HEART FAILURE

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DISCLOSURE

- Consultant / Member of Advisory Boards and Committees:
  - Bristol Myers Squibb, NILE Therapeutics, Novartis, Servier, Torrent

- Speaker:
  - AstraZeneca, BMS, GlaxoSmithKline, MSD, Menarini, Sanofi-Aventis, Servier
NEW STRATEGIES TO PREVENT REMODELING/DEATH IN STEMI

M. Ovize (Lyon, FR) «CIRCUS Trial»
REPERFUSION INJURY

Myocardial ischemia in absence of reperfusion
infarct size, 70%

Myocardial ischemia with reperfusion
Reperfusion reduces infarct size by 40%
Part of the remaining 30% infarct is due to lethal reperfusion injury and is therefore preventable

Myocardial ischemia with reperfusion and cardioprotection
Preventing lethal reperfusion injury reduces infarct size by a further 25%, realizing the full benefits of reperfusion

Infarct Size (%)
REPERFUSION INJURY CAN BE PREVENTED BY CYCLOSPORINE

STEMI < 12 hrs PCI treatment TIMI flow grade 0-1 No visible collateral

Cyclosporine (or saline) (2.5 mg/kg, IV bolus)

Day 1-3 CK / TnI release

Infarct size

Day 5 MRI

Direct stenting

CK release

Piot et al. NEJM 2008
CIRCUS TRIAL: EXPERIMENTAL DESIGN

STEMI → Coronary angiography

Coronary angiography → e-randomization

CicloMulsion®: (2.5 mg/kg, IV bolus) → PCI

PCI: Initial Echo, Discharge, Final Echo

LAD occluded (TIMI 0-1)

• 18 years
• symptom on set < 12 hrs
• ST shift ≥ 0.2 mV in two contiguous anterior leads
• LAD as culprit artery with TIMI flow grade: 0 – 1

CicloMulsion® (Neurovive Pharmaceuticals): lipid emulsion of cyclosporine (no cremophor content)

M. Ovize (Lyon, FR) FP1173
CIRCUS TRIAL CLINICAL ENDPOINTS
Death OR HF < 1 YR, CK RELEASE & LVEF

M. Ovize (Lyon, FR) FP1173
Different conditions between study groups might have influenced the outcome

- PCI procedures, stent types, thrombus aspiration, P2Y12 inhibitors, number of anterior infarctions, duration of AMI until inclusion
- Different formulations of cyclosporine (Cremophor EL versus lipid emulsion)

- Phase II versus phase III trial (type I error)
- Further RCTs to reduce reperfusion injury are needed
Peri-infarct Zone Pacing to Prevent Adverse Left Ventricular Remodeling in Patients with Large Myocardial Infarction

Results from the PRomPT Trial

G. W. Stone

Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up

G. Montalescot

Stone GW et al. Eur Heart J 2015; DOI: http://dx.doi.org/10.1093/eurheartj/ehv436, FP 7065

G. Montalescot (Paris, FR), FP 1167
Between December 2010 and October 2013, 126 patients were randomized at 27 sites in Europe, the Middle East, and the United States.

PRomPT: ENROLLMENT

- LV and RV pacing (n=41)
  - 1 withdrew
  - 1 withdrawn
  - Successful implant (n=37)
  - 1 withdrew
  - 18-month FU (n=38)
    - As-treated (n=37)
    - ITT (n=41)

- LV pacing only (n=40)
  - 1 withdrew
  - 1 withdrawn
  - Successful implant (n=38)
  - 18-month FU (n=36)
    - As-treated (n=38)
    - ITT (n=40)

- No implant (n=45)
  - 5 withdrew
  - 3 lost to FU
  - 1 missed 18-mo FU

Randomized 1:1:1

Stone GW et al. Eur Heart J 2015; DOI: http://dx.doi.org/10.1093/eurheartj/ehv436, FP 7065
Paired echocardiographic results between the baseline and 18-month follow-up visits

PRomPT: PRIMARY ENDPOINT – ΔLVEDV

Stone GW et al. Eur Heart J 2015; DOI: http://dx.doi.org/10.1093/eurheartj/ehv436, FP 7065
AMl (ST+ or ST-) in the first 72hrs

Aldosterone blockade

* iv K+ canrenoate*  
then  
spironolactone**

** Aldactone 25mg od

Randomized Open label N=1600

control

1° End Point: death, resuscitated cardiac death, VF/VT, indication for defibrillator, heart failure up to 6-month FU

G. Montalescot (Paris, FR), FP 1167
PRIMARY END POINT

Death, resuscitated death, VF/VT, indication for ICD or heart failure

HR = 0.97 [0.73-1.28]
P = 0.81

Follow-up (days)

N at risks

<table>
<thead>
<tr>
<th>Standard Therapy</th>
<th>MRA Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>801</td>
<td>802</td>
</tr>
<tr>
<td>687</td>
<td>705</td>
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<tr>
<td>669</td>
<td>683</td>
</tr>
<tr>
<td>645</td>
<td>660</td>
</tr>
<tr>
<td>273</td>
<td>183</td>
</tr>
</tbody>
</table>

MRA: Mineralocorticoid Receptor Antagonist; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia; ICD: Implantable Cardioverter Defibrillator

G. Montalescot (Paris, FR), FP 1167
DEATH IN PRE-SPECIFIED SUBGROUPS

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Death</th>
<th>Hazard ratio [95% confidence interval]</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.65 (0.30, 1.38)</td>
<td>0.57</td>
<td></td>
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<tr>
<td>Age &gt;= 65</td>
<td>0.68 (0.30, 1.54)</td>
<td></td>
<td></td>
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<tr>
<td>Age &lt; 65</td>
<td>0.34 (0.04, 3.26)</td>
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</tr>
<tr>
<td>Women</td>
<td>0.73 (0.13, 4.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.63 (0.27, 1.46)</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>0.20 (0.06, 0.70)</td>
<td>0.01</td>
<td></td>
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<tr>
<td>NSTEMI</td>
<td>3.47 (0.72, 16.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>0.50 (0.20, 1.25)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>MRA better</td>
<td>0.65 (0.10, 4.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy better</td>
<td>0.55 (0.10, 4.70)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

G. Montalescot (Paris, FR), FP 1167
GENE THERAPY IN CHRONIC HF

B. Greenberg (USA) «CUPID 2 Trial»
SERCA2a Deficiency is Central to the Progression of Heart Failure

**SERCA2a: A Critical Enzyme**
Responsible for Driving the Pumping Action of the Heart and Becomes Deficient in Patients with Heart Failure

**Restoration in End-Stage Human Heart Cells**
Can Restore Normal Contractility, Relaxation and Calcium Cycling

AAV1/SERCA2a

DNA: Inverted Terminal Repeats (ITR) Derived from AAV2
CMV Promoter
Human SERCA2a cDNA
PolyA
Endpoints

**Primary Efficacy Endpoint:** Time to recurrent HF-related hospitalizations and ambulatory WHF in presence of terminal events (all-cause death, transplant, dMCS)

**Secondary Efficacy Endpoint:** Time to first terminal event (all-cause death, transplant, dMCS)

**Exploratory Endpoints:** NYHA class, NT-proBNP, 6MWT & KCCQ QOL

**Safety Endpoints:** Disposition, clinical events; AEs including procedure-related AEs; changes in medications, vital signs & weight, physical exam, 12-lead ECG, ICD & lab parameters; time to CV-related death

CUPID 2: Primary Efficacy Endpoint Results

Of the 232 recurrent events that qualified as primary endpoints, 128 were in the placebo group and 104 were in the AAV1/SERCA2a group.

Treatment with AAV1/SERCA2a failed to improve the rate of recurrent events (HR, 0·93; 95% confidence interval [CI] 0·53 to 1·65; p=0·81).
Why did CUPID 2 fail?

- Target?
- Dose & duration?
- Delivery method?
- Patients & endpoints?
CHRONIC HEART FAILURE: PHARMACOTHERAPY & DEVICES

G Filippatos (Gr) ARTS HF
M.Cowie (UK) Serve HF
M. Bohm (D) Optilink
Finerenone (BAY 94-8862) is a novel non-steroidal MRA that has greater receptor selectivity than spironolactone and better receptor affinity than eplerenone in vitro.¹

**Study objective:** to compare the safety and efficacy of different once-daily oral doses of finerenone with eplerenone in patients who presented in emergency departments with worsening chronic HFrEF with type 2 diabetes mellitus and/or chronic kidney disease (CKD)

G. Filippatos et al. (Athens, GR) FP 3150
ARTS-HF: STUDY FLOW

Enrolment

Assessed for eligibility (n = 1286)

Randomized (n = 1066)

Allocation

Eplerenone n = 224

Finerenone 2.5–5 mg n = 173

Finerenone 5–10 mg n = 165

Finerenone 7.5–15 mg n = 169

Finerenone 10–20 mg n = 170

Finerenone 15–20 mg n = 165

Excluded (n = 220)

Did not meet inclusion criteria (n = 191)

Declined to participate (n = 21)

Other reasons (n = 8)

Follow-up

Discontinued study drug (n = 298 [AE, n = 145; death, n = 29; patient withdrawal, n = 99; other reasons, n = 25])

Completed (n = 768)

Eplerenone n = 144

Finerenone 2.5–5 mg n = 121

Finerenone 5–10 mg n = 122

Finerenone 7.5–15 mg n = 123

Finerenone 10–20 mg n = 134

Finerenone 15–20 mg n = 124

SAF

n = 221

n = 172

n = 163

n = 167

n = 169

n = 163

FAS

n = 207

n = 162

n = 157

n = 158

n = 160

n = 158

PPS

n = 131

n = 97

n = 107

n = 104

n = 115

n = 100

AE, adverse event; FAS, full analysis set; PPS, per protocol analysis set; SAF, safety analysis set

G. Filippatos et al. (Athens, GR) FP 3150
The proportion of patients who had an NT-proBNP decrease of more than 30% at day 90 compared with baseline was similar in the finerenone groups and the eplerenone group in the full analysis set.

Error bars show 90% confidence intervals NT-proBNP, N-terminal of prohormone B-type natriuretic peptide

G. Filippatos et al. (Athens, GR) FP 3150
ARTS-HF: DEATH FROM ANY CAUSE, CV HOSPITALIZATION, OR WORSENING CHF

Probability of survival (%)

Eplerenone (n = 207)

Finerenone 7.5–15 mg (n = 158)

Finerenone 2.5–5 mg (n = 162)

Finerenone 10–20 mg (n = 160)

Finerenone 5–10 mg (n = 157)

Finerenone 15–20 mg (n = 158)

Study period

Follow-up

G. Filippatos et al. (Athens, GR) FP 3150
SLEEP-DISORDERED BREATHING IN HEART FAILURE

- 50–75% of all patients with HF suffer from Sleep-Disordered Breathing
  - Obstructive sleep apnoea (OSA)
  - Central sleep apnoea (CSA) which may manifest as Cheyne–Stokes respiration
  - resulting in tissue hypoxia, repetitive arousal from sleep with increased sympathetic nervous system activity

- Small and/or uncontrolled studies (and meta-analyses) suggest multiple beneficial effects of ASV on surrogates in HF

- Post-hoc data from CANPAP(N=258) suggest that CPAP might improve mortality when CSA was controlled (AHI < 15) in HF patients with CSA and EF < 40%

SERVE-HF: ADAPTIVE SERVO-VENTILATION

- Non-invasive ventilatory therapy that supports inspiration when breathing amplitude is reduced and ensures sufficient respiration when respiratory effort is absent (Variable IPAP)

- Upper airway patency is ensured by provision of end-expiratory pressure

- Although algorithms employed by different ASV devices vary slightly, the principle of treatment is the same: back-up rate ventilation with adaptive pressure support

SERVE-HF: BASELINE

<table>
<thead>
<tr>
<th></th>
<th>Control (n=659)</th>
<th>ASV (n=666)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69.3±10.4</td>
<td>69.6±9.5</td>
</tr>
<tr>
<td>Male</td>
<td>90.0%</td>
<td>89.9%</td>
</tr>
<tr>
<td>NYHA class III or IV, n (%)</td>
<td>70.3%</td>
<td>70.5%</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>32.5±8.0</td>
<td>32.2±7.9</td>
</tr>
<tr>
<td>Ischaemic HF aetiology, n (%)</td>
<td>57.0%</td>
<td>59.7%</td>
</tr>
<tr>
<td>Implanted device, n (%)</td>
<td>55.2%</td>
<td>54.5%</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>59.3±20.8</td>
<td>57.8±21.1</td>
</tr>
<tr>
<td>Six-minute walk distance, m</td>
<td>337.9±127.5</td>
<td>334.0±126.4</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>91.5%</td>
<td>92.0%</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>92.7%</td>
<td>91.9%</td>
</tr>
<tr>
<td>Antiarrhythmics, n (%)</td>
<td>13.5%</td>
<td>19.2%</td>
</tr>
</tbody>
</table>

SERVE-HF: PRIMARY ENDPOINT NEUTRAL
TIME TO FIRST EVENT OF ALL-CAUSE DEATH, LIFE-SAVING CARDIOVASCULAR INTERVENTION, OR UNPLANNED HOSPITALIZATION FOR WORSENING CHRONIC HF

Hazard ratio, 1.13 (95% CI, 0.97-1.31)

Cumulative incidence rate (%)

Months since Randomisation

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ASV</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>77</td>
<td>52</td>
</tr>
<tr>
<td>48</td>
<td>136</td>
<td>122</td>
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<tr>
<td>36</td>
<td>222</td>
<td>197</td>
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<tr>
<td>24</td>
<td>365</td>
<td>341</td>
</tr>
<tr>
<td>12</td>
<td>463</td>
<td>435</td>
</tr>
<tr>
<td>0</td>
<td>659</td>
<td>666</td>
</tr>
</tbody>
</table>
SERVE-HF

Death from any cause

Cardiovascular Death

OPTILINK HF STUDY DESIGN

Access arm:
- **Telemedicine** guided,
- **No audible alert** for fluid retention

Control arm:
- Standard clinical assessment,
- No alert for fluid retention

Risk stratified:
- NYHA II vs. III,
- Ischemic vs. Non-Ischemic,
- Atrial Fibrillation,
- Primary vs. Secondary Prevention (VT/VF before Implant)
OPTILINK HF: PRIMARY ENDPOINT: ALL-CAUSE DEATH OR CV HOSPITALISATION

Hazard ratio = 0.867 (0.72, 1.044)  
Stratified log-rank p-value = 0.132

<table>
<thead>
<tr>
<th>Months since Randomisation</th>
<th>Control</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>0</td>
<td>497</td>
<td>505</td>
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<tr>
<td>6</td>
<td>361</td>
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<tr>
<td>12</td>
<td>302</td>
<td>310</td>
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<td>18</td>
<td>175</td>
<td>183</td>
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<tr>
<td>24</td>
<td>84</td>
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<td>30</td>
<td>64</td>
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<td>36</td>
<td>45</td>
<td>58</td>
</tr>
<tr>
<td>42</td>
<td>29</td>
<td>35</td>
</tr>
</tbody>
</table>

Number at risk
HF IN TYPE 2 DM AND DPP4 INHIBITORS

F. Van de Werf (B) «TECOS»
Heart failure events in SAVOR

- Saxagliptin: HR 1.80 (1.29-2.55), P=0.001
  - 0%: 8212, 7856
  - 1.1%: 8280, 8064

- Placebo: HR 1.46 (1.15-1.88), P=0.002
  - 0%: 8036, 7389
  - 1.3%: 8064, 7375

HR 1.27 (1.07-1.51), P=0.007
- 3.5%
- 2.8%

**PRIMARY COMPOSITE CARDIOVASCULAR OUTCOME**

*PER PROTOCOL ANALYSIS FOR NONINFERIORITY*

**HR (95% CI): 0.98 (0.88, 1.09)**

Noninferiority P<0.001

**Percent of patients with an event**

![Graph showing the percent of patients with an event over months in the trial.](image)

**Patients at risk:**

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7,257</td>
<td>7,266</td>
</tr>
<tr>
<td>4</td>
<td>6,857</td>
<td>6,846</td>
</tr>
<tr>
<td>8</td>
<td>6,519</td>
<td>6,449</td>
</tr>
<tr>
<td>12</td>
<td>6,275</td>
<td>6,165</td>
</tr>
<tr>
<td>18</td>
<td>5,931</td>
<td>5,803</td>
</tr>
<tr>
<td>24</td>
<td>5,616</td>
<td>5,421</td>
</tr>
<tr>
<td>30</td>
<td>3,919</td>
<td>3,780</td>
</tr>
<tr>
<td>36</td>
<td>2,896</td>
<td>2,743</td>
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<tr>
<td>42</td>
<td>1,748</td>
<td>1,690</td>
</tr>
<tr>
<td>48</td>
<td>1,028</td>
<td>1,005</td>
</tr>
</tbody>
</table>

**Median FU 2 years**

*CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

F. Van de Werf (Leuven, BE), FP 4128
TIME TO FIRST HOSPITALIZATION FOR HEART FAILURE*

HR (95% CI): 1.00 (0.84–1.20)
P = 0.95

Patients at risk:

- **Sitagliptin**: 7,332 7,189 7,036 6,917 6,780 6,619 4,728 3,515 2,175 1,324
- **Placebo**: 7,339 7,204 7,025 6,903 6,712 6,549 4,599 3,443 2,131 1,315

* ITT population

F. Van de Werf (Leuven, BE), FP 4128
No benefit of cyclosporine, peri infarct pacing or early administration of MRAs after STEMI.

No benefit of SERCA 2a gene transfer in CHF.

ASV should not be used in CHF with central sleep apnoea.

Telemonitoring of fluid retention unsuccessful.

Sitagliptin can be safely used in type 2 DM without concern for new onset or worsening heart failure.