The-First-In-Man Randomized Trial of a β3-adrenoceptor Agonist in Chronic Heart Failure-BEAT HF- COMMENTARY

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Nothing to disclose
SUMMARY: In an innovative single center, double-blind, placebo controlled randomized study, Mirabegron, a β3-AR agonist, did not increase LVEF in HF patients.

Proposed mechanisms of a β3-AR:
- negative inotropy through cGMP, eNOS in the normal heart
- stimulation of NA⁺-K⁺ pump results in reduction cytosolic Na⁺, Ca²⁺, may reduce contractility (but may also prevent Ca²⁺ overload in HF as proposed)
- metabolic effects (lipolysis)

Correct Hypothesis? “With HF and Na overloaded myocytes, a decrease in intracellular Na as proposed should improve LV function”

β₃ agonism results in negative inotropy in non-failing and failing hearts
- Reported in ventricular cardiomyocytes from failing hearts
- Accompanied by reductions in the peak systolic cytosolic [Ca²⁺]ᵢ transients
- Negative inotropy attenuated/prevented by β₃ antagonist

Contrary to down-regulated β₁ receptors, β₃-receptors are increased in failing human hearts

Opposite hypothesis also known to be correct: Inhibition of Na⁺/K⁺ ATPase with digoxin results in increase in intracellular Na⁺ & Ca²⁺ concentration → positive inotropy in HF

β₃ AR appears desensitization-resistant
- Negative inotropic effect can be more prominent if superimposed on downregulated β₁ AR in HF
- Bimodal effect could be detrimental when β₃ AR are upregulated

PROPOSED BIMODAL EFFECT NEGATIVE INOTROPY IN NONFAILING, POSITIVE INOTROPY IN FAILING HEARTS?
- Moving Target
  - Hard to predict unsafe phenotypic transition to recovering/recovered LV or treated HF
  - Uncertainty about interaction with other HF medications

Underline the necessity of more complete characterization of effects of β₃ agonism

No significant decline in mean LVEF or worsening of HF in the treated group in the trial

Methodology

Correct Primary End Point? Change in LVEF by CT (enrollment by echo LVEF)
- LVEF is not a measure of contractile performance
- Cardiac mechanics, contractile performance, hemodynamic characterization after acute and chronic exposure in HF patients unknown
- Drugs that improve LVEF, may not improve HF outcomes: vesnarinone, levosimendan, enoximone, xamoterol, prenalterol, isoproterenol, (digoxin)

Underpowered / Type II error?
- Sample size based on LVEF change of 4%, reported SD of 7-10, analyzed sample of 61, power = 0.59
- 5-8% inter observer variability in LVEF and volume measurements

Selection bias? (n=35 randomized, n=29 analyzed)
Patients who died (SCD, n=2), who discontinued due to adverse events (1 each arm), hospitalizations (n=2), noncompliance (n=3) were not included in analysis and may represent the patients who had an adverse effect

Duration: no interim or short term analysis for acute/subacute effects at 1 or 3 months. Bimodal effects, acute negative inotropy could have been missed at six months

Dose: How was the target dose of mirabegron 300 mg /day identified? Overactive bladder treatment dose is 25-50 mg. Side effect profile is highest at 400 mg
Safety Issues Other than Negative Inotropy

- **Cross stimulation of $\beta_1$-$\beta_2$ receptors**: Though selective, cross-reactivity can occur since human $\beta_3$ARs share amino acid sequences, 51% with the $\beta_1$, 46% with $\beta_2$AR respectively –can result in arrhythmia, tachycardia and worsening of HF

- **Anticholinergic effects**: HTN, constipation, dry mouth, tachycardia, arrhythmia

- **Adverse Event Profile**: SCD (n=2, placebo=0), chest pain (n=2, placebo=0) are concerning, overall SAE (mirabegron=8, placebo=5, small #)

**Phase 1 studies with Mirabegron**:
- Most common AEs were ↑ HR, dose dependent (>200 mg /d)
- Women: higher ↑ in HR than men, higher plasma levels, modest BP ↑
- Weight affects pharmacokinetics

In meta-analyses of RCTs in COPD patients, $\beta_2$-AR-agonists associated with ↑ risk for adverse CV events, predominantly sinus tachycardia, may precipitate ischemia, HF, arrhythmias, and SCD

Safety needs to be tested in larger HF populations
- Negative inotropy, tachycardia, arrhythmia, ischemia
- Off target effects: lipolysis, reduced glucose, insulin, CNS effects, urinary retention
- Certain nonselective $\beta$-blockers like carvedilol demonstrated to block $\beta_3$AR
- **Safety on background HF therapy with $\beta$ blockers** (and other HF meds such as digoxin) unclear

Randomized versus Analyzed Patients: Not-Intent-to-Treat, Exploratory Post-hoc Analysis

<table>
<thead>
<tr>
<th>BASELINE Characteristics by CT</th>
<th>Placebo (n=35)</th>
<th>Mirabegron (n=35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>38±17</td>
<td>40±11</td>
<td>0.32</td>
</tr>
<tr>
<td>LV End Diastolic Volume (ml/m²)</td>
<td>131±45</td>
<td>129±41</td>
<td>0.88</td>
</tr>
<tr>
<td>LVES Volume (ml/m²)</td>
<td>84±42</td>
<td>80±38</td>
<td>0.71</td>
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</tbody>
</table>

LV volumes markedly larger in analysis group at baseline despite only mildly depressed LVEF (due to post-randomization exclusion of 9 patients?)

<table>
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<th>Changes by CT</th>
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<tr>
<td>Analysis Patients</td>
<td>Baseline</td>
<td>F/U</td>
<td>Baseline</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>38±17</td>
<td>40±11</td>
<td></td>
</tr>
<tr>
<td>LVED Volume (ml/m²)</td>
<td>276±114</td>
<td>269±116</td>
<td>263±80</td>
</tr>
<tr>
<td>LVES Volume (ml/m²)</td>
<td>178±103</td>
<td>175±107</td>
<td>160±80</td>
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Caution against post-hoc, subgroup exploratory analysis for patients with LVEF< 40 % is only with a few patients (n=8?) not pre-identified, underpowered
Some patients with LVEF > 40 % (by CT mean LVEF 38±17 / 40±11)

Patients not with advanced HF: VO₂ max 20-21 L/min/m², 6 min walk 487-493 m, but NT-proBNP elevated 66-87 pmol/L (560-700 pg/ml), no NYHA IV patients at baseline

No difference in functional, exercise capacity, NT-pro BNP between groups

It appears within each group, NYHA class got better, despite no differences in other variables

Background medications: Unknown

### Patient Population in Analysis: Borderline Depressed LVEF and Not Very Advanced HF

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<tr>
<td>Analysis Patients</td>
<td>Baseline</td>
<td>F/U</td>
<td>Baseline</td>
</tr>
<tr>
<td>NYHA Class (I/II/III)</td>
<td>0/8/91</td>
<td>16/72/13</td>
<td>0/97/3</td>
</tr>
<tr>
<td>6 min walk (m)</td>
<td>487±101</td>
<td>494±98</td>
<td>493±83</td>
</tr>
<tr>
<td>VO2 max (ml/kg/min)</td>
<td>21±6</td>
<td>21±6</td>
<td>20±7</td>
</tr>
<tr>
<td>NT-proBNP (pmol/l)</td>
<td>87±107</td>
<td>91±129</td>
<td>66±55</td>
</tr>
</tbody>
</table>
In a novel but small study with patients with mildly depressed LVEF, β₃-AR agonism did not result in improvement in LVEF, reversal of remodeling, functional or exercise capacity or NT-proBNP levels
- challenging hypothesis, bimodal negative and positive inotropic effect?
- small / potentially underpowered, loss of randomization, dose, duration?
- not the right target population?
- not the right end-point?

Bimodal effect of β₃ agonism: negative inotropy in the normal heart, positive inotropy in the failing heart; potential toxic effects through cross stimulation of β₁/β₂ receptors, uncertain efficacy and safety in the setting of background HF therapy make this agent a very challenging treatment option for general HF patients

More complete characterization of effects of β₃ agonism needed on
- its effects on other proteins, excitation-contraction coupling
- hemodynamic effects, contractility, reversal of remodeling
- with acute, subacute and chronic exposure