An update on new treatments, guidelines and trials

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Conflict of interest: Received honorarium from Novartis, Vifor, MSD, Servier, Medtronic, Astra Zeneca
Heart failure update

- New guidelines
- New treatments
- New trials
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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### Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs(^a)</td>
<td>Symptoms ± Signs(^a)</td>
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</tr>
<tr>
<td>2</td>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1. Elevated levels of natriuretic peptides; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).</td>
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</table>

**Note:**
- BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.
- \(^a\)Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.
- \(^b\)BNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL.
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Developed in Collaboration With the International Society for Heart and Lung Transplantation

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This document was approved by the American College of Cardiology Board of Trustees and Executive Committee, the American Heart Association Science Advisory and Coordinating Committee and Executive Committee, and the Heart Failure Society of America Executive Committee in April 2016.
# 2016 ACC/AHA/HFSA Focused Update

**New Pharmacological Therapy for Heart Failure**

<table>
<thead>
<tr>
<th>I</th>
<th>ARNI: B-R</th>
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<tbody>
<tr>
<td></td>
<td>In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).</td>
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</tbody>
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<tr>
<th>IIa</th>
<th>B-R</th>
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<tr>
<td></td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).</td>
</tr>
</tbody>
</table>

### CLASS I (STRONG)

**Benefit >> Risk**

- Suggested phrases for writing recommendations:
  - Is recommended
  - Is indicated/useful/effective/beneficial
  - Should be performed/administered/other
  - Comparative-Effectiveness Phrases:
    - Treatment/strategy A is recommended/indicated in preference to treatment B
    - Treatment A should be chosen over treatment B

### CLASS IIa (MODERATE)

**Benefit >> Risk**

- Suggested phrases for writing recommendations:
  - Is reasonable
  - Can be useful/effective/beneficial
  - Comparative-Effectiveness Phrases:
    - Treatment/strategy A is probably recommended/indicated in preference to treatment B
    - It is reasonable to choose treatment A over treatment B

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Figure 2: Algorithm for pharmacotherapy and device therapy in patients with HF-REF, NYHA class II-IV

Beta blocker AND ACE inhibitor
(if intolerant of ACE inhibitor give an ARB)

Ongoing symptoms (NYHA II-IV)

MRA
(added to ACE inhibitor or ARB)

Ongoing symptoms (NYHA II-IV)
Seek specialist advice

Sacubitril/valsartan
(STOP ACE inhibitors and ARBs; CONTINUE beta blocker and MRA)

Ongoing symptoms (NYHA II-IV)

- ICD or CRT-P/CRT-D in selected patients (see Table 5 in section 6.1)
- Ivabradine (if sinus rhythm heart rate ≥75 bpm)
Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction

NICE technology appraisal guidance [TA388]   Published date: 27 April 2016

1 Recommendations

1.1 Sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people:
   - with New York Heart Association (NYHA) class II to IV symptoms and
   - with a left ventricular ejection fraction of 35% or less and
   - who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs).

1.2 Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be performed by the most appropriate team member as defined in NICE’s guideline on chronic heart failure in adults: management.

1.3 This guidance is not intended to affect the position of patients whose treatment with sacubitril valsartan was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.
NICE adoption support resource

NICE technology appraisal adoption support for sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction – insights from the NHS

Health technology adoption programme
Published: 15 July 2016
nice.org.uk

1 Introduction

This resource has been developed to provide practical information and advice relating to NICE technology appraisal guidance on sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction.
New trials

*Drug Rx*
- ATMOSPHERE
- EFFECT HF & IRONOUT

*Devices*
- REM HF
- DANISH

*AHF*
- TRUE HF
- ATHENA HF
7016 patients with symptomatic HFrEF (LVEF < 35%) randomised to Enalapril, Aliskiren or both (median FU 37 months)

Primary outcome occurred in 770 in combination group vs 808 patients in Enalapril group (HR 0.93; 95% CI, 0.85 to 1.03) and 791 patients in Aliskiren group (HR vs Enalapril, 0.99; 95% CI, 0.90 to 1.10)

Pre specified test for non inferiority not met (not supporting the use of Aliskerin as an alternative to Enalapril)

Significantly more hypotension (P=0.005), worsening renal function (P=0.009) and hyperkalaemia (P<0.001) in combination group

? Ceiling in RAASi Rx has been reached
Iron treatment

• EFFECT HF

174 patients with LVEF<45% and serum ferritin <100 µg/L (or 100–300 µg/L if transferrin saturation [TSAT] <20%) and HB<15g/dL randomised to IV ferric carboxymaltose (FCM) on day 0, week 6, and week 12

Significant improvement in peak VO2 at 24 weeks vs standard of care

• IRONOUT

225 patients with LVEF<40% (mean ferritin was 69 ng/mL and mean haemoglobin 12.65 g/dL) were randomized to placebo or oral Iron

No difference in peak VO2 at 16 weeks

Lewis, presented AHA 2016  
van Veldhuisen, presented AHA 2016
REM HF

- UK study, 9 sites, median FU 2.8 years
- 1650 patients with CHF and device (CRTP/CRTD/ICD) randomised to usual care (UC) or care guided by remote monitoring (RM) with weekly downloads
- No significant difference seen in primary end point (CV death and all cause CV hospitalization): 42.4% in RM group vs 40.8% in UC group (HR 1.01; 95% CI: 0.87 to 1.18; P=0.87)
- Think before you rush in with digital health!
1116 patients with symptomatic Non ischaemic HFrREF (LVEF <35%) randomised to primary prevention ICD or standard RX (median FU 68 months)

- 58% of both groups received CRT
- Primary endpoint (all cause mortality) occurred in 120 patients (21.6%) in ICD group vs 131 patients (23.4%) in the control group (HR 0.87; 95% CI, 0.68 to 1.12; P=0.28)
- No difference in CV death
- Results independent of whether patient received CRT or not
- Reduction in Sudden cardiac death (24 patients [4.3%] in ICD group vs 46 patients [8.2%] in control group (HR 0.50; 95% CI, 0.31 to 0.82; P=0.005)
- ? Signal for benefit in younger patients (<68 years)
- Low event rate in trial reflects benefit of medical RX

TRUE HF

- 2157 patients with ADHF received either iv ularitide (synthetic natriuretic peptide) or placebo within 48 hours of admission
- No difference in primary end point, cardiovascular mortality, for ularitide vs placebo over a median follow-up of 27 months [HR: 1.03 (95% CI 0.85–1.25, \( P=0.75 \))]
- However, patients who received placebo experienced more episodes of "heart-failure events" (second primary endpoint) in the first 48 hours than did those receiving ularitide (\( P=0.005 \))
- No difference in length of stay or rehospitalization at 30 days or 6 months
• 3 way randomisation of 100 mg od or 25 mg od of Spironolactone or placebo given to 360 ADHF patients for 96 hours or to discharge (178 patients given 100 mg od, 46 patients given 25 mg od, 132 patients given placebo)

• No difference in primary endpoint (NT pro BNP change between baseline and 96 hours) between any group seen or 30 day secondary endpoints (including breathlessness scores, renal function, serum K⁺)

• ? Wrong trial design or endpoints
Ongoing trials

- PARAGON HF
- RELAX AHF 2
- MOMENTUM III (Heartmate III LVAD trial)
- SGLT2 inhibitors: CANVAS (Canagliflozin), DECLARE & DAPA-HF (dapagliflozin)
- Cardiac Myosin activator: omecamtiv mecarbil
- Vericiguat (stimulator of soluble guanylate cyclase): VICTORIA
Summary

• Recently updated ESC, AHA/ACC & SIGN guidelines 2016
• New NICE guidance will be published next year
• A lot of new trials telling us what not to do
• Ongoing trials