Καιρός να διευρύνουμε τη θεραπεία της καρδιακής ανεπάρκειας. Μεταβολικές/μιτοχονδριακές θεραπείες

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Διευθυντής : Καθ. Καρδιολογίας, Δ.Ν. Τζιακάς
Advisory boards / Lecture fees (minor):

- Astra-Zeneca
- Bayer HealthCare
- Novartis
- Boehringer Ingelheim
- Pfizer
- Actelion
- WinMedica
- MSD
- Servier
History of HF treatment

Unmet need for novel HF treatments

Novel Treatments

Metabolic novel HF treatment
  - Pathophysiology
  - Possible treatment targets
  - Clinical trials

Mitochondrial HF treatment
  - Pathophysiology
  - Possible treatment targets
  - Clinical trials

Future Directions - Concluding remarks
History of HF treatment

3 eras of heart failure

1. **Pre-1980s**  
   Non-pharmacological era: bed rest & fluid and Na\(^+\) -restriction

2. **1980s-1990s**  
   Pharmacological era:  
   - Early: digitalis, diuretics & vasodilators  
   - Late: discovery of neurohormonal pathways  
     (ACE inhibitors, β-blockers, MRA)

3. **2000s -**  
   Device era: ICDs, CRTs, LVADs, hemodynamic monitoring
History of HF treatment
Unmet need for novel treatments

Figure 2.1. Typical progression of acute heart failure, showing a range of clinical courses.

A, good recovery after first episode followed by stable period of variable length; B, first episode not survived; C, poor recovery after first episode followed by deterioration; D, ongoing deterioration with intermittent crises and unpredictable death point.
Unmet need for novel treatments

Figure 1. Illness trajectories: A) Cancer trajectory vs B) end-stage heart or lung failure trajectory.

A) Level of functioning

- 100%: Normal activity
- 50%: Mostly sitting or lying down
- 30%: Bed-bound

Cancer trajectory:
More rapid decline in last months and weeks

Diagnosis -> Usually months to years -> Last few months to weeks -> Death

B) Level of functioning

- 100%: Normal activity
- 50%: Mostly sitting or lying down
- 30%: Bed-bound

End-stage heart or lung failure:
Gradual decline over years or months with intermittent crises or serious episodes; more frequent crises and hospitalizations in the last year

Diagnosis -> Usually years -> Last year -> Death

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Unmet need for novel treatments

Stage A
High risk with no symptoms

Stage B
Structural heart disease, no symptoms

Stage C
Structural disease, previous or current symptoms

Stage D
Refractory symptoms requiring special intervention

- Hospice
- VAD, transplantation
- Inotropes
  - Aldosterone antagonist, nesiritide
  - Consider multidisciplinary team
  - Revascularization, mitral-valve surgery
  - Cardiac resynchronization if bundle-branch block present
  - Dietary sodium restriction, diuretics, and digoxin
  - ACE inhibitors and beta-blockers in all patients
  - ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
  - Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients
  - Risk-factor reduction, patient and family education
Unmet need for novel treatments

An array of possible novel treatments

Table 2. Broad Categories of Targets for Cardiac-Focused Heart Failure Therapies

<table>
<thead>
<tr>
<th>Tissues</th>
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</thead>
<tbody>
<tr>
<td>Cardiomyocytes</td>
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<tr>
<td>Extracellular matrix</td>
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<tr>
<td>Coupling of cardiomyocyte to extracellular matrix</td>
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<tr>
<td>Circulation</td>
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<tr>
<td>Coronary macrocirculation</td>
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<tr>
<td>Coronary microcirculation</td>
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<tr>
<td>Cardiac lymphatics</td>
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<td>Whole organ coordination</td>
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<td>Myocardial scar</td>
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<tr>
<td>Focal</td>
<td></td>
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<tr>
<td>Diffuse</td>
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<tr>
<td>Valvular heart disease</td>
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<tr>
<td>Synchrony</td>
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<tr>
<td>Electric</td>
<td></td>
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<tr>
<td>Mechanical</td>
<td></td>
</tr>
<tr>
<td>Atrioventricular, interventricular, and intraventricular</td>
<td></td>
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<tr>
<td>Right ventricular function</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
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<tr>
<td>Glucose utilization</td>
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<tr>
<td><strong>Mitochondrial function</strong></td>
<td></td>
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<tr>
<td>Calcium handling</td>
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<tr>
<td>Vascular coupling</td>
<td></td>
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<tr>
<td>Venous/arterial interactions</td>
<td></td>
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<tr>
<td>Pulmonary/systemic interactions</td>
<td></td>
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<tr>
<td>Ventricular–vascular coupling</td>
<td></td>
</tr>
</tbody>
</table>

An array of possible novel treatments

**New Targets in Heart Failure**

<table>
<thead>
<tr>
<th>Target</th>
<th>Function</th>
<th>Candidate agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galectin-3</td>
<td>Immune response, inflammation, cell growth, cell differentiation, cardiac fibrosis and remodeling</td>
<td>–</td>
</tr>
<tr>
<td>ST2</td>
<td>Modifies immunologic processes, inflammation, myocardial remodeling</td>
<td>–</td>
</tr>
<tr>
<td>Adrenomedullin</td>
<td>Decreases systemic vascular resistance, promotes natriuresis and diuresis, autocrine/paracrine effector</td>
<td>–</td>
</tr>
<tr>
<td>Copeptin</td>
<td>Stress hormone, neuromodulator</td>
<td>Tolvaptan</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>Vasoconstrictor, pro-inflammatory mediator</td>
<td>Bosentan</td>
</tr>
<tr>
<td>Renin</td>
<td>Triggers reabsorption of Na⁺ and water in the kidneys</td>
<td>Aliskiren</td>
</tr>
<tr>
<td>Neprilysin</td>
<td>Degradates natriuretic peptides</td>
<td>Sacubitril (a component of LCZ696)</td>
</tr>
<tr>
<td>( I_f )</td>
<td>Controls heart rate</td>
<td>Ivabradine</td>
</tr>
<tr>
<td>Rho-kinase</td>
<td>Associated with stress fibers and focal adhesions</td>
<td>Fasudil, Y-27632</td>
</tr>
<tr>
<td>RXFP receptors</td>
<td>Vasodilation</td>
<td>Serelaxin</td>
</tr>
<tr>
<td>ErbB tyrosine kinase receptors</td>
<td>Regulates morphogenesis and organization of many tissues, cell growth, differentiation, survival of cardiac myocytes</td>
<td>Recombinant NRG-1β</td>
</tr>
<tr>
<td>Ryanodine receptors</td>
<td>Regulates heart contractility</td>
<td>JTV519</td>
</tr>
<tr>
<td>SERCA2a</td>
<td>Regulates heart contractility</td>
<td>SERCA2a gene therapy</td>
</tr>
<tr>
<td>cGMP</td>
<td>Myocardial relaxation and hypertrophy</td>
<td>–</td>
</tr>
<tr>
<td>Protein kinase G</td>
<td>Myocardial relaxation and hypertrophy</td>
<td>–</td>
</tr>
</tbody>
</table>

cGMP cyclic guanosine monophosphate, \( I_f \) funny current (pacemaker current), NRG neuregulin, RXFP relaxin family peptide, SERCA2a sarco-plasmic reticulum Ca\(^{2+}\)-ATPase2a, ST2 interleukin 1 receptor like 1
Cardiac metabolism: Pathophysiology

Metabolic signature of HF

1) Systemic and myocardial insulin resistance

2) Weight loss resulting in cachexia

3) Metabolic switch from the predominant FA oxidation for substrate utilization to generate CoA to glucose oxidation

4) Mitochondrial dysfunction in the process of downstream substrate oxidation (Krebs cycle and oxidative phosphorylation)
Cardiac metabolism: Pathophysiology

Pharmacology and Therapeutics (2017), doi:10.1016/j.pharmthera.2017.08.001
Cardiac metabolism: Pathophysiology

Anaerobic oxidation → lactate
Lipotoxicity

European Journal of Heart Failure (2016) 18, 1420–1429
Cardiac metabolism: Possible targets

1) Shift balance to glucose oxidation (blockers of fatty acid oxidation)
   - CTP-1 inhibitors (etomoxir, perhexilline)
   - Thiolase-1 inhibitors (trimetazidine, ranolazine)
   - Amiodarone

2) Stimulators of glucose oxidation
   - pyruvate, dichloroacetate
   - metformin, GIK

3) Stimulators of fatty acid oxidation
   - L-carnitine, L-propionylcarnitine
   - Fenofibrate, Gemfibrozil

4) Indirect modulators of metabolism
   - Istaroxime (SERCA-2 activator – less ATP needed for re-uptake of Calcium)
   - Omecamtive mercabil (myosin activator - increased ATP hydrolysis)

5) Anti-diabetes drugs
   - DPP-4 inhibitors / GLP-1 analogues (reducing insulin resistance)
   - SGLT-2 inhibitor (use of ketone bodies for energy production)
Cardiac metabolism: Possible targets

- Oxfenicine
- Etomoxir
- Perhexiline

- Trimetazidine
- Ranolazine

- Pyruvate

- Dichloroacetate (DCA)

- Meldonium

- L-propionylcarnitine
- L-carnitine

- Istaroxime

- Omecamtiv mecarbil

- CPT1: Decreased fatty acid oxidation, increased glucose oxidation
- Thiolase: Decreased fatty acid oxidation, increased glucose oxidation
- PDH: Increased flux through PDH, increased Krebs cycle flux, increased oxidative metabolism
- PDK1-4: Desinhibition of PDH, increased flux through PDH, increased Krebs cycle flux, increased oxidative metabolism
- γ-butyrobetaine hydroxylase: Decrease of L-carnitine synthesis, stimulate glucose oxidation
- CACT: Increased fatty acid transport across mitochondrial membrane
- NA+/K+ ATPase: Increased SERCA2a reuptake, improved calcium handling, increased contractility
- Myocardial ATPase: Increased ATP hydrolysis in the vicinity of myosin, enhancing effective myosin cross-bridge formation and duration

European Journal of Heart Failure (2016) 18, 1420–1429
Cardiac metabolism: Possible targets
# Cardiac metabolism: Trimetazidine clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Patient Cohort</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li, Li [28]</td>
<td>2016</td>
<td>RCT with follow up period of 12 weeks</td>
<td>140</td>
<td>Patients with coronary heart disease and heart failure</td>
<td>Treatment with trimetazidine and metoprolol in addition to conventional treatment compared to standard treatment alone resulted in:</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Greater improvement in BNP (t = 19.41 pg/mL, &lt;0.01)</td>
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<td></td>
<td>Improved LVEF (t = 1.683%, p &lt; 0.05)</td>
</tr>
<tr>
<td>Grajek, Michalak [29]</td>
<td>2015</td>
<td>Meta-analysis of 3 RCTs</td>
<td>326</td>
<td>Patients with heart failure of various aetiologies and stages</td>
<td>Treatment with trimetazidine compared to placebo resulted in a reduction of all-cause mortality (RR 0.283, p &lt; 0.0001)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Treatment with trimetazidine compared to conventional treatment alone resulted in:</td>
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<td></td>
<td>LVEF improvement (WMD 7.29%, p &lt; 0.01)</td>
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<td></td>
<td>Improved NYHA classification (WMD −0.55, 95% CI −0.81 − −0.28; p &lt; 0.01)</td>
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<td></td>
<td>No difference in exercise tolerance (WMD 18.58, p = 0.15)</td>
</tr>
<tr>
<td>Zhou, Chen [30]</td>
<td>2014</td>
<td>Meta-analysis of 19 RCTs</td>
<td>1042</td>
<td>Patients with heart failure of various aetiologies and stages</td>
<td>No difference in all-cause mortality (RR 0.47, 95% CI 0.12 − 1.78; p = 0.27)</td>
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<tr>
<td></td>
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<td></td>
<td>Reduction in BNP (WMD −157.08 pg/mL; CI −176.55 − 137.62; p &lt; 0.01)</td>
</tr>
<tr>
<td>Zhang et al. [22]</td>
<td>2012</td>
<td>Meta-analysis of 16 RCTs</td>
<td>884</td>
<td>Patients with heart failure of various aetiologies and stages</td>
<td>Treatment with trimetazidine compared to placebo resulted in:</td>
</tr>
<tr>
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<td></td>
<td>No difference in all-cause mortality (RR 0.47, p = 0.27)</td>
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<td>Improved LVEF (WMD 6.46%, p &lt; 0.0001)</td>
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<td>Reduced NYHA functional class (WMD −0.57, p = 0.0003)</td>
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<td>Improved exercise tolerance (WMD 63.75, p &lt; 0.0001)</td>
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<td>Downregulation of BNP (WMD −203.4 pg/mL, p = 0.0002)</td>
</tr>
<tr>
<td>Fragasso et al. [31]</td>
<td>2012</td>
<td>Multi-centre retrospective cohort study</td>
<td>669</td>
<td>Patients with systolic-diastolic heart failure with EF &lt; 45% and NYHA Class II-IV</td>
<td>Treatment with trimetazidine compared to conventional treatment alone (after propensity score was performed) resulted in:</td>
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<td></td>
<td>Mortality risk reduction (HR 0.189; 95% CI 0.079−0.454; p = 0.0002)</td>
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<td></td>
<td>Reduction in CVD death (HR 0.072; 95% CI 0.019−0.286; p = 0.0001)</td>
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<td></td>
<td>10.4% reduction in hospitalization (p &lt; 0.0005)</td>
</tr>
<tr>
<td>Gao et al. [32]</td>
<td>2011</td>
<td>Meta-analysis of 17 randomised studies</td>
<td>955</td>
<td>Patients with heart failure of various aetiologies and stages</td>
<td>Treatment with trimetazidine compared to placebo resulted in:</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Improved LVEF (WMD 7.49%, p &lt; 0.01)</td>
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<td></td>
<td></td>
<td>Reduced NYHA classification (WMD −0.41, p &lt; 0.01)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Increased exercise tolerance (WMD 30.26, p &lt; 0.01)</td>
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<td></td>
<td>Reduced mortality (RR 0.29, 95% CI 0.17−0.49; p &lt; 0.01)</td>
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<td></td>
<td>Reduced cardiovascular events and hospitalisation (RR 0.42; 95% CI 0.30−0.58; p &lt; 0.01)</td>
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</tbody>
</table>
Cardiac metabolism: Ranolazine clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Patient Cohort</th>
<th>Results</th>
</tr>
</thead>
</table>
| Murray, Colombo  | 2014 | Unblinded, non-randomised trial                   | 109             | Systolic or diastolic heart failure patients with NYHA Class II-IV | Treatment with ranolazine compared to standard heart failure therapy alone resulted in:  
Increase LVEF (>7 EFU, p < 0.001)  
Cardiovascular event rate reduction |
| Maier et al.     | 2013 | Prospective, randomised, double-blind, placebo-controlled proof-of-concept study | 20              | Patients with diastolic heart failure with preserved ejection fraction (EF > 45%) | In comparison to placebo, treatment with ranolazine in heart failure resulted in:  
Reduced left ventricular end-diastolic pressure (2.2 mmHg,  
p = 0.04)  
Reduction in cardiac output (0.3 l/min) and stroke volume (3.3 mL) (p = 0.04)  
No difference in exercise tolerance  
No difference in BNP levels |
| Morrow et al.    | 2010 | Randomised, double-blind, placebo-controlled trial | 4543            | Non-ST-segment elevation ACS patients                     | Treatment with ranolazine compared to placebo resulted in:  
13% reduction in the rate of recurrent ischemia (HR 0.87; 95% CI 0.75–0.99; p = 0.03)  
No difference in incidence of new or worsening heart failure  
No difference in exercise performance  
No change in BNP concentration |
## Cardiac metabolism: Ranolazine clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Patient Cohort</th>
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</tr>
</thead>
</table>
| Beadle et al. [50]     | 2015 | Randomised double-blind placebo-controlled trial, parallel-group study | 47              | Patients with systolic heart failure of non-ischemic etiology with NYHA class of II–IV | Treatment of perhexiline compared to placebo in heart failure resulted in: 30% increase in Pcr/ATP ratio ($p < 0.001$) (no change in placebo group) 52% of treated patients improved by 1 NYHA class compared to 20% improving in the placebo group ($p = 0.02$)  
No change in LVEF ($p = 0.68$)  
No change in BNP levels                                                                                                                                                                      |
| Abozguia et al. [51]   | 2010 | Randomised, double-blind, placebo-controlled, parallel-group trial | 46              | Patients with symptomatic exercise limitation caused by non-obstructive hypertrophic cardiomyopathy | Treatment of patients with hypertrophic cardiomyopathy with perhexiline compared to placebo resulted in:  
Improved exercise capacity (VO$_2$ increased by 2.1 mL/kg/min, $p = 0.003$)  
Reportedly less symptoms (MLHFQ score improved by 8, $p < 0.001$)  
Improved NYHA classification in more patients (67% of treated patients compared to 30% of control)  
No significant difference in ejection fraction                                                                                                                                               |
| Phan et al. [52]       | 2009 |                                                  | 151             | Patients with chronic heart failure (LVEF < 40% with NYHA class > IIb) or refractory angina | Treatment of patients with angina or heart failure with perhexiline resulted in the majority of patients reporting subjective symptom reduction (58.9%)                                                                                                           |
| Lee et al. [53]        | 2005 | Randomised double-blind placebo-controlled trial | 56              | Patient with chronic heart failure with EF < 40% and NYHA Class II or III already on optimal treatment | Treatment of with perhexiline compared to placebo in heart failure resulted in:  
Increased VO$_2$ max by 17% ($p < 0.001$) (no change in placebo group)  
Increased LVEF by 10% ($p < 0.001$) with no change in the placebo group  
Reduced symptoms of heart failure (MLHFQ score reduced by 24%, $p = 0.04$) while placebo group score was unchanged  
Mean NYHA classification improved by 21% ($p = 0.02$) with no change in the placebo group                                                                                                                                 |

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Diseases 2017, 5, 14
## Cardiac metabolism: DM clinical trials

<table>
<thead>
<tr>
<th>CV Considerations</th>
<th>Risk of Hypoglycemia</th>
<th>Class</th>
<th>Agents</th>
<th>Key CV Outcome Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV superiority demonstrated as primary end point in RCT by at least 1 agent in each class</td>
<td>Rare</td>
<td>Incretin Agents: GLP-1 Receptor Agonists</td>
<td>Liraglutide</td>
<td>LEADER&lt;sup&gt;95&lt;/sup&gt;</td>
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<tr>
<td></td>
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<td>Dulaglutide</td>
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<td>Exenatide</td>
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<tr>
<td></td>
<td>Rare</td>
<td>SGLT2 Inhibitors</td>
<td>Empagliflozin</td>
<td>EMPA-REG OUTCOME&lt;sup&gt;96&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Canagliflozin</td>
<td></td>
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<td></td>
<td></td>
<td>Dapagliflozin&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>CV safety demonstrated as primary end point in RCT by 1 or more agents in each class</td>
<td>Rare</td>
<td>Incretin Agents: DPP-4 Inhibitors&lt;sup&gt;§&lt;/sup&gt;</td>
<td>Alogliptin&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>EXAMINE&lt;sup&gt;87&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sitagliptin&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>TECOS&lt;sup&gt;88&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>Saxagliptin&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>SAVOR&lt;sup&gt;89&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>Linagliptin&lt;sup&gt;‡&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Rare</td>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>PROACTIVE&lt;sup&gt;90&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>Rosiglitazone&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>RECORD&lt;sup&gt;91&lt;/sup&gt;</td>
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<tr>
<td>Yes</td>
<td>Insulins</td>
<td>Glargine basal insulin</td>
<td></td>
<td>ORIGIN&lt;sup&gt;92&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>Other basal/bolus insulins</td>
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</tr>
<tr>
<td>CV Safety Unknown or RCT results not yet available</td>
<td>None</td>
<td>Weight Loss Agent</td>
<td>Orlistat</td>
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</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Alpha-glucosidase Inhibitors</td>
<td>Acarbose</td>
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<tr>
<td></td>
<td>Yes</td>
<td>Insulin Secretagogues: Meglitinides</td>
<td>Nateglinide</td>
<td>Repaglinide</td>
</tr>
<tr>
<td>Yes</td>
<td>Insulin Secretagogues: Sulfonylureas</td>
<td>Gliclazide</td>
<td>ADVANCE&lt;sup&gt;57,6&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glimepiride&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glyburide</td>
<td></td>
</tr>
</tbody>
</table>
Cardiac metabolism: Ketone bodies

Diagram showing the metabolic pathways involving ketone bodies. Key molecules and pathways highlighted include:
- Lipids and fatty acids
- Acyl CoAs
- Acetyl CoA
- C4-OH carnitine
- C2-carnitine
- Acyl-carnitines
- Acetyl-CoA
- TCA Cycle
- Succinate
- β-OX

Legend:
- Green: Changed in mouse HF
- Yellow: Changed in human HF

Ketone body pathways are also indicated.
Cardiac metabolism: Ketone bodies

1. Increased oxidation of ketone bodies during heart failure.
2. βOHB is a ligand for at least two cell-surface G-protein-coupled receptors.
3. Increasing the cellular pool of acetyl-CoA promotes protein acetylation.
4. βOHB promotes protein acetylation through histone deacetylases (HDAC) inhibition.

Cardiac metabolism: Amino-acids
Cardiac metabolism : Missing link

Energy efficiency via balancing metabolism

should be linked to

- Excitation / contraction coupling
- Extracellular matrix remodelling
- Ca++ handling
Mitochondria: Pathophysiology

A down-ward spiral?

Time (ages)

mt DNA mutations

ROS

Mitochondria dysfunction
Mitochondria: Pathophysiology

A down-ward spiral?

- Less energy production
- Increased ROS leak (oxidative stress)
- Calcium dysregulation
- Less resistance to ischemic insult
- Myocyte cell death
Mitochondria: Pathophysiology

Mitochondria dysfunction: less energy production

- Defects of respiratory chain (III – IV – V)
- Defects of “fuel” transporters
- Shift from FAO → glycolysis
- Defects in cardiolipin of mit. inner membrane
Mitochondria: Pathophysiology

Mitochondria dysfunction: increased ROS production

- Defects of complex I/III
- Increased activity of MAO
- Downregulation of anti-oxidative enzymes
- Leads to Cardiolipin dysfunction
- Leads to MPTP opening
Mitochondria dysfunction: increased ROS production

Increased ROS production (oxidative stress)

- Leads to Cardiolipin dysfunction
- Leads to MPTP opening
  - Respiration defects (less energy production)
  - Calcium overload
  - Increased ROS production
Mitochondria: Pathophysiology

Mitochondrion dysfunction: calcium dysregulation

- Opening of MPTP
- Mitochondrial sodium-calcium exchange components
- Mitochondrial Calcium uniporter
- Leads to ROS production
- Leads to myocyte death
Mitochondria dysfunction: myocyte death
Mitochondria: Pathophysiology

Mitochondria quality control

Mitochondria although valuable for the cell (energy production) due to their genomic “autonomy” are more susceptible to damage. Therefore, cardiomyocytes have developed a quality control system
Mitochondria: Pathophysiology

Mitochondria quality control

- Protein folding / unfolding
- Mitophagy
- Mitochondria derived vesicles
- Mitochondria fusion / fission
- Senescence (programmed cell death)
Mitochondria quality control: fusion and fission

Mitochondria are dynamic organelles that continually alter their morphology by undergoing fission to generate discrete fragmented mitochondria or fusion to form an interconnected elongated phenotype.
Mitochondria: Pathophysiology

Heart failure

Mitochondrial dysfunction
- Mitochondrial capacity
- ROS
- ETC (super) complexes
- Altered fission/fusion
- Abnormal $\text{Ca}^{2+}/\text{Na}^{+}/\text{Fe}^{2+}$
- Membrane fluidity
- Redox buffering

HFrEF
Systolic failure

HFpEF
Diastolic failure

Energy (ATP) demand  ↓ Energy (ATP) supply
Mitochondria: Possible targets

Boosting mitochondria biogenesis

Mitochondria: Possible targets

Mitochondria energy / ROS production

Mitochondria: Possible targets

Mitochondria iron hemostasis

# Mitochondria: Clinical trials

<table>
<thead>
<tr>
<th>Coenzyme Q10</th>
<th>Important component of ETC; Antioxidant</th>
<th>Mitochondrial ROS scavenging</th>
<th>FDA approved As dietary supplement</th>
<th>Phase II</th>
<th>Mortensen et al., 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>MitoQ</td>
<td>Selective mitochondria-targeted antioxidant</td>
<td>Mitochondrial ROS scavenging</td>
<td>FDA approved As dietary supplement</td>
<td>Pre-clinical data only</td>
<td>Spontaneously hypertensive rats: Reduced hypertrophy (P&lt;0.002) and reduced systolic blood pressure (P=0.0001) and improved endothelial function vs control</td>
</tr>
<tr>
<td>SS31</td>
<td>Selective mitochondria-targeted antioxidant</td>
<td>Cardiolipin stabilization; Mitochondrial ROS scavenging</td>
<td>/</td>
<td>Pre-clinical data only</td>
<td>Transverse aortic constricted mice: Reduced hypertrophy (P&lt;0.05), fibrosis (P=0.005) and abolished mitochondrial oxidative damage (P&lt;0.05) vs control</td>
</tr>
<tr>
<td>Elapipetide</td>
<td>Selective mitochondria-targeted antioxidant</td>
<td>Cardiolipin stabilization; Cardiolipin peroxidase inhibition</td>
<td>/</td>
<td>Pre-clinical data only – Phase II trials commenced</td>
<td>Canine microembolization-induced HF: Increase in LVEF (P&lt;0.05), reduced plasma BNP (P&lt;0.001) and increased ATP/ADP ratio (P&lt;0.001) vs placebo</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Xanthine oxidase inhibitor</td>
<td>Mitochondrial ROS scavenging</td>
<td>FDA approved For hyperuricemia</td>
<td>Phase II</td>
<td>Increased cardiac PCr/ATP ratio (P&lt;0.02) and mean CK flux (P&lt;0.007) vs placebo</td>
</tr>
</tbody>
</table>
## Mitochondria: Elamipretide or Bendavia Clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daubert et al. [79]</td>
<td>2016</td>
<td>Phase I randomised, placebo-controlled trial</td>
<td>36 patients with stable heart failure (EF &lt; 45% and NYHA Class II–III)</td>
<td>Heart failure treated with elamipretide compared to placebo resulted in: Reduced left ventricular end-systolic volume (between-group difference $-13.7 \pm 4.8$; $p = 0.005$) and end-diastolic volume (between-group difference $-17.9 \pm 5.2$; $p = 0.009$). Elamipretide was well tolerated with no influence on blood and pressure and heart rate.</td>
</tr>
<tr>
<td>Sabbah et al. [71]</td>
<td>2016</td>
<td>Canine experiment</td>
<td>14 dogs</td>
<td>Treatment of dogs with heart failure with elamipretide compared to intravenous saline resulted in: Improved EF (6% increase compared to pretreatment, $p &lt; 0.05$) with no change in control. Reduced end-systolic LV volume (3 mL, $p &lt; 0.05$) compared to increased volume in the control group. Increased maximum rate of ATP synthesis and increased ATP/ADP ratio ($p &lt; 0.05$). No effect on heart rate, mean aortic pressure, systemic vascular resistance or LV end-diastolic volume.</td>
</tr>
<tr>
<td>Gupta et al. [78]</td>
<td>2016</td>
<td>Canine experiment</td>
<td>14 dogs</td>
<td>Treatment of dogs with heart failure with elamipretide resulted in restoration of near normal levels of cMyBPC-S282 in the left ventricle ($p &lt; 0.05$).</td>
</tr>
<tr>
<td>Dai et al. [77]</td>
<td>2014</td>
<td>Murine experiment</td>
<td>56 rats</td>
<td>Rats treated with elamipretide compared to water after acute MI showed improved LV function and prevention of adverse left ventricle remodelling.</td>
</tr>
<tr>
<td>Sabbah et al. [80]</td>
<td>2014</td>
<td>Canine experiment</td>
<td>12 dogs</td>
<td>Dogs with heart failure treated with elamipretide compared to normal saline resulted in normalised expression of cardiolipin-remodelling genes and proteins ($p &lt; 0.05$).</td>
</tr>
</tbody>
</table>
Comparison 1. Coenzyme Q10 versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Left ventricular ejection fraction</td>
<td>2</td>
<td>60</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-2.26 [ -15.49, 10.97]</td>
</tr>
<tr>
<td>2 Exercise capacity (measured by a graded exercise evaluation using the Naughton protocol)</td>
<td>2</td>
<td>85</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>12.79 [ -140.12, 165.70]</td>
</tr>
<tr>
<td>3 Baseline and post-therapeutic serum levels of coenzyme Q10</td>
<td>3</td>
<td>112</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>1.46 [ 1.19, 1.72]</td>
</tr>
</tbody>
</table>
...more drugs on the horizon

Agents in clinical trials

- Serelaxin
- SERCA2a activator
- Novel MRA (finesterone)
- Aldosterone synthase inhibitor
- CD-NP (synthetic natriuretic peptide)
- Urocortin
- sGC stimulator
- GLP-1 R agonists

Future potential treatment targets

- Anti-inflammatory agents
  - iv immunoglobulin, pentoxifylline, plasma exchange
- Anti-inflammatory agents (TGF-β inhibitor)
- Ryanodine receptor stabilizer (JTV519)
- Gene therapy
- Nitric oxide metabolism (eNOS enhancer, sodium nitrite/nitrate)
- Matrix regulation - Cross-link breakers
- Mitochondria-targeting peptides

Slides ESC 2017, courtesy Wallner Markus
Approved for prevention and treatment of CVD

Increases
- All-cause mortality
- CV mortality

Improves mental health
- Hypertension ↓
- LDL-C & non-HDL-C ↓
- Beneficial effects on body weight & D2M

Exercise Training
- eNOS activity ↑
- ROS scavenger ↑
- NADPH Oxidase ↓
- TGF-β ↓
- Collateral formation Angiogenesis ↑
- NO bioavailability ↑
- Arterial stiffness ↓
- Endothelial function ↓
- miRNA-29
- PI3K / Akt miRNA-21

Keep moving!