How should we treat beta-blocker resistance?
Personalized HF care

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Declaration of interests

- Research grants from ResMed, Boston Scientific, St Jude Medical, Bayer
- Consultancy advice and speaker’s fees from Medtronic, ResMed, Boston Scientific, St Jude Medical, Respicardia, Sorin, Servier, Pfizer, Novartis, Daiichi-Sankyo
Who is resistant?

And how can we improve the situation??
Resist(ə)ns

1. the refusal to accept or comply with something: "they displayed a narrow-minded resistance to change"
   - synonyms: opposition to, hostility to, aversion to, refusal to accept, unwillingness to accept, disinclination to accept, reluctance to accept, lack of enthusiasm for:
     "they displayed a narrow-minded resistance to change"

2. the ability not to be affected by something, especially adversely:
   "some of us have a lower resistance to cold than others"
Who is resistant?

And how can we improve the situation??
The evidence base

(a) Mortality

- Copernicus
- Carvedilol
- Placebo
- \( p = 0.00013 \)
- 35\% risk reduction

(b) Survival

- US carvedilol study
- Carvedilol \( (n=696) \)
- Placebo \( (n=396) \)
- Risk reduction = 65\%
- \( p < 0.001 \)

(c) Survival

- CIBIS-II
- Bisoprolol
- Placebo
- Risk reduction = 34\%
- \( p < 0.0001 \)

(d) Mortality %

- MERIT-HF
- Placebo
- Metoprolol CR/XL
- Risk reduction = 34\%
- \( p = 0.0062 \)

References:

a) Packer M et al. Circ 2002; 106: 2194 – 2199
c) Lancet 1999; 353: 9-13
d) Hjalmarson A et al. JAMA 2000; 283; 1295 - 1302

TRENDS in Pharmacological Sciences
European Society of Cardiology
Heart failure guideline 2016

Patient with symptomatic* HFrEF

- Therapy with ACE-I and beta-blocker (Up-titrte to maximum tolerated evidence-based dose)
  - Still symptomatic and LVEF ≤35%
    - No
  - Add MR antagonist** (Up-titrte to maximum tolerated evidence-based dose)
    - Yes
    - Still symptomatic and LVEF ≤35%
  - Sinus rhythm, QRS duration ≥130 msec
    - Sinus rhythm, HR ≥70 bpm
    - Yes
    - Evaluation for CRT
    - Evaluate need for CRT
    - Ivabradine
    - ARNI to replace ACE-I
    - Able to tolerate ACEI (or ARB)†
    - No
    - Consider digoxin or H-ISDN or LVAD, or heart transplantation
    - No further action required

“Treatments recommended in ALL symptomatic patients with HFrEF”

Eur Heart J 2016 (20 May 2016)
DOI: 10.1093/eurheartj/ehw128
UK national hospital audit
2013-14

Overall treatment on discharge for LVSD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total prescribed (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>73</td>
</tr>
<tr>
<td>ARB</td>
<td>19</td>
</tr>
<tr>
<td>ACEI and/or ARB</td>
<td>85</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>85</td>
</tr>
<tr>
<td>MRA</td>
<td>51</td>
</tr>
<tr>
<td>ACEI and/or ARB, beta blocker and MRA</td>
<td>41</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>91</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>5</td>
</tr>
<tr>
<td>Digoxin</td>
<td>22</td>
</tr>
</tbody>
</table>

CLINICAL INDICATOR GROUPS: THE 4 HEART FAILURE INDICATORS: UNDERLYING ACHIEVEMENT

Heart failure means a heart is not pumping blood around the body as it should. The most common reason for this is that the heart muscle is damaged. Heart muscles can be damaged by heart attack, high blood pressure or cardiomyopathy.

The contractor establishes and maintains a register of patients with heart failure

The percentage of patients with a diagnosis of heart failure (diagnosed on or after 1 April 2006) which has been confirmed by an echocardiogram or by specialist assessment 3 months before or 12 months after entering on to the register

<table>
<thead>
<tr>
<th>Percentage of patients from register</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying achievement (net of exceptions)</td>
<td>88.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Percentage of patients receiving the intervention</td>
<td>84.2%</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exceptions</td>
<td>5.8%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

In those patients with a current diagnosis of heart failure due to left ventricular systolic dysfunction, the percentage of patients who are currently treated with an ACE-i or ARB

<table>
<thead>
<tr>
<th>Percentage of patients from register</th>
<th>10%</th>
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<th>30%</th>
<th>40%</th>
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<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying achievement (net of exceptions)</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Percentage of patients receiving the intervention</td>
<td>100.0%</td>
<td></td>
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</tr>
<tr>
<td>Exceptions</td>
<td>0.0%</td>
<td></td>
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</tr>
</tbody>
</table>

In those patients with a current diagnosis of heart failure due to left ventricular systolic dysfunction who are currently treated with an ACE-i or ARB, the percentage of patients who are additionally currently treated with a beta-blocker licensed for heart failure

<table>
<thead>
<tr>
<th>Percentage of patients from register</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
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<th>60%</th>
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<td>100.0%</td>
<td></td>
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</tr>
<tr>
<td>Exceptions</td>
<td>0.0%</td>
<td></td>
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</tr>
</tbody>
</table>

CLINICAL PREVALENCE:

<table>
<thead>
<tr>
<th>Percentage of practice list size</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>9.33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GP performance on -blockade

http://qof.hscic.gov.uk/search/index.asp
August 2000
July 2001
July 2002

% CHF patients
Prescribed
-blocker

Benchmark =
Top 12.5% at
August 2000
What about dose?
547 centers in 36 countries

7092 Adults with LVEF ≤ 40% and previous hospitalization enrolled between August 2012 and December 2014

Use of β-blockers

- Yes: 87%
- No: 13%

Reasons for non-prescription:
- ‘Not indicated’: 35.3%
- Contraindicated: 22.4%
- Not tolerated: 36.3%

Additional statistics:
- Patients at Target Dose: 14.8%
- Patients at ≥ 50% Target Dose: 51.8%

But so what?
Is dosage the be-all and end-all?
All cause mortality by treatment-related heart rate reduction tertile in the randomised trials of β-blocker therapy in HFrEF

Univariable Meta-regressions evaluating the effects of individual co-variates on death benefits of β-blockers in heart failure

<table>
<thead>
<tr>
<th>Potential Modifier</th>
<th>Trials, n</th>
<th>Patients, n</th>
<th>Ratio of Relative Risks (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of men</td>
<td>21</td>
<td>18773</td>
<td>0.93 (0.79–1.10) per 10% increment</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean age</td>
<td>21</td>
<td>18773</td>
<td>1.04 (0.86–1.24) per decade</td>
<td>0.69</td>
</tr>
<tr>
<td>Percentage with an ischemic cause</td>
<td>21</td>
<td>18773</td>
<td>0.99 (0.86–1.14) per 20% increment</td>
<td>0.88</td>
</tr>
<tr>
<td>Mean baseline LVEF</td>
<td>20</td>
<td>18392</td>
<td>1.04 (0.92–1.18) per 5% increment</td>
<td>0.54</td>
</tr>
<tr>
<td>Percentage with NYHA class III or IV symptoms</td>
<td>21</td>
<td>18773</td>
<td>1.00 (0.96–1.05) per 10% increment</td>
<td>0.84</td>
</tr>
<tr>
<td>Percentage with atrial fibrillation</td>
<td>8</td>
<td>8915</td>
<td>1.00 (0.91–1.19) per 5% increment</td>
<td>0.95</td>
</tr>
<tr>
<td>Percentage of digoxin use</td>
<td>19</td>
<td>18336</td>
<td>1.01 (0.96–1.06) per 10% increment</td>
<td>0.64</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>19</td>
<td>17981</td>
<td>1.07 (0.88–1.32) per 5 beats/min</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Heart rate reduction</strong></td>
<td>17</td>
<td>17831</td>
<td>0.82 (0.71–0.94) per 5 beats/min</td>
<td>0.006</td>
</tr>
<tr>
<td>β-Blocker dose</td>
<td>17</td>
<td>17660</td>
<td>1.02 (0.93–1.10) per increment</td>
<td>0.69</td>
</tr>
<tr>
<td>Mean baseline SBP</td>
<td>17</td>
<td>17516</td>
<td>1.00 (0.73–1.35) per 20 mm Hg</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean SBP reduction</td>
<td>10</td>
<td>5462</td>
<td>1.02 (0.87–1.20) per 2 mm Hg</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Agent</strong></td>
<td>21</td>
<td>18773</td>
<td>Reference</td>
<td>–</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>–</td>
<td>–</td>
<td>1.05 (0.82–1.35)</td>
<td>0.68</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>–</td>
<td>–</td>
<td>1.03 (0.77–1.38)</td>
<td>0.85</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>–</td>
<td>–</td>
<td>0.89 (0.29–2.76)</td>
<td>0.83</td>
</tr>
<tr>
<td>Atenolol</td>
<td>–</td>
<td>–</td>
<td>1.36 (1.09–1.69)</td>
<td>0.009</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>–</td>
<td>–</td>
<td>1.30 (0.99–1.71)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

For every 5 beats/min reduction in mean heart rate, the risk ratio decreases by 18% (95% CI 6-29%)

Meta-regression line for magnitude of heart rate reduction and risk ratio of all-cause mortality

But so what?
All my patients have good heart rate control
My clinical practice

audit of 100 consecutive patients in sinus rhythm with EF < 40%

- Average age 65 (range 22-90)
- 74% Men
- 63% IHD
- 20% Diabetes
- Of the 100 patients:
  - 20 intolerant of BB (wheeze, hypotension)
  - 17 ‘low’ dose, unable to go higher
  - 15 ‘moderate’ dose, and unable to go higher
  - 22 full dose BB
  - Leaving 26 with BB dose to be pushed up

Patients in sinus rhythm and completed β-blocker uptitration (N=54) or intolerant of a β-blocker (N=20)

53.4% HR > 70 bpm
20.3% HR > 80 bpm

Ivabradine: ‘pure’ heart rate reduction

Ivabradine

$I_f$ inhibition reduces the diastolic depolarization slope, and thereby lowers heart rate

Systolic Heart Failure treatment with the $I_f$ Inhibitor Ivabradine Trial

**SHIFT**

- D0: Initiate Procoralan 5 mg bid
- D14: Up or down titrate Procoralan to 2.5, 5, or 7.5 mg bid according to HR and tolerability

**Screening**
- Matching placebo, bid
- 7 to 30 days

**n = 3241**
- D0
- D14
- D28
- M4
- n = 3264

- 677 centres in 37 countries
- 6505 patients
- Symptomatic CHF, NYHA Class II to IV
- LV systolic dysfunction (EF 35%)
- HR 70 bpm, sinus rhythm*

- Admitted to hospital for HF in last 12 months
- All aetiologies – 68% ischaemic
- Median follow up 22.9 months
- On stable, guideline-based therapy for heart failure

*The licenced population for Procoralan in EU includes patients with HR $\geq$75bpm

Primary objective

To evaluate whether the $I_f$ inhibitor ivabradine improves cardiovascular outcomes in patients with:

1. Moderate to severe chronic heart failure
2. Left ventricular ejection fraction 35%
3. Heart rate 70 bpm in sinus rhythm
4. Best recommended therapy

Ivabradine 5mg bd or placebo, titrated to 7.5mg/5mg/2.5mg according to tolerability
Chronic heart failure background treatment

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>89, 90</td>
</tr>
<tr>
<td>ACEIs and/or ARBs</td>
<td>91, 91</td>
</tr>
<tr>
<td>Diuretics</td>
<td>84, 83</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>61, 59</td>
</tr>
<tr>
<td>Digitalis</td>
<td>22, 22</td>
</tr>
<tr>
<td>ICD/CRT</td>
<td>3, 4</td>
</tr>
</tbody>
</table>

Mean heart rate reduction

Heart rate (bpm)

Placebo
Ivabradine

64
75
67
75

0 2 weeks 1 4 8 12 16 20 24 28 32
Months

Primary composite end point
(CV death or hospital admission for worsening HF)

HR = 0.82 (0.75–0.90)
P < 0.0001

18% RRR
5% ARR

Ivabradine
Placebo

Cumulative frequency (%)

Months

Death from heart failure

Cumulative frequency (%)

HR = 0.74 (0.58–0.94)
P = 0.014

26% RRR
2% ARR

Placebo
Ivabradine

Hospitalisation for worsening heart failure

Cumulative frequency (%)

HR = 0.74 (0.66–0.83)
P < 0.0001

26% RRR
5% ARR

Effect of ivabradine on total HF hospitalisations

Cumulative incidence of HF hospitalizations (first and repeated)- a post-hoc analysis

IRR (95% CI) = 0.75 (0.65; 0.87)

\[ P = 0.0002 \]

Placebo vs. Ivabradine

N=1186

902 events with ivabradine vs. 1211 events with placebo

## Effect of ivabradine on major outcomes for heart rate ≥ 75 bpm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>ARR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite end point</td>
<td>0.76</td>
<td>0.68-0.85</td>
<td>6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.83</td>
<td>0.71-0.97</td>
<td>2%</td>
<td>0.0166</td>
</tr>
<tr>
<td>Hospitalisation for worsening HF</td>
<td>0.70</td>
<td>0.61-0.80</td>
<td>6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death from HF</td>
<td>0.61</td>
<td>0.46-0.81</td>
<td>2%</td>
<td>0.0006</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.83</td>
<td>0.72-0.96</td>
<td>2%</td>
<td>0.0109</td>
</tr>
<tr>
<td>All-cause hospitalisation</td>
<td>0.82</td>
<td>0.75-0.90</td>
<td>5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any cardiovascular hospitalisation</td>
<td>0.79</td>
<td>0.71-0.88</td>
<td>6%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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**Post hoc analysis**

Heart rate is a predictor of CV death and/or hospitalizations for HF

Risk increases by 3% per 1 bpm increase, and by 16% per 5 bpm increase

European Society of Cardiology
Heart failure guideline 2016

- Patient with symptomatic* HFrEF
  - Therapy with ACE-İ and beta-blocker
    (Up-tritrate to maximum tolerated evidence-based dose)
    - Still symptomatic and LVEF <35%
      - No
    - Add MR antagonist++
      (up-tritrate to maximum tolerated evidence-based dose)
      - Yes
      - Still symptomatic and LVEF <35%
        - No
  - “Treatments recommended in ALL symptomatic patients with HFrEF”

- Diuretics to relieve symptoms and signs of congestion
  - If LVEF <35% despite OMT or a history of symptomatic-VT/VE, implant ICD
  - “Other treatments recommended in SELECTED symptomatic patients with HFrEF”

- Able to tolerate ACE-I or ARB
  - Sinus rhythm, QRS duration ≥130 msec
  - MRI to replace ACE-I
    - Evaluate need for CRT
    - Ivabradine
  - These above treatments may be combined if indicated
    - Resistant symptoms
      - Yes
        - Consider digoxin or H-ISDN or LVAD, or heart transplantation
      - No
        - No further action required
        - Consider reducing diuretic dose

Eur Heart J 2016 (20 May 2016)
Doi:10.1093/eurheartj/ehw128
LV remodeling: echo substudy

- TTE baseline and 8 months
- Core lab readings
- 611 patients
- Change in LVESVI
- Other measurements:
  - ΔLVEF
  - ΔLVESV
  - ΔLVEDV
  - ΔLVEDVI

Post hoc analysis
Tardif JC et al, Eur Heart J (2011) 32, 2507–2515
Primary Endpoint: ΔLVESVI

Post hoc analysis
LVESVI at Baseline and 8 months.

E (SE) = -5.8 (1.6); P < 0.001
95% CI [-8.8, -2.7]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Month 8</th>
<th>Change ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine</td>
<td>65.2 ± 29.1</td>
<td>58.2 ± 28.3</td>
<td>-7.0 (16.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>63.6 ± 30.1</td>
<td>62.8 ± 28.7</td>
<td>-0.9 (17.1)</td>
</tr>
</tbody>
</table>

, change ± standard deviation; E (SE), estimate (standard error of treatment effect).

Tardif JC et al, Eur Heart J (2011) 32, 2507–2515
Distribution by classes of ΔLVESVI

Post hoc analysis

Relative change in LVESVI from baseline to 8 months

- Ivabradine
- Placebo

P = 0.005

NS

Tardif JC et al, Eur Heart J (2011) 32, 2507–2515
Quality of life
Improvement in health-related QOL related to heart rate lowering

Post hoc analysis

European Society of Cardiology
Heart failure guideline 2016

Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.</td>
<td>I</td>
<td>B</td>
<td>178, 179</td>
</tr>
<tr>
<td>Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.</td>
<td>IIa</td>
<td>B</td>
<td>178, 179</td>
</tr>
<tr>
<td><strong>Angiotensin receptor neprilysin inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA.</td>
<td>I</td>
<td>B</td>
<td>162</td>
</tr>
<tr>
<td><strong>If-channel inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).</td>
<td>IIa</td>
<td>B</td>
<td>180</td>
</tr>
<tr>
<td>Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).</td>
<td>IIa</td>
<td>C</td>
<td>181</td>
</tr>
<tr>
<td><strong>ARB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA).</td>
<td>I</td>
<td>B</td>
<td>182</td>
</tr>
<tr>
<td>An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.</td>
<td>IIb</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hydralazine and isosorbide dinitrate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF &lt;45% combined with a dilated LV in NYHA Class III-IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.</td>
<td>IIa</td>
<td>B</td>
<td>183</td>
</tr>
<tr>
<td>Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.</td>
<td>IIb</td>
<td>B</td>
<td>184</td>
</tr>
</tbody>
</table>

Eur Heart J 2016 (20 May 2016)
Doi:10.1093/eurheartj/ehw128
European Society of Cardiology
Heart failure guideline 2016

Patient with symptomatic* HFrEF
- Therapy with ACE-I and beta-blocker (Up-titrated to maximum tolerated evidence-based dose)
  - Still symptomatic and LVEF <35%
    - No
    - Add MR antagonist** (Up-titrated to maximum tolerated evidence-based dose)
      - Still symptomatic and LVEF <35%
        - Yes
        - No
      - Yes
      - No
- Able to tolerate ACEI (or ARB)*
- Sinus rhythm, QRS duration ≥130 msec
- Sinus rhythm*, HR >70 bpm
- ARNI to replace ACE-I
- Evaluate need for CKTV
- Ivabradine
- These above treatments may be combined if indicated
  - Yes
  - No
  - Resistant symptoms
    - Yes
    - Consider digoxin or H-ISDN or LVAD, or heart transplantation
    - No
    - No further action required
    - Consider reducing diuretic dose

“Treatments recommended in ALL symptomatic patients with HFrEF”

“Other treatments recommended in SELECTED symptomatic patients with HFrEF”

“Other treatments with less certain benefits in symptomatic patients with HFrEF”

Eur Heart J 2016 (20 May 2016)
Doi:10.1093/eurheartj/ehw128
Other treatments with less-certain benefits

**Digoxin**

Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).

*Eur Heart J* 2016 (20 May 2016) Doi:10.1093/eurheartj/ehw128
DIG-HF trial: post-hoc analyses

Other heart rate lowering agents

- Non-dihydropyridine Ca\(^{++}\) antagonists
  - -ve chronotropism
  - -ve dromotropism
  - -ve inotropism (particularly verapamil)
  - “Treatment believed to cause harm” in HFrEF
  - Role in HFpEF??

- Amiodarone
  - Only anti-arrhythmic recommended in HFrEF (other than β-blocker)
  - “Better” heart rate control in HFrEF with AF, if β-blocker ± digoxin not tolerated?
AF and heart rate control?

- How (and for whom) can we optimise rhythm control?
- How hard should we strive to return to SR?
- What is an appropriate heart rate in HF with AF?
- Which drugs are least toxic?
- How can we make sure oral anticoagulation is used?
Conclusions

- Measuring heart rate is simple and a good biomarker of risk in HFrEF
- Firmest evidence exists for HFrEF with sinus rhythm
- Beta-blockade is universally recommended
- Ivabradine is a useful tool to optimise heart rate control, usually on top of β-blocker
- Digoxin has been downgraded in most recent ESC guidelines: “less certain benefits”
- β-blocker resistance can be in both patient and physician!