Discussion:

Effects of heart rate reduction with ivabradine on left ventricular remodeling and function:

Results of the SHIFT echocardiography sub study

JC Tardif, E O’Meara, M Komajda, M Böhm, JS Borer, I Ford, L Tavazzi, K Swedberg
on behalf of the SHIFT Investigators

Discussant: Prof. Dr. Burkert Pieske

Department of Cardiology

Medical University Graz, Austria

No Disclosures related to this trial
Background

1. High heart rate associated with poor outcomes in heart failure

2. The extent of heart rate reduction with beta blockers relates to their beneficial effects on reverse remodeling and outcome

3. Ivabradine is a selective \( I_f \) channel blocker that reduces sinus node depolarisation rate
What did the authors do?

1. Prespecified echo substudy of the SHIFT trial in 411 (out of 6505) patients from 89 centers/21 countries
2. They used a state-of-the-art central echo core lab for standardised echo readings
3. They assessed LV volumes and EF at baseline and after 8 months therapy with the sinus node inhibitor Ivabradine or placebo
4. They related remodeling to outcome
Major findings of SHIFT echo substudy

Heart rate lowering with Ivabradine associated with substantial reverse remodeling after 8 months:

LVESVI - 5.8 mL/m²  
LVEDVI - 5.5 mL/m²  
EF + 2.7 %

P < 0.001 – 0.002 vs. Placebo

Pronounced LV reverse remodeling (reduction in LVESVI ≥15%) in significantly more patients with Ivabradine (38%) vs. Placebo (25%; p=0.005)
Major findings of SHIFT echo substudy

Remodeling and reverse remodeling associated with outcome:

LVESVI > median at study entry with significant more endpoints during F.U

Largest reduction of LVESVI at 8 month associated with lowest event rate
SHIFT compared to prior Echo HF studies

Δ ESVI (ml/m²) vs. placebo

PHARMACOLOGICAL

- IVABRADINE
  - SHIFT n=422, Δ ESVI = -5.8
  - BEAUTIFUL* n=426, Δ ESVI = -2.6

- EPLERENONE
  - REVERT n=149, Δ ESVI = -10.8
  - METOPROLOL-SUCC.
    - 50 mg n=66, Δ ESVI = -14.5
    - 200 mg n=66, Δ ESVI = -12.9

- NEBIVOLOL
  - SENIORS** n=33, Δ ESVI = -10.8

- CARVEDILOL/ENALAPRIL
  - CARMEN*** n=572, Δ ESVI = -14.5

- CRT
  - REVERSE# n=610, Δ ESVI = -19.6
  - MADIT-CRT# n=1372

* stable CAD and LVSD, HR>60
** estimate (LVESV/2)
*** estimate from Fig. 3 of publication, Δ vs. baseline, not vs. placebo

Udelson JE et al, Circulation Heart Fail 2010 (Eplerenone); Colucci WS et al., Circulation 2007 (REVERT);
Hole T et al., Echocardiography 2004 (MERIT-HF); Ghio S et al., Eur Heart J 2006 (SENIORS); Remme WJ et al., Cardiovasc Drugs Ther 2003; St. John Sutton M et al., Circulation 2009 (REVERSE); Solomon SD et al., Circulation 2010 (MADIT-CRT)
Merits of SHIFT Echo Substudy

1. One of the largest, well conducted echo substudy on reverse remodeling in HF therapy

2. Patients well pretreated with antineurohumoral therapy (92%BB, 96% ACEI/ARB, 72%Aldo-Antag.)

3. Impressive documentation of Ivabradine´s effects on clinically relevant reduction in LV size and improvement in LV function

4. Underscores the importance of reverse remodeling as marker for improved outcome
Considerations and Open questions

1. Similar effectiveness of Ivabradine if more patients on recommended (higher) Beta-blocker doses?

2. Ivabradine only effective in a subset of HF patients: SR and elevated heart rates (in SHIFT, HR≥70/min), relevant reverse remodeling in 38% of those

3. Ancillary mechanisms involved, such as $I_f$ channel inhibition in cardiomyocytes (prevents Ca$^{2+}$ overload)?

4. Effective in conditions with CI/no established indication for BB, such as acute HF or HFprEF?
My conclusions....

Congratulations to the authors and the study team!

Convincing mechanistic data that encourage use of Ivabradine on top of optimised standard HF therapies if in SR and HR above 70 bpm

More studies in selected subgroups and potential new indications warranted!