 2 week interval

**LCZ696- Chronic HF**

- Replacement for ACE/ARB
  - Little evidence for de novo HF
- Indicated for those on ACE/ARB and increased BNP
- Limited by hypotension, potassium, creatinine (< 5.2 mmol/L and eGFR ≥ 30 mL/min)
- Wash out period 36 hrs (ACEI)
- Not affected by HR
- Two titrations (50, 100, 200) for 6-12 weeks
LCZ696 and Ivabradine

- Likely clinical scenario will dictate order and use of each drug
  - For those with cardiorenal/ high K+ or hypotension, first choice Ivabradine
  - For those with borderline HR and good renal function etc, first choice LCZ696

- Over time, one or both of these drugs (more likely LCZ) will become de novo therapy
**Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction**

**Patient with LVEF <40%**

- **NYHA I**
  - SR, HR $\geq 70$ bpm
  - Continue triple therapy

- **NYHA II-IV:**
  - SR with HR $<70$ bpm or AF or pacemaker
  - ADD Ivabradine and SWITCH ACEi or ARB to LCZ696 for eligible patients

**NYHA II-IV:**

- **NYHA II-IV:**
  - SR, HR $\geq 70$ bpm
  - Continue triple therapy

- **NYHA II-IV:**
  - SR with HR $<70$ bpm or AF or pacemaker
  - ADD Ivabradine and SWITCH ACEi or ARB to LCZ696 for eligible patients

**NYHA I or LVEF >35%**

- **NYHA I-III**
  - Refer to ICD/CRT algorithm

- **NYHA IV**
  - Consider:
    - Hydralazine/nitrates
    - Referral for advanced HF therapy (mechanical transplant)
    - Advance HF referral

**NYHA I-III and LVEF $\leq 35%$**

- **NYHA I-III**
  - Refer to ICD/CRT algorithm

- **NYHA IV**
  - Consider:
    - Hydralazine/nitrates
    - Referral for advanced HF therapy (mechanical transplant)
    - Advance HF referral

**Diuretics to Relieve Congestion**

- Titrated to minimum dose to maintain euvolemia
- Reassess every 1-3 years or with clinical status change

**Advance Care Planning and Documentation of Goals of Care**

- Non-pharmacologic therapies (teaching self care, exercise)
- Consider LVEF reassessment every 1-5 years
- Reassess as needed according to clinical status
New In Heart Failure
EMPA-REG OUTCOME
Empagliflozin vs. Placebo (DM and high CV risk)

Zinman. NEJM 2016
Omecamtiv Mecarbil (selective cardiac myosin activator)

- **ATOMIC-AHF:**
  - Improved Ejection Time and Dyspnea

- **COMET-HF:**
  - Improvement Ejection time and LV size
  - NT- pro BNP reduction
Vericiguat (cGMP modulator)

- SOCRATES-REDUCED

Geroghiades. JAMA 2015
Other ongoing trials

**Serelaxin** (a recombinant form of human relaxin-2). RELAX-AHF II

**Ularitide** (a synthetic analogue of urodilatin). TRUE-AHF
The spectrum of HF

**ACC/AHA**
- **Stage A**
  - High risk, no symptoms
- **Stage B**
  - Structural disease
  - No symptoms
- **Stage C**
  - Symptomatic
- **Stage D**
  - Refractory symptoms
  - Very advanced HF

**NYHA**
- **Class I**
  - No symptoms
- **Class II**
  - Limited with activity
- **Class III**
  - Limited with less than ordinary activity
- **Class IV**
  - Severely limited any activity

**INTERMACS**
- **Walking wounded**
- **Housebound**
- Frequent hospitalizations
- Inotrope dependent
- Sliding on inotropes
- Crash and burn

**Risk of hospitalization for AHF**
Stage A

- Hypertension
- Statins in high-risk patients
- ACEI in asymptomatic HF patients
- Beta Blockers in asymptomatic HF patients with prior MI

2016 ESC guidelines
PATIENT WITH SUSPECTED HF* (non-acute onset)

ASSESSMENT OF HF PROBABILITY

1. Clinical history:
   History of CAD (MI, revascularization)
   History of arterial hypertension
   Exposition to cardiotoxic drug/radiation
   Use of diuretics
   Orthopnoea / paroxysmal nocturnal dyspnoea

2. Physical examination:
   Rales
   Bilateral ankle oedema
   Heart murmur
   Jugular venous dilatation
   Laterally displaced/broadened apical beat

3. ECG:
   Any abnormality

≥1 present

Assessment of natriuretic peptides not routinely done in clinical practice

ECHOCARDIOGRAPHY

NATRIURETIC PEPTIDES

- NT-proBNP ≥125 pg/mL
- BNP ≥35 pg/mL

All absent

HF unlikely: consider other diagnosis

No

Yes

Normal

If HF confirmed (based on all available data):
   determine aetiology and start appropriate treatment

2016 ESC guidelines
Patient with suspected AHF

Urgent phase after first medical contact

1. Cardiogenic shock?
   - Yes: Circulatory support
     - Pharmacological
     - Mechanical
   - No

2. Respiratory failure?
   - Yes: Ventilatory support
     - Oxygen
     - Non-invasive positive pressure ventilation (CPAP, BiPAP)
     - Mechanical ventilation
   - No

Immediate phase (initial 60–120 minutes)

Identification of acute aetiology:
- C: acute Coronary syndrome
- H: Hypertension emergency
- A: Arrhythmia
- M: acute Mechanical cause
- P: Pulmonary embolism

- No
- Yes: Immediate initiation of specific treatment

Immediate stabilization and transfer to ICU/CCU

Follow detailed recommendations in the specific ESC Guidelines

Diagnostic work-up to confirm AHF
Clinical evaluation to select optimal management

2016 ESC guidelines
Advanced Heart Failure

Listed for HTx

Acute Cardiogenic shock
Unknown HTx status

Ineligible for HTx

Short-term VAD support

Bridge To Transplant

Long-term Mechanical circulation support

Bridge To Decision

Bridge To Recovery

HTx, possible DT

Recovery

DT, possible HTx

Peura et al., Circ 2012
Intermacs - Implants per Year by Device Strategy
Primary Prospective Implants: June 23, 2006 to March 31, 2016

- Bridge to Transplant - Listed
- Bridge to Candidacy
- Destination Therapy
- Bridge to Recovery
- Other

Year

Number of Patients


- Bridge to Transplant - Listed: 434, 146, 1, 54, 62, 138, 161, 134, 685, 845
- Bridge to Candidacy: 165, 48, 141, 36, 141, 107, 515, 1015
- Destination Therapy: 165, 48, 141, 36, 141, 107, 515, 1015
- Bridge to Recovery: 1, 47, 1, 1, 1, 1, 1, 1
- Other: 1, 1, 1, 1, 1, 1, 1, 1
Intermacs - Kaplan-Meier Survival for Intermacs Overall
Primary Prospective Implants: June 23, 2006 to March 31, 2016

% Percent Survival

Intermacs Overall (n = 16930, Deaths = 5006)

Shaded areas indicate 70% confidence limits
p (log-rank) = N/A
Event: Death (censored at transplant or recovery)
Intermacs - Kaplan-Meier Survival by Flow Type and Device
Primary Prospective Implants: June 23, 2006 to March 31, 2016

Flow Type and Device
- Continuous - LVAD (n = 15068, Deaths = 4263)
- Continuous - BiVAD (n = 518, Deaths = 239)
- Pulsatile - LVAD (n = 612, Deaths = 241)
- Pulsatile - BiVAD (n = 348, Deaths = 136)
- Pulsatile - TAH (n = 362, Deaths = 117)

Shaded areas indicate 70% confidence limits
p (log-rank) = <.0001
Event: Death (censored at transplant or recovery)
Intermacs - Kaplan-Meier Survival for Continuous Flow LVADs (with or without RVAD implant at time of LVAD operation) by Pre-Implant Device Strategy

Primary Prospective Implants: June 23, 2006 to March 31, 2016

Shaded areas indicate 70% confidence limits
p (log-rank) = <.0001
Event: Death (censored at transplant or recovery)
Patient Selection
<table>
<thead>
<tr>
<th>PROFILE-LEVEL</th>
<th>Official Shorthand</th>
<th>General time frame for support</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERMACS LEVEL 1</td>
<td>“Crash and burn”</td>
<td>Hours</td>
</tr>
<tr>
<td>INTERMACS LEVEL 2</td>
<td>“Sliding fast”</td>
<td>Days to week</td>
</tr>
<tr>
<td>INTERMACS LEVEL 3</td>
<td>Stable but Dependent</td>
<td>Weeks</td>
</tr>
<tr>
<td>INTERMACS LEVEL 4</td>
<td>“Frequent flyer”</td>
<td>Weeks to few months, if baseline restored</td>
</tr>
<tr>
<td>INTERMACS LEVEL 5</td>
<td>“Housebound”</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>INTERMACS LEVEL 6</td>
<td>“Walking wounded”</td>
<td>Months, if nutrition and activity maintained</td>
</tr>
<tr>
<td>INTERMACS LEVEL 7</td>
<td>Advanced Class III</td>
<td></td>
</tr>
</tbody>
</table>
Intermacs - Kaplan-Meier Survival for Continuous Flow LVADs (with or without RVAD implant at time of LVAD operation) by Pre-Implant Patient Profile
Primary Prospective Implants: June 23, 2006 to March 31, 2016

% Percent Survival

Months After Device Implant

Pre-Implant Patient Profile
- Blue: Level 1 - Critical Cardiogenic (n = 2326, Deaths = 742)
- Red: Level 2 - Progressive Decline (n = 5710, Deaths = 1732)
- Green: Level 3 - Stable but Inotrope (n = 4848, Deaths = 1241)
- Brown: Level 4 - Resting Symptoms (n = 2080, Deaths = 608)
- Purple: Levels 5, 6, 7 - All Others (n = 608, Deaths = 175)

Shaded areas indicate 70% confidence limits
p (log-rank) = < .0001
Event: Death (censored at transplant or recovery)
Ventricular Assist Device Innovation

1st Generation
- Pulsatile Flow
- Valves
- Mechanical bearings

2nd Generation
- Continuous Flow
- Axial Design
- Bearing with mechanical pivot

3rd Generation
- Continuous Flow
- Centrifugal Design
- Noncontact bearing design

- Minaturization
- Durability
Impella

Outflow (aortic root) → Flow → MAP → Wall Tension → LVEDP and LVEDV → Mechanical Work

Inflow (ventricle) → Microvascular Resistance → Coronary Perfusion → Cardiac Power Output

MAP

- Pre-Support: 62.7 ± 19.2
- On Support: 94.4 ± 23.1
- Increase: 51% (n=143)

- Cardiac Output
  - Pre-Support: 3.4 ± 1.3
  - On Support: 5.3 ± 1.7
  - Increase: 56% (n=23)

- Cardiac Power Output
  - Pre-Support: 0.48 ± 0.17
  - On Support: 1.06 ± 0.48
  - Increase: 120% (n=23)

- PCWP
  - Pre-Support: 31.9 ± 11.1
  - On Support: 19.2 ± 9.7
  - Decrease: 40% (n=25)

End Organ Perfusion

Unloading to Myocardial Recovery
<table>
<thead>
<tr>
<th>PMCC</th>
<th>Heart-ware</th>
<th>Heart-mate II</th>
<th>Impella</th>
<th>Centrimag</th>
<th>ECMO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Durable MCS</strong></td>
<td>LV support</td>
<td>Short Term MCS – LV, RV or BiV support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Centrifugal flow</td>
<td>Axial flow</td>
<td>Axial flow</td>
<td>Centrifugal</td>
<td>Centrifugal pump in circuit</td>
</tr>
<tr>
<td><strong>Long-term support</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>7 days</td>
<td>30 days</td>
<td></td>
</tr>
<tr>
<td><strong>RV support</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>BTT</td>
<td>BTT</td>
<td>Bridge to recovery, Bridge to recovery, Post-op shock</td>
<td>Acute</td>
<td>Acute LV failure, poor oxygenation</td>
</tr>
</tbody>
</table>
Cardiac Transplantation
Adult Heart Transplants

% of Patients Bridged with Mechanical Circulatory Support* (Transplants: January 2000 – December 2013)

* LVAD, RVAD, TAH, ECMO
Adult Heart Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1982 – June 2013)

Median survival (years):

All pair-wise comparisons were significant at p < 0.05.

JHLT. 2014 Oct; 33(10): 996-1008
JHLT. 2015 Oct; 34(10): 1244-1254
Adult Heart Transplants
Kaplan-Meier Survival by Era Conditional on Survival to 1 Year (Transplants: January 1982 – June 2013)

All pair-wise comparisons were significant at $p < 0.05$ except 1992-2001 vs. 2009-6/2013.

Median survival (years):
Transplantation

• Immunosupression

• Monitoring of Rejection
Adult Heart Transplants
Induction Immunosuppression
(Transplants: January 2009 – June 2014)

Analysis is limited to patients who were alive at the time of the discharge.
Adult Heart Transplants

Maintenance Immunosuppression at Time of Follow-up (Follow-ups: January 2009 – June 2014)

Analysis is limited to patients who were alive at the time of the follow-up.

NOTE: Different patients are analyzed in Year 1 and Year 5.
Individualize Therapies

- Myocardial Cells
- Peripheral Blood Mononuclear Cells (Cargo Study)
Gene Expression Profiling

• Endomyocardial biopsy gold standard

• GEP(Allomap ®) has shown a high NPV in those with low risk

• Score of ≤ 34 has a NPV of 98.3

• Use in selected patients
Donor Derived Cell Free DNA

- DNA that originates from the donor organ and circulates in the blood of the recipient
- Elevated levels relative to normal recipient-derived background levels may indicate on-going or acute organ damage
- Combination with Allomap®?
Tailored Immunotherapy

Infection

Stable immune therapy

Rejection

Therapeutic Window
The Future in Heart Failure