Complementary treatment concepts in patients with chronic heart failure

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Conflict of Interest:
Speaker honoraria from SERVIER

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In the current Guidelines on the diagnosis and treatment of acute and chronic heart failure, a precise recommendation how to implement drug treatment in patients heart failure and reduced ejection fraction (HFrEF) is presented.
In these recommendations, the first line of treatment involves the therapy with an ACE-inhibitor (ACEI) and a beta-blocker (BB). It is important to uptitrate these drugs to the maximal tolerated doses. In the case of beta-blockers, a target heart rate between 60 and 70 beats per minute (bpm) should be achieved.

If patients are still symptomatic and their left ventricular (LV) ejection fraction (EF) is 35% or less, then the addition of a mineralocorticoid receptor (MR) antagonist, such as spironolactone or eplerenone, is recommended (all class IA recommendations).

Ponikowski et al., Eur J Heart Fail 2016
If after the addition of an MR antagonist to the ACEI and BB, a patient is still symptomatic, and his/her LVEF is 35% or less, then one or more of the following three actions should be taken, depending on the indication:

1) Replace the ACEI with an Angiotensin-Receptor/Neprilysin-Inhibitor (ARNI). Based on the positive results of the PARADIGM trial, in which LCZ-696 was superior to the ACE-inhibitor enalapril (for total and cardiovascular mortality), this should be performed in stable patients who tolerate high doses of an ACEI…
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

… It is important to wash out the ACEI for at least 36 hours before the first application of an ARNI, since the combination of LCZ-696 with an ACEI could provoke angioedema, based on synergistic (inhibitory) effects of both drugs towards bradykinin clearance. Since LCZ-696 lowers blood pressure more than an ACEI alone, patients switched to LCZ-696 should have a blood pressure of at least 100 mmHg.

2) If the patient is in sinus rhythm (SR) and his QRS duration is 130 msec or larger, then he may be a candidate for a cardiac resynchronization therapy (CRT). `The wider the QRS complex is, the bigger is the benefit from CRT, and patients with a left bundle branch block (LBBB) have more benefit than patients with non-LBBB.

3) If the patient is in SR and his heart rate 70 bpm or more despite optimal doses of a BB, then the addition of ivabradine to treatment is recommended.

In the following, we will discuss how ivabradine improves LV function in patients with systolic heart failure, and thereby learn that ivabradine has complimentary effects to a BB instead of being a different form of the same thing (i.e., a drug that lowers heart rate, HR).
Improving systolic function with Ivabradine

To understand this, it is important to understand how ivabradine improves systolic function in patients with HF acutely, but also in the long term.
During each heart beat, calcium (Ca) enters heart cells through Ca channels and triggers an even greater release of Ca from the Ca stores of the cell, i.e., the sarcoplasmic reticulum (SR). This Ca is available for contraction at the myofilaments. During diastole, Ca is taken back up into the SR by the SR Ca ATPase (SERCA). The Ca that entered the cell via Ca channels is exported by a Na/Ca exchanger.
In patients with systolic heart failure, contractile function of the heart is impaired primarily related to defects in cardiomyocyte Ca handling. Two major problems are that the expression and activity of SERCA are decreased, and that the SR Ca release channel, the ryanodine receptor, is leaky. This leads to decreased Ca load of the SR, which decreases the amount of Ca that is released on every heart beat, and that the Ca levels during diastole are increased, which hampers diastolic function.
Systolic and diastolic dysfunction are aggravated at higher heart rates in CHF (in vitro)

While these defects are mostly compensated at low heart rates, higher heart rates pose substantial problems to Ca handling in human failing myocardium. When the heart rate increases in a normal heart, more Ca enters the cell via Ca channels, and since the Ca export via the Na/Ca exchanger is rather slow, Ca accumulates in the cell. With a well functioning SERCA pump, this Ca is taken up into the SR, so that there is more Ca released from the SR on every heart beat.

This increases the force of contraction, and the optimum of this „positive force-frequency“ (also known as the „Bowditch effect“) is in the range of 180 beats per minute.

Mulieri et al., Circulation 1992;85:1743-1750; Hasenfuss et al., Circulation 1999;99:641-648
Systolic and diastolic dysfunction are aggravated at higher heart rates in CHF (in vitro)

In contrast, in patients with heart failure, due to the defects in SERCA function, the extra Ca that enters the cell via the Ca channels at higher heart rates is not sufficiently taken up into the SR, and this decreases SR Ca load (and thereby, SR Ca release during systole) and increases diastolic Ca levels, impairing diastolic function (see figure on the right).

Taken together, high heart rates impair myocardial function in heart failure, while low heart rates improve it.

Systolic dysfunction is aggravated at higher heart rates in CHF (in vivo)

- Cardiac Index
- LVEF

- n=9 pat. with dilated cardiomyopathy (DCM)
- n=8 normal controls

Hasenfuss et al., Eur Heart J 1994;15:164-170
Systolic dysfunction is aggravated at higher heart rates in CHF (in vivo)

The negative force-frequency relationship is not only observed in isolated muscle strip preparations (as on the slide before), but can also be observed in patients with heart failure in vivo, as shown by this study by Hasenfuss et al., where cardiac index (left) and LV ejection fraction decrease with elevated heart rates (induced by external pacing).
These studies bring up the question whether in patients with heart failure, reduction of heart rate with ivabradine can improve systolic function.
Short-term effects of ivabradine on LV function

At 4 hours:
Heart rate: -27%
Stroke volume: +51%
Cardiac index ↔

10 patients with CHF (NYHA class III; LVEF 21±7%) Ivabradine infusion for 3 h Hemodynamic monitoring for 24 h

In this study on 10 patients with systolic heart failure and a baseline heart rate of 93/min, a 3h infusion of ivabradine reduced heart rate to 68/min. Over the same time course, stroke volume increased by 51%. Thereby, cardiac output (or index) as the product of stroke volume times heart rate remained unchanged despite a 51% reduction in heart rate.
How ivabradine improves cardiac function acutely

Intrinsic myocardial mechanisms

C.O. \( = \) SV \( \uparrow \times \) HR \( \downarrow \)

Ivabradine

Taken together, in patients with systolic heart failure, ivabradine increases stroke volume by lowering heart rate, thereby maintaining cardiac output despite the heart rate reduction.
Short- and long-term hemodynamic effect of β-blockade in patients with heart failure

This is in contrast to the action of a beta-blocker, which can acutely decrease LV function.

In this study on 26 patients with systolic heart failure, the treatment with metoprolol led to an improvement of LV ejection fraction after three months of treatment. One day after the initiation of metoprolol, however, LVEF decreased, which may be related to negative inotropic effects of a beta-blocker.

In the heart, norepinephrine binds to beta-adrenergic receptors and increases the production of cyclic AMP, which phosphorylates protein kinase A, which then phosphorylates all major Ca-transporting enzymes in the cell, thereby increasing force of contraction and relaxation kinetics. Beta-blockers not only block the actions of the agonist, but have an intrinsic own effect on receptor activity:
Negative inotropic effects of β-blockers

In this study, we prestimulated human failing myocardium with the beta-receptor agonist isoproterenol (Iso) and then added either carvedilol (left) or metoprolol (right) at concentrations that block either 50% or 100% of beta-receptors.

It can be seen that while carvedilol reduces force of contraction back to baseline values, metoprolol decreases force even further far below baseline levels. This property is termed „inverse agonist activity“ and provides a good explanation why...

Short- and long-term hemodynamic effect of β-blockade in patients with heart failure

...LV ejection is decreased on the first day of treatment with a beta-blocker.

n=26 pat. with CHF
(DCM; n=16 metoprolol;
n=10 standard therapy)

Intolerance to β-Blockers during initiation

In fact, in the MERIT-HF trial, more patients on metoprolol withdrew from the study in the first three months due to intolerance compared to placebo treated patients. In the time after three months, the opposite was the case, indicating that now the long-term beneficial effects of beta-blockade had unfolded. One important effect of a long-term beta-blocker treatment is an upregulation of SERCA expression, thereby improving the intrinsic biology of the heart.

Gottlieb et al, Circulation 2002;105:1182-1188
Short-term hemodynamic effects of $\beta$-blockers or ivabradine in patients with heart failure

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Taken together, although both beta-blockers and ivabradine reduce heart rate acutely, stroke volume, cardiac output and blood pressure decrease with a beta-blocker, while ivabradine increases stroke volume, thereby maintaining cardiac output and blood pressure despite the (energetically favourable) heart rate reduction.
Despite the acute negative inotropic effect of a beta-blocker, its long-term improvement of cardiac function in the long term leads to a reduction of morbidity and mortality.

Long-term effects of Ivabradine on cardiac function

Therefore, it is important to consider the effects of ivabradine on cardiac function in the long term.
Ivabradine in patients with CHF (SHIfT)

- n=6558 Patients
- NYHA II-III
- LVEF ≤35%
- SR, HR ≥70/min
- Ivabradine 2x7.5 mg vs. Placebo

- Age 61 years
- 76% male
- LVEF 29%
- 68% ICM / 32% DCM
- ACEi/ARB 93%
- BB 90%
- MRA 60%

- Primary Endpoint: CV Death, CHF hospitalization

In the SHIfT trial, 6558 patients with systolic heart failure in sinus rhythm and a heart rate of 70 beats per minute or more were treated with ivabradine or placebo. Of these patients, 90% were already treated with a beta-blocker. The treatment with ivabradine led to a sustained reduction in heart rate over 32 months.

Swedberg et al., Lancet 2010;376:875-85
Ivabradine improves morbidity an HF mortality

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- LVEF ≤35%
- SR, HR ≥70/min
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- Primary Endpoint:
  CV Death,
  CHF hospitalization

This reduction of heart rate with ivabradine reduced the composite endpoint of cardiovascular death and hospitalization for heart failure by 18%.

Swedberg et al., Lancet 2010;376:875-85
Ivabradine reduces HF hospitalizations

- n=6558 Patients
  - NYHA II-III
  - LVEF ≤35%
  - SR, HR ≥70/min
  - Ivabradine 2x7.5 mg vs. Placebo

- Age 61 years
- 76% male
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- ACEi/ARB 93%
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- MRA 60%

- Primary Endpoint:
  - CV Death,
  - CHF hospitalization

Also, the time to first hospital admission due to heart failure was reduced by 26% by ivabradine.

Swedberg et al., Lancet 2010;376:875-85
What were the effects of ivabradine on systolic function?
Ivabradine induces reverse cardiac remodeling

In the echocardiography substudy on the SHIfT population, ivabradine (compared to placebo) decreased left ventricular end-diastolic- and end-systolic volumes and increased LV ejection fraction. While on this first view, the effects of ivabradine appear to be small, they are yet quite substantial when comparing these effects to the effects of a beta-blocker.

Tardif et al. Eur Heart J. 2011;32:2507-15
Reverse cardiac remodeling in CHF by carvedilol and/or ivabradine

In fact, beta-blockers (in contrast to ACE inhibitors) were the first drugs that led to a so-called "reverse remodeling" of the left ventricle. As can be seen from this echocardiographic substudy of the ANZ carvedilol trial, carvedilol reduced LV end-diastolic volumes, while patients on placebo had progressive maladaptive remodeling, indicated by a further dilation of the LV (left figure). Together with this reverse remodeling by Carvedilol, LVEF improved with carvedilol, but not placebo.

Reverse cardiac remodeling in CHF by carvedilolol and/or ivabradine

When superimposing the results from the SHiFT echo substudy on these data, one can see that ivabradine in fact also led to a reverse remodeling that adds to the effect of a beta-blocker per se, since the placebo treated patients were mostly treated with beta-blockers. And in fact, also the increase in LV EF is roughly in the range of improvement as observed with a beta-blocker.

Ivabradine improves exercise capacity and lowers NT-proBNP

n=60 pat. with CHF, NYHA II-III; LVEF 30±5%
Ivabradine (n=30) vs. placebo (n=30) for 3 months

These improvements of LV function also led to improvements of exercise duration, maximal O$_2$ uptake and a reduction in NT-proBNP, and indicator of LV filling pressures.

Sarullo et al., J Cardiovasc Pharmacol Ther 2010;15:349-355
How ivabradine may improve systolic function in patients with CHF (acute and long-term)

Taken together, in patients with heart failure, (1) heart rate reduction with ivabradine improves LV systolic function by reversing the negative force-frequency relationship acutely. (2) In the long term, additional factors come into play, such as an improvement of vascular function, which by decreased fibrosis and stiffness reduces the afterload of the heart. A reduction of afterload is known to improve the energetic situation in the heart and may lower oxidative stress in the heart. (3) These effects may in the long term explain the reverse remodeling of the heart in ivabradine treated patients.
Dose-dependent effects of carvedilol in patients with HF

MOCHA trial Carvedilol vs. placebo
n=345 patients with HF (NYHA II-III)

In patients with heart failure, the treatment with carvedilol led to dose-dependent improvements of LVEF, morbidity and mortality. Therefore, uptitration of beta-blocker doses to a maximum tolerated dose is important to gain the maximum benefit from this treatment.

Bristow et al., Circulation 1996;94:2807-2816
# Target doses of evidence-based treatments

## ESC-HF Pilot Survey
Prescribed β-blockers and doses (n=2,774 patients)

<table>
<thead>
<tr>
<th>β-blocker</th>
<th>Rate of use (%)</th>
<th>Dose (mg/die), median (IQR)</th>
<th>Target dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvediol</td>
<td>42,8</td>
<td>25 (12,9-50)</td>
<td>37,3 (target dose 50 mg/die)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>32,3</td>
<td>5 (2,5-7,5)</td>
<td>20,7 (target dose 10 mg/die)</td>
</tr>
<tr>
<td>Metroprolol</td>
<td>18,9</td>
<td>100 (50-150)</td>
<td>21,4 (target dose 200 mg/die)</td>
</tr>
<tr>
<td>Other β-blockers</td>
<td>6,0</td>
<td></td>
<td></td>
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</tbody>
</table>

However, a large European heart failure survey revealed that in clinical reality, beta-blockers are often underdosed.

Maggioni et al., Eur J Heart Fail 2010;12:1076-84
Short-term hemodynamic effects of β-blockers or ivabradine in patients with heart failure

Due to their complimentary profiles, ivabradine may be suitable to help uptitrate a β-blocker.

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Due to their complimentary profiles, ivabradine may be suitable to help uptitrate a β-blocker.
Combining ivabradine/carvedilol facilitates uptitration of the β-blocker dose in stable patients with chronic HF.

This was tested in a study on 69 patients with heart failure, who were either uptitrated with carvedilol alone or in combination with ivabradine.

Bagriy et al., Adv Ther 2015;32:108-119
Combining ivabradine/carvedilol facilitates uptitration of the β-blocker dose in stable patients with chronic HF.

In fact, the combination of ivabradine with carvedilol increased the maximum achieved carvedilol dose, and the combination led to a more pronounced reduction of heart rate over the initial 20 weeks.

Bagriy et al., Adv Ther 2015;32:108-119
Combining ivabradine and carvedilol improves LV function and symptoms

This was associated with a more pronounced improvement of LVEF and NYHA functional class by the combination of ivabradine with carvedilol compared to carvedilol alone.

Bagriyet et al., Adv Ther 2015;32:108-119
Recurring Hospitalisations Impair Outcome

In patients with chronic heart failure, recurrent hospitalizations are associated with high mortality, and it is assumed that with each heart failure hospitalization, myocardial and renal damage lead to a further deterioration of the disease.

Heart rate 1 week post discharge predicts outcome

In this analysis from the EVEREST trial, heart rate one week after discharge from hospital due to acute heart failure was an important prognostic predictor, with higher heart rates being associated with adverse outcome.

Greene et al, *J Am Coll Cardiol HF* 2013; 488-496; EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) Trial
Synergistic effects of ivabradine and β-blockers efficiently reduce heart rate after acute HF

In this study by Hidalgo et al., patients with systolic heart failure who were hospitalized for acute heart failure were randomized to either beta-blockers alone or beta-blockers in combination with ivabradine, initiated within 24 hours after hospitalization. It could be observed that at discharge (p=0.05) and 4 weeks after discharge, a higher percentage of patients had achieved heart rates below 70 beats per minute, and after 4 months, a trend still remained.

Hidalgo et al., Int J Cardiol 2016;217:7-11
Combination of ivabradine and β-blocker improves LVEF

This was associated with higher LVEF in patients treated with the combination of ivabradine and a beta-blocker compared to patients on a beta-blocker alone.

Hidalgo et al., Int J Cardiol 2016;217:7-11
Take home messages

In patients with chronic heart failure:

- The vulnerable phase after discharge is the first 30 days
- Recurrent hospitalizations predict mortality
- Hemodynamic optimization before discharge may prevent rehospitalization
- Ivabradine improves cardiac function acutely and in the long term
- The effect of ivabradine is complementary with β-blockers regarding hemodynamic effects facilitating initiation of treatment
- Ivabradine reduces hospitalization and improves outcome of HF patients
- This may facilitate the initiation of beta-blocker treatment.

Therefore, the early combination of ivabradine with beta-blockers may improve LV function, symptoms and outcome of patients with heart failure.