Heart Failure and Arrhythmia - treatment

Prof. Vera Regitz-Zagrosek
Director, Institute of Gender in Medicine (GiM),
& Center Cardiovascular Research, & DHZB

Charité
Topics

- **Chronic Heart Failure**
  - Relevance
  - Guideline based treatment:
    - Life style changes, Drugs, HTX, devices (defibrillators, resynchronization, assist devices, )
  - Novel developments

- **Arrhythmia**
  - Guideline based treatment
    - Drugs
    - Catheter based ablation therapy
  - Novel developments
Clinical Relevance of HF

- High prevalence
  - US: 5 million people with HF in 2005
  - Medicare: higher spending than for any other disease,
    total cost of 27.9 billion USD in 2005; 2.7 billion on drugs
  - ESC member states (900 million people):
    - 10 million with symptomatic HF
    - 10 million with asymptomatic cardiac dysfunction
    - Lifetime risk at age 55: 29 and 33% for women*
- Broad spectrum of conventional, novel and high tech diagnostic and therapeutic strategies available

*Bleumink G S, Rotterdam Study, EHJ 2004
*ESC guidelines EHJ 2005
Age and gender adjusted survival after onset of HF is improving

Framingham cohort 2-year survival is 71% in women and 63% in men

Men

Women, 2 years mortality 29%

Levy, NEJM 2002
**Guideline based Treatment: Classes of recommendation and levels of evidence**

### Table 1: Classes of recommendations

<table>
<thead>
<tr>
<th>Classes of Recommendations</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence/opinion is in favour of usefulness/efficacy.</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion.</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td>
</tr>
</tbody>
</table>

### Level of Evidence

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Evidence A</td>
<td>Data derived from multiple randomized clinical trials or meta-analyses.</td>
</tr>
<tr>
<td>Level of Evidence B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies.</td>
</tr>
<tr>
<td>Level of Evidence C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</td>
</tr>
</tbody>
</table>
Guidelines for diagnosis of HF – ESC, AHA, German cardiac society

Suspected LV dysfunction because of signs

**Routine tests**..ECG, Echo, CXR..+BNP!
- Tests abnormal

More Imaging, TDE, MRT..for LVEF
- Tests abnormal
  - Assess aetiology, degree, precipitating factors and type of cardiac dysfunction
  - Choose therapy

Suspected Heart Failure because of symptoms and signs

Normal
- Heart Failure or LV dysfunction unlikely

Heart Failure or LV dysfunction unlikely

Problem: impaired cardiac function
Fluid accumulation

RIGHT HEART FAILURE: CYANOSIS, ENGORGEMENT OF JUGULAR VEINS, ENLARGEMENT OF LIVER, ASCITES, DEPENDENT EDema, ELEVATED VENOUS PRESSURE
Guidelines for the diagnosis and therapy of HF: DGK, ESC, AHA

At risk for heart failure

Heart failure

At high risk for HF but without structural heart disease or symptoms of HF.

Structural heart disease without signs or symptoms of HF.

Structural heart disease with prior or current symptoms of HF.

Refract. s at rest

Symptoms

Drugs

ACEI, ARB, β-blockers

Devices in selected pts:

ICD

Biventricular pacing

Therapy

Options:

HTX

Ventricular assist device

Circulation, 2005
Euro Heart Failure Survey: Insufficient echocardiographic diagnosis: women >> Men

Cross sectional study in patients hospitalised for HF in Europe, 115 Hosp, 47600 Pat

- Underuse of standard echocardiography for diagnosis of HF, particularly in women

Standard Echo

% of patients with echo

<table>
<thead>
<tr>
<th></th>
<th>CXR</th>
<th>Echo-men</th>
<th>E-women</th>
<th>LVEF</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
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<td>10</td>
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<tr>
<td>70</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

EHJ, Cleland 2003;
Agvall B, Scand Prim Health care, 2001
(Why) is echocardiography and BNP underused? - EuroHeart Failure Survey

Facts: Standard echo: 66 % of men; 50 % of women

Tissue doppler and BNP: estimated < 10 % in women and men

Reasons for underuse of Echo:
- Lack of adequate equipment
- Lack of skills and knowledge of guidelines

Reasons for underdiagnosis in women:
- Lack of awareness of guidelines?
- Lack of trust in guidelines?

The second heavily underused technique
- BNP determinations - in special populations
- Lack of knowledge and availability, cost effectiveness
Treatment options

Non-pharmacological management
- General advice and measures
- Exercise and exercise training

Pharmacological therapy
- ACE-inhibitors
- Diuretics
- Beta-adrenoceptor antagonists
- Aldosterone receptor antagonists
- Angiotensin receptor antagonists
- Cardiac glycosides
- Vasodilator agents (nitrates/hydralazine)
- Positive inotropic agents
- Anti-coagulation
- Anti-arrhythmic agents
- Oxygen

Devices and surgery
- Revascularization (catheter interventions and/or surgery)
- Other forms of surgery (mitral valve repair)
- Bi-ventricular (multi-site) pacing
- Implantable cardioverter defibrillator (ICD)
- Heart transplantation, ventricular assist devices, and artificial heart
Treatment algorithms

Figure 2. A treatment algorithm for patients with symptomatic heart failure and reduced ejection fraction.
Exercise training in HF

- Evidence: mainly meta-analysis of trials.

- Mechanisms: reducing sympathetic activation, peripheral resistance and oxidative stress

- Animal model: Voluntary or forced exercise in mice/rats
Guideline based HF treatment - drugs

Level I
- Diuretics (and salt retention) if fluid retention
- ACE Inhibitors, ARB
- ß-blockers
- Withdrawal of NSAR, most anti-arrhythmic agents, most Ca-blockers
- Exercise training
- ICD in selected patients
- Cardiac resynchronization therapy in selected patients
- MR antagonists in selected patients
HF treatment in Europe depends on the country....

EHJ, 2003, 24: 464, study group on HF
.....and HF-treatment differs by sex

Male gender increases likelihood of adequate therapy in multivariate analysis – and female gender decreases it.

EHJ, 2003, 24: 464, study group on HF
### Pharmacological therapy - example

#### Table 3. Cardiovascular Medications Useful for Treatment of Various Stages* of Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benazepril</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Captopril</td>
<td>H, DN</td>
<td>Post MI</td>
<td>HF</td>
</tr>
<tr>
<td>Enalapril</td>
<td>H, DN</td>
<td>HF</td>
<td>HF</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>H, DN</td>
<td>Post MI</td>
<td>HF</td>
</tr>
<tr>
<td>Moexipril</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Perindopril</td>
<td>H, CV Risk</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Quinapril</td>
<td>H</td>
<td>—</td>
<td>HF</td>
</tr>
<tr>
<td>Ramipril</td>
<td>H, CV Risk</td>
<td>Post MI</td>
<td>Post MI</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>H</td>
<td>Post MI</td>
<td>Post MI</td>
</tr>
<tr>
<td><strong>Angiotensin Receptor Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>H</td>
<td>—</td>
<td>HF</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>H, DN</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Losartan</td>
<td>H, DN</td>
<td>CV Risk</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Valsartan</td>
<td>H, DN</td>
<td>Post MI</td>
<td>Post MI, HF</td>
</tr>
<tr>
<td><strong>Aldosterone Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>H</td>
<td>Post MI</td>
<td>Post MI</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>H</td>
<td>—</td>
<td>HF</td>
</tr>
</tbody>
</table>

#### Beta Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atenolol</td>
<td>H</td>
<td>Post MI</td>
<td>—</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>H</td>
<td>—</td>
<td>HF</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nadolol</td>
<td>H</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Nifedipine</td>
<td>H</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Nitroprusside</td>
<td>H</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Propranolol</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Timolol</td>
<td>H</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td>—</td>
<td>—</td>
<td>HF</td>
</tr>
</tbody>
</table>

Asymptomatic CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; LVSD, asymptomatic left ventricular systolic dysfunction; and Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

*See Figure 1 for explanation of stages of heart failure.
Novel developments in HF treatment

- Novel MR antagonists
- V1a/V2 Vasopressin Rezeptor Antagonisten
- Soluble Guanylate cyclase activators
- MMP inhibitors
BAYER has discovered potent and selective, non-steroidal Dihydropyridine-based MR antagonists.
Cardiac and Renal Protection by a New Mineralocorticoid Receptor Antagonist in Salt-Sensitive Arterial Hypertension

Peter Kolkhof1, Ingo Flamme1, Santiago Figueroa Perez2, Lars Baerfacker2, Elke Hartmann3, Matthias Rinke3, Stefan Schäfer1

BAYER HealthCare AG, Global Drug Discovery, Wuppertal, Germany
1Institute for Cardiovascular Research & Screening, 2Institute for Chemistry Research, 3 Institute for Toxicology

PURPOSE

Activation of the mineralocorticoid receptor (MR) via aldosterone may contribute to hypertension, end-organ damage and mortality in salt sensitive individuals. We therefore investigated the effect of specific MR blockade on blood-pressure, renal and cardiac impairment, and mortality in two animal models of salt sensitive hypertension.

METHODS

DOCA-salt loaded rat: Uninephrectomized male Sprague Dawley rats (n=38) were exposed to DOCA (30 mg/kg/wk s.c.) and NaCl (1% in drinking water) and treated for five weeks with either vehicle control, BAY (10 & 30 mg/kg/d), or Eplerenone (100 mg/kg/d). Blood pressure was measured by the tail cuff method, total protein was determined in urine collected over 24 hours, and hearts and kidneys were weighed after 36 days of treatment.

Stroke-prone spontaneously hypertensive rat (SHRSP): After a treatment period of 8 weeks mortality was significantly decreased in the BAY treated group (6/10) versus placebo treated animals (9/10). Protection by Eplerenone and Spironolactone was moderate (3/9 deaths in both groups, Figure 2).

Histopathological evaluation of the kidneys demonstrated significant reduced hypertensive lesions (i.e. vasculopathy, glomerulopathy, and tubular degeneration) in the BAY treated animals in comparison to all other groups.

RESULTS

DOCA-salt loaded rat: The novel non steroidal MR antagonist BAY and Eplerenone reduced systolic blood pressure to a similar extent (Figure 1A). BAY substantially reduced heart weight as well as proteinuria in this model of arterial hypertension (Figure 1B C). Similarly, kidney weights were reduced by BAY, but not by Eplerenone.

Stroke-prone spontaneously hypertensive rat (SHRSP): After a treatment period of 8 weeks mortality was significantly decreased in the BAY treated group (0/9) versus placebo treated animals (6/10). Protection by Eplerenone and Spironolactone was moderate (3/9 deaths in both groups, Figure 2).

Histopathological evaluation of the kidneys demonstrated significant reduced hypertensive lesions (i.e. vasculopathy, glomerulopathy, and tubular degeneration) in the BAY treated animals in comparison to all other groups.

CONCLUSIONS

We have discovered a novel selective, non steroidal MR antagonist which:
- reduces blood pressure
- prevents end organ damage
- improves survival
in salt sensitive hypertension.

Figure 1: Changes in A) systolic blood pressure, B) relative heart weights and C) urinary protein excretion after 36 days of treatment with either vehicle, BAY or Eplerenone. *p≤0.05, **p≤0.01, ***p≤0.005, ns not significant.

Figure 2: Survival benefit from different MR Antagonists in salt loaded SHRSPs.

Figure 3: Histopathological kidney lesions. Vehicle group, grade 3 (A), BAY group, grade 1 (B), Representative sections at higher magnifications showing glomerulopathy in BAY group, grade 1 (C), and Eplerenone group, grade 2 (D).
Pharmacological Characterization of a Mutant Mineralocorticoid Receptor Responsible for Severe, Early-Onset Hypertension

PETER KOLDROF, VERONICA JILG, AND STEFFEN SCHALLER
BAYER HealthCare AG, Global Drug Discovery, Whippany, Germany
Institute for Cardiovascular Research

PURPOSE

Monogenic aldosterone levels and, consequently, overactivation of the mineralocorticoid receptor (MR) cause life-threatening arterial hypertension and organ damage. Recently, a gain-of-function mutation in the sterol system that has been identified by a recent report on novel mutations (p.Ala124Val), leading to pathological activation, rather than loss-of-function, of the receptor by the intense increase in aldosterone biosynthesis. Clinically, this mutation is linked to early-onset hypertension in men and gestational hypertension in women. We have recently discovered a selective, non-receptor MR antagonist (S-NATA) in preclinical studies. In the present study, we investigated the pharmacological characterization of the mutant, steroidal MR antagonist (S-NATA) in comparison to EN-402 in vitro and in vivo.

RESULTS

Aldosterone levels in wildtype MR were significantly higher than in the mutant MR. A selective, non-receptor MR antagonist (S-NATA) was able to block the aldosterone-effect on cell viability and proliferation in the presence of MR agonists (DHEA, DHEA, and DHEA-S). In contrast, the aldosterone effect on cell viability and proliferation was not inhibited by the selective, non-receptor MR antagonist (S-NATA).

METHODS

We developed a stable murine cell line that was treated with aldosterone and mutant S-NATA. MR. The initial MR was generated by overexpression of the wildtype MR. Overactivation of the wildtype MR by DHEA or aldosterone did not alter the wildtype MR. Overactivation of the mutant MR by DHEA or aldosterone did alter the wildtype MR. This compound exhibited a potential for the treatment of hypertension.

CONCLUSIONS

Aldosterone levels in wildtype MR were significantly higher than in the mutant MR. A selective, non-receptor MR antagonist (S-NATA) was able to block the aldosterone-effect on cell viability and proliferation in the presence of MR agonists (DHEA, DHEA, and DHEA-S). In contrast, the aldosterone effect on cell viability and proliferation was not inhibited by the selective, non-receptor MR antagonist (S-NATA).

73th Annual Meeting of the German Cardiac Society
- HF induced by tachypacing in adult mongrels
  - Determination of hemodynamic effects in anaesthetized dogs with heart failure induced by prolonged tachypacing
  - AVP was infused (up to 4mU/kg/min) in order to achieve constant pathophysiological levels of AVP
  - CO recording via Swan Ganz catheter

Parameters at 20 minutes post application

- BR-5489 decreases total peripheral resistance while Tolvaptan slightly increases TPR
- BR-5489 increases cardiac output while Tolvaptan is without effects
Additional aspects in HF treatment

- Special populations
  - Women,
  - Ethnic subgroups,
  - Elderly
  - Cancer patients
- Anticoagulation
- Management of cardiac arrhythmias
- Device therapy
  - Resynchronization
  - ICD
Acute Hemodynamic Effects of Atrio-Biventricular Pacing in Humans

Andrew H. Foster, MD, Michael R. Gold, MD, PhD, and Joseph S. McLaughlin, MD

Division of Thoracic and Cardiovascular Surgery, Department of Surgery, and Division of Cardiology, Department of Medicine, The University of Maryland School of Medicine, Baltimore, Maryland
# Resynchronization therapy

**Table 1. Baseline Demographic and Clinical Characteristics of the Patients.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ICD-Only Group (N=731)</th>
<th>CRT-ICD Group (N=1089)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>64±11</td>
<td>65±11</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>553 (75.6)</td>
<td>814 (74.7)</td>
</tr>
<tr>
<td>Race — no./total no. (%) †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>657/724 (90.7)</td>
<td>979/1083 (90.4)</td>
</tr>
<tr>
<td>Black</td>
<td>56/724 (7.7)</td>
<td>87/1083 (8.0)</td>
</tr>
<tr>
<td>Other</td>
<td>11/724 (1.5)</td>
<td>17/1083 (1.6)</td>
</tr>
<tr>
<td>Cardiac history — no. (%)</td>
<td></td>
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</tr>
<tr>
<td>Ischemic heart disease</td>
<td></td>
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</tr>
<tr>
<td>NYHA class I</td>
<td>113 (15.5)</td>
<td>152 (14.0)</td>
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<tr>
<td>NYHA class II</td>
<td>288 (39.4)</td>
<td>446 (41.0)</td>
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<tr>
<td>Nonischemic heart disease</td>
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<tr>
<td>NYHA class II</td>
<td>330 (45.1)</td>
<td>491 (45.1)</td>
</tr>
<tr>
<td>NYHA class III or IV &gt;3 mo before enrollment — no. (%)</td>
<td>73 (10.0)</td>
<td>109 (10.0)</td>
</tr>
</tbody>
</table>

Moss, NEJM 2009
Figure 2. Kaplan–Meier Estimates of the Probability of Survival Free of Heart Failure.

There was a significant difference in the estimate of survival free of heart failure between the group that received cardiac-resynchronization therapy plus an implantable cardioverter–defibrillator (CRT–ICD) and the group that received an ICD only (unadjusted $P<0.001$ by the log-rank test).

Moss, NEJM 2009
Moss, NEJM 2009
### Figure 3. Risk of Death or Heart Failure, According to Selected Clinical Characteristics.

The hazard ratios for death or nonfatal heart failure (whichever came first) are shown for various subgroups among patients who received cardiac-resynchronization therapy plus an implantable cardioverter-defibrillator (CRT–ICD) and those who received an ICD only. The dashed vertical line represents the results for the entire study (hazard ratio in the CRT–ICD group, 0.66), and the horizontal lines indicate 95% confidence intervals. LVEDV denotes left ventricular end-diastolic volume, LVEF left ventricular ejection fraction, LVESV left ventricular end-systolic volume, and NYHA New York Heart Association. Two subgroup treatment interactions were identified, for sex (P=0.01) and QRS duration (P=0.001). All other interaction P values exceeded 0.10.
## Update ESC guidelines - 2009

### Recommendation in patients with heart failure in New York Heart Association function class III/IV

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Patient population</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-P/CRT-D is recommended to reduce morbidity and mortality&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NYHA function class III/IV, LVEF ≤35%, QRS ≥120 ms, SR, Optimal medical therapy, Class IV patients should be ambulatory&lt;sup&gt;b&lt;/sup&gt;</td>
<td>I</td>
<td>A</td>
<td>5–19</td>
</tr>
</tbody>
</table>

### Recommendation in patients with heart failure in New York Heart Association function class II

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Patient population</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NYHA function class II, LVEF ≤35%, QRS ≥150 ms, SR, Optimal medical therapy</td>
<td>I</td>
<td>A</td>
<td>9, 20–22</td>
</tr>
</tbody>
</table>

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

<sup>d</sup>The guideline indication has been restricted to patients with HF in NYHA function class II with a QRS width ≥150 ms, a population with a high likelihood of a favourable response. CRT = cardiac resynchronization therapy; CRT-D = CRT with defibrillator function; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.
## Recommendation in patients with severe heart failure ineligible for transplant

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Patient population</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref.&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| LVAD may be considered as destination treatment to reduce mortality | NYHA function class III/IV  
LVEF ≤25%  
peak VO<sub>2</sub> < 14 mL/kg/min<sup>d</sup> | IIb              | B                | 49–53           |

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
<sup>d</sup>If obtainable.  
LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.
Diastolic Dysfunction

Evidence based
- Control of hypertension
- Control of ventricular rate in a fib
- Use of diuretics

Treatment of comorbidities
**Heart Failure - Treatment of comorbidities**

**Table 24** Management of patients with heart failure and atrial fibrillation

<table>
<thead>
<tr>
<th>General recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitating factors and co-morbidities should be identified</td>
</tr>
<tr>
<td>HF treatment should be optimized</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rhythm control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate electrical cardioversion is recommended for patients with new-onset AF and myocardial ischaemia, symptomatic hypotension or symptoms of pulmonary congestion or rapid ventricular response not controlled by appropriate pharmacological measures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rate control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin alone or in combination with β-blocker is recommended</td>
</tr>
</tbody>
</table>

**Prevention of thromboembolism**

- Antithrombotic therapy is recommended, unless contraindicated
- Optimal approach should be based on risk stratification:
  - in patients at highest risk of stroke [prior stroke, transient ischaemic attack (TIA), or systemic embolism] oral anticoagulant therapy with vitamin K antagonist is recommended

EHJ, 2008; 29:2388
Guidelines for end stage HF

Level I
- Meticulous fluid control
- HTX
- Specialized Management programs
- End of life care

IIa
- Ventricular assist Devices (VAD)

IIb
- Mitral valve repair
- others
- Left ventricular failure
- Obstruction of Coronary arteries
- Ischemic Mitral incompetence
- Left ventricular ANeurysm
LOCIMAN

Coronary Artery Obstruction

Ischemic Mitral Incompetence

Left Ventricular Aneurysm
Questions

- **What is the relative contribution to left ventricular failure of**
  - hibernating myocardium
  - ischemic mitral incompetence
  - left ventricular aneurysm / akinesia

- **What is the relative benefit of**
  - coronary bypass
  - mitral repair
  - ventricular restoration / aneurysmectomy
Further Questions

- When is an implantable VAD indicated for temporary use and ventricular recovery?

- When is a permanent VAD or TAH indicated?
78 year-old male iCMP (LOCIMAN)

- CABG and Aneurysmectomy 1991
- Implantation of ICD in 1997 and CRT in 2001
- REDO CABG and Aneurysmectomy 2002
- PTCA and Stenting 2003
- PTCA and Stenting 2004
- Hypertension, chronic renal failure, pulmonary hypertension
- July 29, 2009 progressive heart failure and implantation of HeartMate II via left lateral thoracotomy for permanent support
- July 2010: Patient well at home

Support ongoing at 357 days
Long-Term MCS at DHZB 2010

- Pulsatile: Paracorporeal implanted CardioWest
- Axial flow: Total Artificial Heart EXCOR® VAD
- Rotational: JARVIK 2000
- Radial flow: DeBakey VAD®

Mobile Driving System
Women are less frequently/later referred for heart transplantation than men.

Prospective DHZB Study:
- Women were underrepresented.
- Women had more severe disease.
  - Higher NYHA stage
  - Lower exercise tolerance
  - Lower kidney function
- Less relative contraindications - diabetes

\[ \text{NYHA >III} \quad \text{VO2} \quad \text{Crea-cl} \quad \text{diabetes} \]

* \( P<0.05 \)

Transplantation, 2009
Heart Transplantation: Women are more frequent donors and men recipients

n = 1263

- Males donate 32 and receive 18% of organs
- Females donate 146 and receive 11.5% of organs
- Males donate 83 and receive 6.5% of organs
- Females donate 266 and receive 21% of organs

Deutsches Herzzentrum Berlin
Gender differences in kidney and heart transplant rejection

Kidney

Hypotheses
Testosterone leads to stronger activation of vasoconstrictive and inflammatory pathways
Estradiol and 2-ME mediate counter regulation

Heart

Survival [%]

p < 0.05

Survival [ % ]

in days

CUM. SURVIVAL
Arrhythmia treatment

Table 9  Examples of drugs causing torsades de pointes

| Frequent (greater than 1%) (e.g., hospitalization for monitoring recommended during drug initiation in some circumstances) |
| Disopyramide |
| Dofetilide |
| Ibutilide |
| Procainamide |
| Quinidine |
| Sotalol |
| Ajmaline |
| Less frequent |
| Amiodarone |
| Arsenic trioxide |
| Bepridil |
| Cisapride |
| Anti-infectives: clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin |
| Anti-arrhythmics: domperidone, droperidol |
| Antipsychotics: chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide |
| Opioid dependence agents: methadone |

Table 10  Risk factors for drug-induced torsades de pointes

| Female gender |
| Hypokalemia |
| Bradycardia |
| Recent conversion from atrial fibrillation |
| Congestive heart failure |
| Digitalis therapy |
| High drug concentrations (exception: quinidine), often due to drug interactions |
| Rapid rate of intravenous drug administration |
| Baseline QT prolongation |
| Ventricular arrhythmia |
| Left ventricular hypertrophy |
| Congenital long QT syndrome |
| Certain DNA polymorphisms |
| Severe hypomagnesemia |
| Concomitant use of 2 or more drugs that prolong the QT interval |
| Combination of QT-prolonging drug with its metabolic inhibitor |


DNA = deoxyribonucleic acid.

See www.torsades.org for up-to-date listing.
Comparison: amiodarone and ICD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amiodarone (N=845)</th>
<th>Placibo (N=847)</th>
<th>ICD Therapy (N=829)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>60.4</td>
<td>59.7</td>
<td>60.1</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>51.7–68.3</td>
<td>51.2–67.8</td>
<td>51.9–69.2</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>206 (24)</td>
<td>192 (23)</td>
<td>190 (23)</td>
</tr>
<tr>
<td>Nonwhite race — no. (%)</td>
<td>196 (23)</td>
<td>204 (24)</td>
<td>189 (23)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>25.0</td>
<td>25.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>20.0–30.0</td>
<td>20.0–30.0</td>
<td>19.0–30.0</td>
</tr>
<tr>
<td>Diabetes — no. (%)</td>
<td>243 (29)</td>
<td>271 (32)</td>
<td>253 (31)</td>
</tr>
<tr>
<td>Pulmonary disease — no. (%)</td>
<td>147 (17)</td>
<td>158 (19)</td>
<td>175 (21)</td>
</tr>
<tr>
<td>Hypercholesterolemia — no. (%)</td>
<td>442 (52)</td>
<td>456 (54)</td>
<td>431 (52)</td>
</tr>
<tr>
<td>Hypertension — no. (%)</td>
<td>469 (56)</td>
<td>478 (56)</td>
<td>453 (55)</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter — no. (%)</td>
<td>132 (16)</td>
<td>117 (14)</td>
<td>141 (17)</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia — no. (%)</td>
<td>193 (23)</td>
<td>180 (21)</td>
<td>210 (25)</td>
</tr>
<tr>
<td>Syncope — no. (%)</td>
<td>54 (6)</td>
<td>56 (7)</td>
<td>52 (6)</td>
</tr>
<tr>
<td>Electrophysiological study — no. (%)</td>
<td>148 (18)</td>
<td>130 (15)</td>
<td>129 (15)</td>
</tr>
</tbody>
</table>

Bardy, NEJM 2005
Comparison: amiodarone and ICD

Figure 1. Kaplan–Meier Estimates of Death from Any Cause.
Cl denotes confidence interval.

Bardy, NEJM 2005
Ventricular arrhythmia – ICD – therapy

Figure 2. Major implantable cardioverter-defibrillator (ICD) trials. Hazard ratios (vertical line) and 95% confidence intervals (horizontal lines) for death from any cause in the ICD group compared with the non-ICD group. *Includes only ICD and amiodarone patients from CASH. For expansion of trial names, see Appendix 3. CABG = coronary artery bypass graft surgery; EP = electrophysiological study; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; N = number of patients; NICM = nonischemic cardiomyopathy; NSVT = nonsustained ventricular tachycardia; PVCs = premature ventricular complexes; SAECG = signal-averaged electrocardiogram.
Summary

- Guidelines for diagnosis and therapy
- Novel drugs
- Use of CRT
- Use of conventional HF surgery, assist devices and Heart transplantation
- Antiarrhythmic treatment: ICD
Thanks to the working group and to the sponsors

DFG Graduate training

EUGeneHeart

DFG Research Group 1054

EUGIM - EU