Experimental treatment of heart failure

Soluble guanylate cyclase activators

Veselin Mitrovic, Kerckhoff Heart-Center, Bad Nauheim, Germany
Disclosure

VM has received consultancy fees/honoraria from Bayer HealthCare AG and CardioPep Pharma GmbH
Chronic Heart Failure Therapy

**pharmacological therapy**
- diuretics
- beta blockers
- \(I_f\)-inhibitor ivabradine (SHIFT Study)
- ACE inhibitors
- AT-1 antagonists
- Ferric Iron replacement carboxymaltose (FAIR-HF Study)
- digitalis
- Aldosterone antagonists Eplerenone (EMPHASIS Study)

**non-pharmacological therapy**
- ICD-CRT
- CCM
- ultrafiltration
- immunoadsorption
- VADs

**ICD-CRT**
**CCM**
**ultrafiltration**
**immunoadsorption**
**VADs**
DRUGS

old approved

diuretics
beta blockers
ACE inhibitors
AT-1 antagonists
digitalis
aldosterone antagonists

new in research
endothelin-ant
TNF-α-ant.
Adenosine A₁R-α-ant.
vasopeptidase-inh.
metalloproteinase inh.
SERCA 2a activators
calcium sensitizer
vasopressin-ant
Natriuretic peptides.
New drugs on the horizon

**sGC-Modulators**
(Cinaciguat, Riociguat, BAY 60-4552)

**Myosine Activators**
(CK 1827-452)

**ECE + NEP-Inhibitors**
(Daglutril)

**New Polypeptides**
(Relaxin)

**Na⁺-K⁺ +SERCA-ATPase Inhibitors**
(Istaroxime)

**New Natriuretic Peptides**
(Ularitide, Nesiritide, CD-NP)

**AGE-Breakers**
(TRC 4185)

**Renin-Inhibitors**
(Aliskiren)

**Aldosterone-Syntase-Inhibitors**
(LCI, FAD 286)
History of cyclic nucleotides

- **1960s**
  - First Identification of cAMP and cGMP

- **1971**
  - Nobel Prize to Earl W. Sutherland for formulating the second-messenger concept in hormone signaling

- **1980s**
  - Discovery of cGMP synthesis
    - Stimulation of pGC by ANP leads to cGMP synthesis
    - Stimulation of sGC by NO leads to cGMP synthesis

- **1998**
  - Nobel Prize to R.F. Furchgott, L.J. Ignarro, and F. Murad for discovering the NO-sGC-cGMP pathway

physiologist who, together with colleague Theodore W. Rall, isolated cyclic adenosine monophosphate (cyclic AMP) in 1956. Following its isolation, he demonstrated the involvement of cyclic AMP in numerous metabolic processes and elucidated the mechanisms and actions of hormones at the cellular level. In 1971 he was awarded the Nobel Prize in Physiology or Medicine for his discoveries concerning the mechanisms of hormone action.
Guanylate Cyclase Modulators

Particulate Guanylate Cyclase

- pGC Stimulators
  (NPs: ANP, BNP, Ularitide)

Soluble Guanylate Cyclase (sGC)

- sGC-Activators
  (BAY 58-2667 – Cinaciguat, HMR 1766)

- sGC-Stimulators
  (BAY 63-2521 – Riociguat, BAY 60-4552, YC-1, A-350619, CF-1571)
cGMP signaling pathway

- Organic nitrates → Nitric oxide
- Natriuretic peptides
  - BNP analogues
- BAY compounds
- Oxidative stress
- Oxidized sGC
- Cation channels
  - Oxidative stress
  - cGMP
  - cGKs
  - GMP
  - PDEs
  - PDE5 inhibitors
- Myosin phosphatase
- IRAG
- VASP
- cAMP

- Phototransduction
- Smooth muscle relaxation
- Platelet inhibition
- Cell growth and differentiation

- Erectile dysfunction
- Angina pectoris
- Pulmonary hypertension
- Atherosclerosis
- Thrombosis
- Angiogenesis

Soluble Guanylate Cyclase (sGC)

Regulators Domain

Dimerization Domain

Catalytic Domain

NO

GTP

cGMP
Pathology of ADHF and mechanism of action of BAY 58-2667
Targeting Oxidized Soluble Guanylate Cyclase

Evgenov et al., Nat. Rev. - Drug Discov. 5: 755-768, 2006
**Soluble Guanylate Cyclase (sGC) Signaling**

- **Soluble guanylate cyclase (sGC)** is activated by endothelial-cell-derived nitric oxide (NO)
- **Activated sGC** produces cyclic guanosine monophosphate (cGMP)
- **cGMP** activates cGMP-dependent protein kinases, leading to vasodilation

**Diagram Details:**
- L-arginine to NO Synthase
- NO to sGC Fe(II) heme
- GTP to cGMP
- cGMP to PDE
- cGMP pathways:
  - Vasodilatation
  - Anti-aggregation
  - Anti-remodeling
  - RV-hypertrophy
Aberrant sGC signalling in ADHF

- In heart failure, NO production is decreased because of decreased expression of endothelial NO synthase and diminished endothelial NO synthase-mediated NO production
- Aberrant NO/sGC/cGMP signalling and oxidative stress in ADHF are associated with loss of potency of NO-based therapy

sGC Stimulators and sGC Activators

**sGC Stimulator**
- Amplifies protective effects of NO in the cardiovascular system
- Potential indications are hypertension, nephropathy, pulmonary arterial hypertension

**sGC Activator**
- Selective vasodilation of diseased or oxidative stress impaired blood vessels
- Potential indications are heart failure, nephropathy, angina pectoris
From Screening Hit to Development Compound

Optimization by synthesis of about 800 compounds

We identified with BAY 58-2667 a new type of sGC activator
Cellular cGMP Accumulation under Oxidative Conditions

**Enhanced cGMP formation induced by BAY 58-2667 under oxidative stress conditions**
Haemodynamics in Anaesthetized Dogs

- **BAY 58-2667**
  - 1.0 µg/kg iv (n=4)
  - 3.0 µg/kg iv (n=3)
  - 10.0 µg/kg iv (n=3)

- **GTN**
  - 0.3 µg/kg iv (n=4)
  - 1.0 µg/kg iv (n=4)
  - 3.0 µg/kg iv (n=4)

- **Right atrial pressure**
  - **Pulmonary artery pressure**
  - **Heart rate**
  - **Mean arterial pressure**

Similar haemodynamic profile of BAY 58-2667 and GTN
Duration of action distinctly longer for BAY 58-2667
Heart failure was induced in 7 dogs by rapid ventricular pacing for 10 days 0.1 and 0.3 µg/kg/min BAY 58-2667

Boerrigter, Burnett et al., Hypertension (accepted)
Heart Failure

Cinaciguat (BAY 58–2667) Improves Cardiopulmonary Hemodynamics in Patients With Acute Decompensated Heart Failure

Harald Lapp, MD; Veselin Mitrovic, MD; Norbert Franz, MD; Hubertus Heuer, MD; Michael Buerke, MD; Judith Wolfertz, MD; Wolfgang Mueck, PhD; Sigrun Unger, MSc; Georg Wensing, MD; Reiner Frey, MD
Change in PCWP and RAP

Change in PCWP

<table>
<thead>
<tr>
<th>BAY 58-2667 infusion</th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
<th>2 h follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP change from baseline (mmHg)</td>
<td>-4.1</td>
<td>-6.9</td>
<td>-7.9</td>
<td>-5.2</td>
</tr>
</tbody>
</table>

Change in RAP

<table>
<thead>
<tr>
<th>BAY 58-2667 infusion</th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
<th>2 h follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP change from baseline (mmHg)</td>
<td>-1.9</td>
<td>-2.1</td>
<td>-2.9</td>
<td>-1.3</td>
</tr>
</tbody>
</table>

* *p < 0.05
** *p < 0.0005
*** *p < 0.0001

(compared with baseline)
Change in SVR and CO

**Change in SVR**

<table>
<thead>
<tr>
<th>BAY 58-2667 infusion</th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
<th>2 h follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR, change from baseline (dyn·sec/cm²)</td>
<td>–318.6</td>
<td>–462</td>
<td>–596.6</td>
<td>–444.1</td>
</tr>
</tbody>
</table>

**Change in CO**

<table>
<thead>
<tr>
<th>BAY 58-2667 infusion</th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
<th>2 h follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO, change from baseline (L/min)</td>
<td>0.662</td>
<td>1.054</td>
<td>1.679</td>
<td>1.041</td>
</tr>
</tbody>
</table>

* *p < 0.05
*** *p < 0.0001

(compared with baseline)
Proof of Concept Study – Hemodynamic Results

Preliminary Results

PCWP

Cardiac Output

mmHg

L/min

BAY 58-2667 after

BL  2h  4h  6h  FU 2h

24,7  20,7  18,2  16,9  19,0

4,35  5,04  5,59  6,04  5,37

KERCKHOFF HERZ- UND THORAXZENTRUM
Effect on dyspnoea score

BAY 58-2667 infusion

Proportion of patients (%)
Cinaciguat, a soluble guanylate cyclase activator, unloads the heart in acute decompensated heart failure

Erland Erdmann, Marc J. Semigran, Markku S. Nieminen, Rahul Agrawal, Veselin Mitrovic and Alexandre Mebazaa on behalf of the investigators
Patient flow

Patients screened (N = 158)

Patients randomized 2:1 (N = 150*)

Cinaciguat

97

95

90

64

Placebo

51

Safety

Intent-to-treat

Per protocol: titration

Primary endpoint

Per protocol: maintenance

*Two patients in the cinaciguat group received no study medication.
Dosing schedule and titration scheme

**Cinaciguat or placebo on top of conventional treatment**

- **Run-in**: ≤ 48 h
- **Titration phase**: 8 h
- **Maintenance phase**: 16–40 h
- **Follow-up**: 30 days

**Primary endpoint**

- Infusion duration: 24–48 h

**SBP ≥ 100 mmHg / HR ≤ 110 bpm**: up-titrate dose
- **SBP 90–100 mmHg / HR ≤ 110 bpm**: maintain dose
- **SBP < 90 mmHg / HR > 110 bpm**: determine PCWP

HR, heart rate; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure
## Baseline demographics and haemodynamics

Data are mean ± standard deviation except where specified.

*Data from per protocol titration group (cinaciguat, N = 90; placebo, N = 49)

<table>
<thead>
<tr>
<th>Patients valid for safety analysis</th>
<th>Cinaciguat (N = 97)</th>
<th>Placebo (N = 51)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.7 (± 11.7)</td>
<td>60.5 (± 10.5)</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>88 (90.7)</td>
<td>38 (74.5)</td>
<td></td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>96 (99.0)</td>
<td>50 (98.0)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.8 (± 5.1)</td>
<td>29.5 (± 6.3)</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>81.9 (± 13.6)</td>
<td>75.1 (± 13.5)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>122.6 (± 18.2)</td>
<td>123.2 (± 15.7)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>75.9 (± 14.1)</td>
<td>73.8 (± 12.9)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mmHg*</td>
<td>25.7 (± 5.1)</td>
<td>25.0 (± 5.3)</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, mmHg*</td>
<td>38.9 (± 8.6)</td>
<td>38.8 (± 8.2)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyn.s/cm⁵*</td>
<td>268.2 (± 178.2)</td>
<td>290.4 (± 141.3)</td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn.s/cm⁵*</td>
<td>1566.3 (± 539.2)</td>
<td>1677.5 (± 495.8)</td>
<td></td>
</tr>
<tr>
<td>Cardiac output, L/min*</td>
<td>4.4 (± 1.3)</td>
<td>4.1 (± 1.3)</td>
<td></td>
</tr>
</tbody>
</table>
Hemodynamic Effects of Cinaciguat or Placebo

Graphs showing the changes in PCWP, RAP, PAP, and Cardiac index over time for Cinaciguat and Placebo.
Cinaciguat caused vasorelaxation without a clinically relevant change in heart rate.

Systolic blood pressure

Heart rate

Mean change in systolic blood pressure from baseline (mmHg)

Mean change in heart rate from baseline (bpm)

Time point from start of treatment

Conventional therapy + cinaciguat

Conventional therapy + placebo
Cinaciguat showed consistent haemodynamic effects

Titration phase, 8 h

<table>
<thead>
<tr>
<th></th>
<th>Mean change from baseline</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cinaciguat* (N = 90)</td>
<td>Placebo* (N = 49)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>−19.15</td>
<td>−5.40</td>
</tr>
<tr>
<td>PAP_{mean} (mmHg)</td>
<td>−7.81</td>
<td>−1.85</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>−2.74</td>
<td>−0.57</td>
</tr>
<tr>
<td>PVR (dyn.s/cm^5)</td>
<td>−89.10</td>
<td>+17.55</td>
</tr>
<tr>
<td>SVR (dyn.s/cm^5)</td>
<td>−682.16</td>
<td>−174.35</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>+1.82</td>
<td>+0.34</td>
</tr>
</tbody>
</table>
## List of adverse events

<table>
<thead>
<tr>
<th>Primary system organ class / preferred term</th>
<th>Cinaciguat* (N = 97)</th>
<th>Placebo* (N = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>Any adverse event(^1)</td>
<td>75</td>
<td>(77.3)</td>
</tr>
<tr>
<td>Any treatment-emergent event(^2)</td>
<td>69</td>
<td>(71.1)</td>
</tr>
<tr>
<td>– Hypotension</td>
<td>49</td>
<td>(50.5)</td>
</tr>
<tr>
<td>– Ventricular tachycardia</td>
<td>6</td>
<td>(6.2)</td>
</tr>
<tr>
<td>– Headache</td>
<td>6</td>
<td>(6.2)</td>
</tr>
<tr>
<td>Any drug-related treatment-emergent event</td>
<td>58</td>
<td>(59.8)</td>
</tr>
<tr>
<td>Any serious adverse event(^3)</td>
<td>22</td>
<td>(22.7)</td>
</tr>
<tr>
<td>Any serious treatment-emergent event</td>
<td>9</td>
<td>(9.3)</td>
</tr>
</tbody>
</table>

\(^*\)In addition to conventional therapy.

\(^1\)Adverse event as defined individually by the investigator.

\(^2\)Adverse event starting after first application of double-blind study drug up to 2 days after stop of double-blind study drug.

\(^3\)Adverse event that is life threatening, leads to death, leads to or prolongs hospitalization (duration of stay \(\geq 12\) h), results in persistent or significant disability or incapacity, or is an important medical event.
Cinaciguat did not adversely affect 30-day mortality

![Graph showing 30-day mortality for conventional therapy with cinaciguat and conventional therapy with placebo. The graph shows thatcinaciguat group had a 2.1% mortality while placebo group had 5.9%.](image)
Conclusion

- Cardiovascular diseases are associated with oxidative stress which causes resistance to nitric oxide.

- Cinaciguat as activator of soluble Guanylate Cyclase is an effective pulmonary and systemic vasodilator in ADHF.

- The addition of cinaciguat to conventional therapy in patients with severe heart failure and depressed EF improved central haemodynamics significantly, despite higher doses being associated with decreases in blood pressure.

- The hypotension did not, however, result in an increase in major cardiac adverse events such as stroke or 30-day mortality.

- These results support further currently ongoing trials (Compose 1 and Compose 2) of cinaciguat at doses less than 200 μg/h.
Thank You!