Clinical correlates and outcome associated with changes in 6-Minute Walking Distance in Patients with Heart Failure
Ferreira, João Pedro; Metra, Marco; Anker, Stefan D.; Dickstein, Kenneth; Lang, Chim; Ng, Leong Loke

Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.1380

Publication date:
2019

Document Version
Peer reviewed version

Link to publication in Discovery Research Portal

Citation for published version (APA):
### Table 1. Characteristics of 1,714 patients who performed baseline 6MWT by 6MWT tertiles

<table>
<thead>
<tr>
<th>6MWT (tertiles)</th>
<th>≤240 m</th>
<th>241-360 m</th>
<th>&gt;360 m</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.</td>
<td>591</td>
<td>586</td>
<td>537</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>73 ± 10</td>
<td>67 ± 12</td>
<td>62 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>374 (63%)</td>
<td>453 (77.3%)</td>
<td>465 (86.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient visit</td>
<td>391 (66%)</td>
<td>329 (56.1%)</td>
<td>252 (46.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>27.8 ± 5.4</td>
<td>27.5 ± 4.9</td>
<td>27.7 ± 4.8</td>
<td>0.68</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>82 ± 19</td>
<td>79 ± 19</td>
<td>79 ± 21</td>
<td>0.002</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>125 ± 21</td>
<td>125 ± 20</td>
<td>126 ± 20</td>
<td>0.92</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>345 (59.2%)</td>
<td>278 (48.5%)</td>
<td>157 (30.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>343 (68.2%)</td>
<td>271 (55.2%)</td>
<td>167 (39.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated JVP</td>
<td>127 (32.6%)</td>
<td>95 (23.2%)</td>
<td>72 (18.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>421 (72.3%)</td>
<td>312 (54.4%)</td>
<td>203 (38.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>196 (33.3%)</td>
<td>150 (25.6%)</td>
<td>105 (19.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>30 (25-38)</td>
<td>30 (25-35)</td>
<td>30 (25-35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF &gt;40%</td>
<td>74 (12.5%)</td>
<td>40 (6.8%)</td>
<td>23 (4.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic HF</td>
<td>295 (49.9%)</td>
<td>256 (43.7%)</td>
<td>195 (36.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>223 (37.7%)</td>
<td>192 (32.8%)</td>
<td>151 (28.1%)</td>
<td>0.003</td>
</tr>
<tr>
<td>HFH in the last 12 months</td>
<td>228 (38.6%)</td>
<td>193 (32.9%)</td>
<td>162 (30.2%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>299 (50.6%)</td>
<td>246 (42.0%)</td>
<td>217 (40.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>61 (10.3%)</td>
<td>40 (6.8%)</td>
<td>33 (6.1%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Peripherial arterial disease</td>
<td>73 (12.4%)</td>
<td>42 (7.2%)</td>
<td>45 (8.4%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hypertension</td>
<td>404 (68.4%)</td>
<td>380 (64.8%)</td>
<td>307 (57.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Device therapy</td>
<td>151 (25.5%)</td>
<td>133 (22.7%)</td>
<td>113 (21.0%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Current smoking</td>
<td>73 (12.4%)</td>
<td>78 (13.3%)</td>
<td>80 (14.9%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>238 (40.3%)</td>
<td>173 (29.5%)</td>
<td>132 (24.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>138 (23.4%)</td>
<td>90 (15.4%)</td>
<td>64 (11.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>25 (4.2%)</td>
<td>15 (2.6%)</td>
<td>9 (1.7%)</td>
<td>0.032</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.7 ± 1.8</td>
<td>13.3 ± 1.8</td>
<td>13.9 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>56.9 ± 21.5</td>
<td>64.8 ± 23.6</td>
<td>72.3 ± 21.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Urea (mmol/L)</td>
<td>15.8 ± 10.3</td>
<td>13.3 ± 10.8</td>
<td>12.2 ± 8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Sodium (mmol/L)</td>
<td>139.1 ± 4.1</td>
<td>139.4 ± 3.5</td>
<td>140.0 ± 3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Potassium (mmol/L)</td>
<td>4.2 ± 0.6</td>
<td>4.2 ± 0.5</td>
<td>4.3 ± 0.5</td>
<td>0.66</td>
</tr>
<tr>
<td>Plasma Glucose (mmol/L)</td>
<td>7.2 ± 3.1</td>
<td>6.9 ± 2.9</td>
<td>6.7 ± 2.4</td>
<td>0.047</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.1 ± 1.37</td>
<td>4.4 ± 1.3</td>
<td>4.5 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.3</td>
<td>0.52</td>
</tr>
<tr>
<td>NT-pro BNP (NPX)</td>
<td>3.3 ± 1.3</td>
<td>2.7 ± 1.3</td>
<td>2.4 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TnI (pg/mL)*</td>
<td>14.5 (7.8-33.2)</td>
<td>11.1 (6.3-23.8)</td>
<td>8.3 (5.0-15.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRA</td>
<td>289 (49.1%)</td>
<td>327 (55.8%)</td>
<td>302 (56.2%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>590 (&gt;99%)</td>
<td>582 (&gt;99%)</td>
<td>534 (&gt;99%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Digoxin</td>
<td>110 (18.6%)</td>
<td>108 (18.4%)</td>
<td>102 (19.0%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>475 (80.4%)</td>
<td>513 (87.5%)</td>
<td>465 (86.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Beta-blocker &gt;=50% at 3 mo.</td>
<td>196 (33.2%)</td>
<td>222 (37.9%)</td>
<td>223 (41.5%)</td>
<td>0.014</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>408 (69.0%)</td>
<td>449 (76.6%)</td>
<td>418 (77.8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>ACEi/ARB &gt;=50% at 3 mo.</td>
<td>282 (47.7%)</td>
<td>324 (55.3%)</td>
<td>342 (63.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6MWT (meters)*</td>
<td>154 (100-200)</td>
<td>310 (280-337)</td>
<td>422 (390-475)</td>
<td>-</td>
</tr>
</tbody>
</table>

Legend: BMI, body mass index; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HFH, heart failure hospitalization; COPD, chronic
obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker. *median (pct25-75).
Table 2. Multivariable linear regression for baseline 6MWT (m) as dependent variable

<table>
<thead>
<tr>
<th>Continuous 6MWT (baseline)</th>
<th>Std. beta-coefficient</th>
<th>Std. Err.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yr)</td>
<td>-33.0 (-39.2 to -26.7)</td>
<td>3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>59.2 (43.1 to 75.3)</td>
<td>8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient</td>
<td>-68.4 (-85.6 to -51.2)</td>
<td>8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (per 10 bpm)</td>
<td>-6.1 (-9.5 to -2.7)</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>-58.9 (-75.2 to -42.6)</td>
<td>8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>-31.5 (-47.6 to -15.4)</td>
<td>8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>-32.8 (-47.3 to -18.3)</td>
<td>7.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>-37.2 (-60.6 to -13.7)</td>
<td>11.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Current malignancy</td>
<td>-46.2 (-83.9 to -8.6)</td>
<td>19.2</td>
<td>0.016</td>
</tr>
<tr>
<td>Serum Sodium (per 1 mmol/L)</td>
<td>4.0 (2.3 to 5.7)</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP (per NPX doubling)</td>
<td>-12.4 (-18.0 to -6.9)</td>
<td>2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LogTnI (per each Log10)</td>
<td>-28.8 (-42.2 to -15.5)</td>
<td>6.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Model adjusted $R^2$ = 0.35
Constant = 147.6

The standardized (std.) beta-coefficient compares the strength of the effect of each individual independent variable to the dependent variable (6MWT). The higher the absolute value of the beta coefficient, the stronger the effect.
Table 3. Cox-proportional hazards models investigating the relationship between baseline 6MWT and outcome

<table>
<thead>
<tr>
<th>HFH or Death</th>
<th>N. (%) of events</th>
<th>Crude HR (95%CI)</th>
<th>P-value</th>
<th>Adjusted HR (95%CI)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous 6MWT (m)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per each 50m less</td>
<td>641 (37.4%)</td>
<td>1.19 (1.15-1.22)</td>
<td>&lt;0.001</td>
<td>1.08 (1.04-1.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tertile 6MWT (m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;360 m</td>
<td>118 (22.0%)</td>
<td>Reference</td>
<td>-</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>241-360 m</td>
<td>210 (35.8%)</td>
<td>1.85 (1.47-2.31)</td>
<td>&lt;0.001</td>
<td>1.44 (1.14-1.80)</td>
<td>0.002</td>
</tr>
<tr>
<td>≤240 m</td>
<td>313 (53.0%)</td>
<td>3.07 (2.48-3.79)</td>
<td>&lt;0.001</td>
<td>1.73 (1.38-2.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. (%) of events</td>
<td>385 (22.5%)</td>
<td>1.25 (1.19-1.30)</td>
<td>&lt;0.001</td>
<td>1.14 (1.09-1.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tertile 6MWT (m)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;360 m</td>
<td>57 (10.6%)</td>
<td>Reference</td>
<td>-</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>241-360 m</td>
<td>109 (18.6%)</td>
<td>1.88 (1.37-2.60)</td>
<td>&lt;0.001</td>
<td>1.49 (1.08-2.06)</td>
<td>0.016</td>
</tr>
<tr>
<td>≤240 m</td>
<td>219 (37.1%)</td>
<td>4.11 (3.08-5.50)</td>
<td>&lt;0.001</td>
<td>2.41 (1.76-3.29)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted on the BIOSTAT-CHF risk model including: age, heart failure hospitalizations in previous year, systolic blood pressure, presence of peripheral edema, NT-proBNP, hemoglobin, sodium, HDL cholesterol, and the use of beta-blockers (https://biostat-chf.shinyapps.io/calc/).

Total n. = 1,714; Tertile n. ≤240m = 591; 241-360m = 586; >360m = 537.
Table 4. Logistic regression of association between 6MWT and likelihood of titration of disease-modifying therapy to >50% of guideline-recommended target doses

<table>
<thead>
<tr>
<th>Treatment up-titration</th>
<th>OR (95%CI)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi/ARB or β-blocker ≥50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous 6MWT (m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT per each 50m decline</td>
<td>0.91 (0.85-0.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>Tertile 6MWT (m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;360 m</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>241-360 m</td>
<td>0.66 (0.47-0.92)</td>
<td>0.014</td>
</tr>
<tr>
<td>≤240 m</td>
<td>0.63 (0.43-0.92)</td>
<td>0.016</td>
</tr>
<tr>
<td>ACEi/ARB ≥50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous 6MWT (m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT per each 50m decline</td>
<td>0.95 (0.90-1.01)</td>
<td>0.052</td>
</tr>
<tr>
<td>Tertile 6MWT (m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;360 m</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>241-360 m</td>
<td>0.76 (0.56-1.02)</td>
<td>0.075</td>
</tr>
<tr>
<td>≤240 m</td>
<td>0.75 (0.54-1.04)</td>
<td>0.088</td>
</tr>
<tr>
<td>β-blocker ≥50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous 6MWT (m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT per each 50m decline</td>
<td>0.91 (0.85-0.96)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tertile 6MWT (m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;360 m</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>241-360 m</td>
<td>0.85 (0.63-1.16)</td>
<td>0.31</td>
</tr>
<tr>
<td>≤240 m</td>
<td>0.66 (0.46-0.94)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

*Adjusted on the “best” up-titration prediction model including: age, sex, race, heart failure duration, heart failure hospitalization in the previous year, heart failure of ischemic etiology, diabetes mellitus, hypertension, body mass index, systolic blood pressure, heart rate, left ventricular ejection fraction, NT-pro BNP, and estimated glomerular filtration rate.
Table 5. Logistic and linear regression for the association of medication up-titration with 6MWT change in meters (from baseline to 9-months)

<table>
<thead>
<tr>
<th>Up-titration</th>
<th>6MWT decrease*</th>
<th>6MWT increase</th>
<th>OR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi/ARB or BB ≥50%</td>
<td>339 (71.8%)</td>
<td>889 (71.3%)</td>
<td>0.97 (0.77-1.23)</td>
<td>0.83</td>
</tr>
<tr>
<td>ACEi/ARB ≥50%</td>
<td>266 (56.4%)</td>
<td>705 (56.5%)</td>
<td>1.01 (0.81-1.25)</td>
<td>0.95</td>
</tr>
<tr>
<td>Beta-blocker ≥50%</td>
<td>200 (42.4%)</td>
<td>497 (39.9)</td>
<td>0.90 (0.73-1.12)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Linear regression for 6MWT change as continuous variable

<table>
<thead>
<tr>
<th>Up-titration</th>
<th>6MWT change : beta coefficient (95%CI)</th>
<th>Std. error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi/ARB or beta-blocker ≥50%</td>
<td>4.42 (-13.78 to 22.63)</td>
<td>9.28</td>
<td>0.63</td>
</tr>
<tr>
<td>ACEi/ARB ≥50%</td>
<td>2.78 (-13.80 to 19.37)</td>
<td>8.46</td>
<td>0.74</td>
</tr>
<tr>
<td>Beta-blocker ≥50%</td>
<td>-7.21 (-23.95 to 9.53)</td>
<td>8.54</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Legend: 6MWT, 6-minute walking test distance in meters; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; *6MWT decrease group includes 0 i.e., no change.
The standardized beta-coefficient compares the strength of the effect of each individual independent variable to the dependent variable (6MWT). The higher the absolute value of the beta coefficient, the stronger the effect.
Table 6. Cox-proportional hazards models investigating the relationship between 6MWT distance change from baseline to 9 months and outcome

<table>
<thead>
<tr>
<th>HFH or Death</th>
<th>Crude HR (95%CI)</th>
<th>P-value</th>
<th>Adjusted HR (95%CI)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per each 50m decrease (continuous)</td>
<td>1.09 (1.06-1.12)</td>
<td>&lt;0.001</td>
<td>1.09 (1.06-1.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6MWT (decrease vs. increase)</td>
<td>1.56 (1.30-1.85)</td>
<td>&lt;0.001</td>
<td>1.54 (1.30-1.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>Crude HR (95%CI)</td>
<td>P-value</td>
<td>Adjusted HR (95%CI)*</td>
<td>P-value</td>
</tr>
<tr>
<td>Per each 50m decrease (continuous)</td>
<td>1.09 (1.04-1.14)</td>
<td>&lt;0.001</td>
<td>1.09 (1.04-1.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6MWT (decrease vs. increase)</td>
<td>1.59 (1.20-2.08)</td>
<td>&lt;0.001</td>
<td>1.64 (1.25-2.13)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted on the BIOSTAT-CHF risk model including: age, heart failure hospitalizations in previous year, systolic blood pressure, presence of peripheral edema, NT-proBNP, hemoglobin, sodium, HDL cholesterol, and the use of beta-blockers (https://biostat-chf.shinyapps.io/calc/).