NOVEDADES SOBRE IMPACTO CLINICO DE LOS DISPOSITIVOS ELECTRONICOS DE MONITOREO HEMODINAMICO IMPLANTABLE AMBULATORIO
ANTECEDENTES
Intrathoracic Impedance Monitoring, Audible Patient Alerts, and Outcome in Patients With Heart Failure

Dirk J. van Veldhuisen, MD; Frieder Braunschweig, MD; Viviane Conraads, MD; Ian Ford, PhD; Martin R. Cowie, MD; Guillaume Jondeau, MD; Josef Kautzner, MD; Roberto Muñoz Aguilera, MD; Maurizio Lunati, MD; Cheuk Man Yu, MD; Bart Gerritse, PhD; Martin Borggreve, MD;
for the DOT-HF Investigators

A

Hazard ratio, 1.52 [CI, 0.97-2.37]
P = 0.063

Death or Hospitalization for Heart Failure (%)

No. at Risk
Access Arm: 168 156 144 130 97 66 47
Control Arm: 167 156 151 136 113 67 46

Months since randomization
Impact of Remote Telemedical Management on Mortality and Hospitalizations in Ambulatory Patients With Chronic Heart Failure

The Telemedical Interventional Monitoring in Heart Failure Study

Friedrich Koehler, MD; Sebastian Winkler, MD; Michael Schieber, MD; Udo Sechtem, MD; Karl Stangl, MD; Michael Böhm, MD; Herbert Boll, MD; Gert Baumann, MD; Marcus Honold, MD; Kerstin Koehler, MD; Goetz Gelbrich, PhD; Bridget-Anne Kirwan, PhD; Stefan D. Anker, MD, PhD; on behalf of the Telemedical Interventional Monitoring in Heart Failure Investigators

A. Death from Any Cause

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>RTM</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>354</td>
<td>356</td>
</tr>
<tr>
<td>3</td>
<td>352</td>
<td>352</td>
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<tr>
<td>6</td>
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<td>9</td>
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<td>12</td>
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<td>15</td>
<td>249</td>
<td>243</td>
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<td>18</td>
<td>239</td>
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<td>21</td>
<td>229</td>
<td>60</td>
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<tr>
<td>24</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proportion with Event (%) vs. Months

P = 0.67

Koehler et al Circulation 2011
Telemonitoring in Patients with Heart Failure

Sarwat I. Chaudhry, M.D., Jennifer A. Mattera, M.P.H., Jeptha P. Curtis, M.D.,
John A. Spertus, M.D., M.P.H., Jeph Herrin, Ph.D., Zhenqiu Lin, Ph.D.,
Christopher O. Phillips, M.D., M.P.H., Beth V. Hodshon, M.P.H., J.D., R.N.,
Lawton S. Cooper, M.D., M.P.H., and Harlan M. Krumholz, M.D.

A  Readmission for Any Reason or Death from Any Cause

![Graph showing readmission rates over time for usual care and telemonitoring]

- **Usual care**
- **Telemonitoring**

Hazard ratio for readmission or death with telemonitoring, 1.04 (95% CI, 0.91–1.19)

\( P = 0.58 \)

<table>
<thead>
<tr>
<th>Days since Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

No. at Risk
- Usual care: 827, 587, 468, 402
- Telemonitoring: 826, 564, 454, 395
Conclusions

- In heart failure trials, endpoints composed of sign assessment only, will probably give underpowered results.

- Such endpoints do not reflect the important symptomatology and functional status present in CHF.

- Composite clinical endpoints should be explored where functional status and symptoms are included in order to allow important treatment effects to be evaluated properly.
NOVEDADES SOBRE EL DEFICIT DE LA SERCA EN INSUFICIENCIA CARDIACA CRÓNICA
The Concept

- Pre-clinical studies demonstrate that:
  - Expression of SERCA 2a in cardiomyocytes normalizes calcium cycling.
  - Gene transfer of SERCA 2a reverses cardiac dysfunction in large animal models.
<table>
<thead>
<tr>
<th>Study</th>
<th>Gene</th>
<th>Route</th>
<th>End Points (6 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUPID (n=39)</td>
<td>AAV1-SERCA2a</td>
<td>Intra-coronal</td>
<td>Dose ranging, Symptoms, 6 mo walking distance/peak VO2, NT-proBNP, LV function</td>
</tr>
<tr>
<td>SERCA LVAD (n=24)</td>
<td>AAV1-SERCA2a high dose</td>
<td>Intra-coronal stopped</td>
<td>Safety / Feasibility</td>
</tr>
<tr>
<td>AGENT HF (n=44)</td>
<td>AAV1 SERCA2a High dose</td>
<td>Intra-coronal suspended</td>
<td>6 Mo LVESV (CT scan)</td>
</tr>
<tr>
<td>AC6 (n=56)</td>
<td>AAV5 Adenyl Cyclase 6</td>
<td>Ongoing</td>
<td>12 weeks Exercise capacity, LV function (Echo), dp/dt</td>
</tr>
</tbody>
</table>
CUPID 2: A Phase 2b Trial Investigating the Efficacy and Safety of the Intracoronary Administration of AAV1/SERCA2a in Patients with Advanced Heart Failure

917 – Hot Line V – Heart Failure
Tuesday, 1 September 2015, 11:00-12:30, London, Main Auditorium
Presentation No. 7165

Barry Greenberg, MD
Distinguished Professor of Medicine
Director, Advanced Heart Failure Treatment Program
University of California, San Diego

On Behalf of the CUPID 2 Trial Investigators & Executive Steering Committee

ClinicalTrials.gov Identifier: NCT01643330
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
Rationale for CUPID 2

- Gene transfer with AAV1/SERC2a has been shown to improve cardiac performance and outcomes in a variety of experimental models.

- A Phase 1/Phase 2a study in heart failure patients (CUPID 1) suggested that AAV1/SERCA2a stabilized or improved several independent measures of patient wellbeing and cardiac function and that it was associated with a reduction in the recurrent heart failure event rate compared to a placebo-treated control population.

- CUPID 2 study was designed to confirm the beneficial effects of the percutaneous intra-coronary administration of AAV1/SERCA2a on clinical outcomes in patients with moderate to severe heart failure symptoms and reduced ejection fraction and to assess the safety of this approach.
Main Inclusion and Exclusion Criteria

**Inclusion**

- 18-80 years of age
- Diagnosis of NYHA Class II-IV chronic HF due to ischemic or non-ischemic cardiomyopathy
- LVEF ≥ 0.35
- Optimal tolerated stable medical therapy for ≥30 days
- Elevated natriuretic peptide or history of HF-related hospitalization within 6 months of enrollment
- <1:2 or equivocal anti-AAV1 neutralizing antibody

**Exclusion**

- Hypertrophic, restrictive and obstructive cardiomyopathy; acute myocarditis; amyloidosis; discrete LV aneurysm
- Cardiac surgery, PCI, valvuloplasty or IV therapy for HF within 30 days prior to screening
- Surgically implanted LVAD
- Significant liver or renal impairment (>3x ULN; GFR ≤20 mL/min/1.73 m²)
- History of cancer within the past 5 years
- Active infection
AAV1/SERCA2a Administered Via Percutaneous Intracoronary Artery Perfusion

- One time antegrade epicardial coronary artery infusion over 10 minutes
- Infusion pump & commercially available guide or diagnostic catheters
- 60 mL divided into 1, 2 or 3 infusions depending on anatomy
- Nitroglycerin just prior to infusion (5 µg/min titrated up to MTD)
- Aim was to provide diffuse homogenous left ventricular exposure to AAV1/SERCA2a
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 Study Design

Pre-Screening

Screening, Randomization & Enrollment

Days Prior to Screening

Days Prior to Day 0

12-Month Active Observation Period

Months Post-Infusion

Day 0 (Infusion)

Pre-Screen

Screen

Randomize

N=125

AAV1/ SERCA2a X 10^13 DRP

Observe for 12 Months

Long-Term Follow-Up

Observe for 12 Months

Long-Term Follow-Up

Placebo

Long-Term Follow-Up
CUPID 2: Secondary Efficacy Endpoint Results

Of the 65 terminal events that qualified as secondary endpoints, 29 were in the placebo group and 36 were in the AAV1/SERCA2a group.

Treatment with AAV1/SERCA2a failed to improve time to first terminal event (HR, 1.27; 95% CI 0.72 to 2.24; \( p=0.40 \))
Terminal Event-Free

AAV1/SERCA2a

Placebo

Cumulative Probability

Hazard ratio, 1.27 (0.72-2.24)
P=0.41

Days Since Treatment
Exploratory Efficacy Endpoints

Compared to placebo, treatment with AAV1/SERCA2a had no significant effect on change from baseline in:

- NYHA Functional Class
- Percentage of patients who improved ≥ 1 NYHA Functional Class
- Distance walked over 6 minutes
- KCCQ overall score
- NT-proBNP levels
Hi Light
Rafael Porcile
NOVEDADES SOBRE LA FISIOLOGÍA DEL SUEÑO Y LA INSUFICIENCIA CARDÍACA
Treatment of Sleep-Disordered Breathing With Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure and Reduced Ejection Fraction (SERVE-HF)

Martin R Cowie
Professor of Cardiology, National Heart & Lung Institute
Imperial College London (Royal Brompton Hospital)
m.cowie@imperial.ac.uk
Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure

Martin R. Cowie, M.D., Holger Woehrle, M.D., Karl Wegscheider, Ph.D.,
Christiane Angermann, M.D., Marie-Pia d'Ortho, M.D., Ph.D.,
Erlend Erdmann, M.D., Patrick Levy, M.D., Ph.D., Anita K. Simonds, M.D.,
Virend K. Somers, M.D., Ph.D., Faiez Zannad, M.D., Ph.D.,
and Helmut Teschler, M.D.
Adaptive Servo-Ventilation (ASV)

- ASV is a 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 (fixed or variable EPAP)
- Although algorithms employed by different ASV devices vary slightly, the principle of treatment is the same: back-up rate ventilation with adaptive pressure support

Rationale for ASV in Heart Failure with CSA

- Small and/or uncontrolled studies (and meta-analyses) suggest multiple beneficial effects of ASV on surrogate markers in heart failure (HF) patients with central sleep apnoea (CSA):\(^1-^5\)
  - Improvements in LVEF, plasma BNP levels, quality of life and functional outcomes

- Post-hoc data from a randomised trial (CANPAP; N=258) suggest that CPAP might improve mortality when CSA is controlled (AHI <15/h) in HF patients with CSA and EF <40\(^6\)
SERVE-HF: Design

- 91 centres in 11 countries (Germany, France, UK, Sweden, Australia, Denmark, Norway, Czech Republic, Finland, Switzerland, Netherlands)
- Randomized, parallel, event-driven design
- Guideline-based medical management:
  - Alone (control group)
  - Plus ASV (Auto Set CS™, ResMed)
- ASV titration in hospital (PG or PSG)
  - Starting at default settings
  - Expiratory positive airway pressure manually increased to control obstructive sleep apnoea (OSA) and maximum pressure support increased to control central sleep apnoea (CSA)
Primary Endpoint: Neutral

Time to first event of all-cause death, life-saving cardiovascular intervention, or unplanned hospitalization for worsening chronic HF

HR 1.13, 95% CI 0.97,1.31, P= 0.10

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>0</td>
<td>659</td>
</tr>
<tr>
<td>12</td>
<td>463</td>
</tr>
<tr>
<td>24</td>
<td>365</td>
</tr>
<tr>
<td>36</td>
<td>222</td>
</tr>
<tr>
<td>48</td>
<td>136</td>
</tr>
<tr>
<td>60</td>
<td>77</td>
</tr>
</tbody>
</table>
Symptoms and Quality of Life

- No significant differences in QoL between ASV and control groups
  - Minnesota Living with Heart Failure Questionnaire
  - EuroQol-5D

- No significant difference in NYHA functional status between ASV and control groups throughout trial

- Decreased exercise capacity in ASV recipients
  - 6MWD declined in both groups, but to a greater extent in the ASV group (p=0.04)
Conclusions

• Addition of ASV to guideline-based medical management does not improve outcomes in patients with HFrEF and predominant CSA, despite effective control of CSA
  – Inconsistent with results in previous studies
  – Pathophysiology of the increased cardiovascular mortality remains to be elucidated

• These results apply only to the population studied
  – Cannot be generalised to patients with HF with preserved ejection fraction, or those with predominant OSA
Take home message: What to do with heart failure patients with sleep apnea

- **NO** indication to initiate ASV to improve morbidity or mortality in HFrEF patients.
- Assess OSA pts on ASV for LVEF ≤ 45%, discontinue
- HFpEF: no data for harm

Treatment: optimize GDMT and CRT, nocturnal O2
?CPAP judicious use for OSA symptoms only
NOVEDADES SOBRE CHAGAS
Randomized Trial of Benznidazole for Chronic Chagas Cardiomyopathy

BENznidazole Evaluation For Interrupting Trypanosomiasis (BENEFIT Trial)

Carlos A. Morillo and Jose Antonio Marin-Neto
Co-Principal Investigators on behalf of the BENEFIT Investigators
Rationale

• Chagas disease
  – Third most common parasitic disease globally
  – Most common form of non-ischemic cardiomyopathy in Latin America
  – 5–7 million infected, 1.4 - 2.1 million develop cardiomyopathy within 20-30 yrs.

• *T. cruzi* low level parasitemia may directly or through an autoimmune mechanism cause cardiomyopathy

• Role of trypanocidal therapy in Chagas cardiomyopathy is unknown
BENEFIT Objectives

**Primary**
- To evaluate whether the use of trypanocidal therapy with benznidazole (BNZ) reduces mortality and progression in Chagas cardiomyopathy.

**Secondary**
- Determine effects of BNZ on parasite detection rates by conventional PCR.
- Evaluate safety and tolerability of BNZ.
Study Design

Chronic Chagas Cardiomyopathy
Aged 18 to 75 years, ≥2 positive serological tests for *T. cruzi*, ECG Abnormalities

R

BNZ 300 mg daily

Placebo

Follow-up: 11, 21 days, end of treatment, 6-mos, annually until study end
(mean 5.4 yrs)

Primary Outcome:
Composite: death, resuscitated cardiac arrest, sustained VT, pacemaker/ICD, cardiac transplant, new or hospitalized HF, stroke/TIA and systemic or pulmonary embolism
BENEFIT: 49 sites, 5 countries
2854 patients randomized (2004 to 2011)

Global Coordinating Center:
Population Health Research Institute

*PCR Core labs:
Argentina, Brazil & Colombia

**BENEFIT Echo Core lab:
Ribeirao Preto, Brazil

El Salvador (78)
Brazil (1359)
Colombia (502)
Bolivia (357)
Argentina (559)

LA Coordinating Center:
Instituto Dante Pazzanese
Sao Paulo, Brazil
Study Procedures

- BNZ or matching placebo for 40-80 days

- Adverse events, liver function tests during treatment period and 12-lead ECGs annually, 2-D Echo at baseline, 2 yrs and final visit.

- Blood samples for qualitative conventional PCR to detect circulating T. cruzi kinetoplast DNA (kDNA)* at end of treatment, 2 years and final follow-up (> 5 yrs).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Benznidazole N=1431</th>
<th>Placebo N=1423</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>55.4 years</td>
<td>55.2 years</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>93.3%</td>
<td>94.8%</td>
</tr>
<tr>
<td>Previous Heart Failure</td>
<td>9.9%</td>
<td>9.0%</td>
</tr>
<tr>
<td>NYHA Class I</td>
<td>74.4%</td>
<td>73.5%</td>
</tr>
<tr>
<td>Mean LVEF</td>
<td>54.4%</td>
<td>54.6%</td>
</tr>
<tr>
<td>Wall-motion Abnormality</td>
<td>38.3%</td>
<td>37.6%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>30.4%</td>
<td>29.9%</td>
</tr>
<tr>
<td>ACE-Inhibitor or ARB</td>
<td>49.6%</td>
<td>49.2%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>31.0%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>19.9%</td>
<td>18.8%</td>
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</table>
## PCR Negativization

<table>
<thead>
<tr>
<th></th>
<th>Placebo (Pts with Events%)</th>
<th>Benznidazole (Pts with Events%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.O.T</td>
<td>33.5</td>
<td>66.2</td>
</tr>
<tr>
<td>Year 2</td>
<td>35.3</td>
<td>55.4</td>
</tr>
<tr>
<td>&gt;5 Years</td>
<td>33.1</td>
<td>46.7</td>
</tr>
<tr>
<td><strong>Brazil</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.O.T</td>
<td>24.3</td>
<td>86.3</td>
</tr>
<tr>
<td>Year 2</td>
<td>31.1</td>
<td>80.8</td>
</tr>
<tr>
<td>&gt;5 Years</td>
<td>27.4</td>
<td>35.3</td>
</tr>
<tr>
<td><strong>Argentina, Bolivia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.O.T</td>
<td>28.6</td>
<td>73.0</td>
</tr>
<tr>
<td>Year 2</td>
<td>34.1</td>
<td>62.9</td>
</tr>
<tr>
<td>&gt;5 Years</td>
<td>30.2</td>
<td>61.4</td>
</tr>
<tr>
<td><strong>Colombia, El Salvador</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.O.T</td>
<td>45.6</td>
<td>43.9</td>
</tr>
<tr>
<td>Year 2</td>
<td>38.5</td>
<td>42.6</td>
</tr>
<tr>
<td>&gt;5 Years</td>
<td>40.2</td>
<td>35.4</td>
</tr>
</tbody>
</table>
Primary Outcome

Log-Rank p-value: 0.31

- DNZ
- Placebo

Years of Follow-up
# Primary Outcome Components

<table>
<thead>
<tr>
<th></th>
<th>Benznidazole (N=1431) (%)</th>
<th>Placebo (N=1423) (%)</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>394 (27.5%)</td>
<td>414 (29.1%)</td>
<td>0.93</td>
<td>0.81-1.07</td>
<td>0.31</td>
</tr>
<tr>
<td>Death</td>
<td>246 (17.2%)</td>
<td>257 (18.1%)</td>
<td>▶</td>
<td>0.79-1.13</td>
<td></td>
</tr>
<tr>
<td>Resuscitated Cardiac Arrest</td>
<td>10 (0.7%)</td>
<td>17 (1.2%)</td>
<td>0.58</td>
<td>0.27-1.28</td>
<td></td>
</tr>
<tr>
<td>Sustained VT</td>
<td>33 (2.3%)</td>
<td>41 (2.9%)</td>
<td>0.80</td>
<td>0.50-1.26</td>
<td></td>
</tr>
<tr>
<td>Pacemaker/ICD</td>
<td>109 (7.6%)</td>
<td>125 (8.8%)</td>
<td>0.86</td>
<td>0.66-1.11</td>
<td></td>
</tr>
<tr>
<td>New/Worsening HF</td>
<td>109 (7.6%)</td>
<td>122 (8.6%)</td>
<td>0.88</td>
<td>0.68-1.15</td>
<td></td>
</tr>
<tr>
<td>Cardiac Transplant</td>
<td>3 (0.2%)</td>
<td>9 (0.6%)</td>
<td>0.33</td>
<td>0.09-1.22</td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA, SE or PE</td>
<td>54 (3.8%)</td>
<td>61 (4.3%)</td>
<td>0.88</td>
<td>0.61-1.27</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- BNZ with a 40-80 day course in established Chagas cardiomyopathy did not significantly reduce clinical progression, despite significantly reducing PCR blood *T. cruzi* detection.

- BNZ was well tolerated and permanent discontinuation was lower than previously reported.
Hi Light
Rafael Porcile
1992: Edwin G Krebs and Edmond H. Fischer

"Reversible protein phosphorylation as a biological regulatory mechanism"
Protein kinases:
Key regulators of Na$^+$ and Ca$^{2+}$ homeostasis in atrial fibrillation

Niels Voigt

Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Germany
Increased phosphatase activity and reduced $I_{Ca,L}$ in AF

L-type Ca$^{2+}$ current ($I_{Ca,L}$)

- Sinus rhythm (Ctl)
- Atrial fibrillation (AF)

Protein

- $\alpha_1$-C
  - Ctl: 190 kDa
  - AF: 35 kDa

- GAPDH
  - Ctl: 0.6
  - AF: 0.7

Phosphatases (PP)

- CaMKII

- Phosphatase activity (nmol/min/mg)

Christ et al., Circulation 2004;110:2651
Basic mechanisms of atrial fibrillation

Vulnerable substrate

- \( I_{Ca,L} \) down
- \( \downarrow \text{APD} \)
- CaMKII

Ectopic activity

- ↑DADs

“trigger”

“driver”

Re-entry

Atrial fibrillation (AF)
Basic mechanisms of atrial fibrillation

Vulnerable substrate

Ectopic activity

"trigger"

"driver"

Re-entry

Atrial fibrillation (AF)

↑ Metabolic Stress

APD = Action-potential duration
DADs = Delayed afterdepolarisations

Heijman, Voigt and Dobrey, Future Cardiol 2013;9:71
More spontaneous $\text{Ca}^{2+}$ release events (SCaE) in AF

Diastole

Cytosol

NCX

3 Na$^+$

$\text{Ca}^{2+}$

I$_{\text{NCX}}$

SCaEs

RyR2

Sarcoplasmic Reticulum

$\text{Ca}^{2+}$

$\text{Ca}^{2+}$

$\text{Ca}^{2+}$

$\text{Ca}^{2+}$

DADs

AF promotion

Line-Scan recording

Confocal $[\text{Ca}^{2+}]_i$ imaging

10 µm

200 ms

10 µm

$\text{Ca}^{2+}$-sparks

Boigt et al., Circulation 2012;125:2059

Wehrens et al., unpublished
Increased CaMKII expression in atrial fibrillation (AF)

CaMKII-holoenzyme:

CaMKII-<br>monomer:

Active-CaM bound

Active-CaM "Trapped"

CaMKIIδC (cytosolic)

Relative to Ctl (norm. to GAPDH)

0.0 0.5 1.0 1.5 2.0 2.5

10 10 10 10

CaMKII-Thr287δC

CaMKII-Thr287δB

CaMKIIδB-total

CaMKIIδC-total

GAPDH

56 kDa

56 kDa

37 kDa