**Supplementary Material**

**Guideline directed medical therapy in advanced heart failure with reduced ejection fraction: an analysis of the HELP-HF Registry**

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**Short Title:** GDMT in advanced HFrEF.

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| **Supplementary Table 1. Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction (from 2021 ESC guidelines for the management of acute and chronic HF(1))** |
| **ACE-I**Captopril, 50 mg t.i.d.Enalapril, 10-20 mg b.i.d.Lisinopril, 20-35 mg o.d.Ramipril, 5 mg b.i.d.Trandolapril, 4 mg o.d. |
| **ARNI**Sacubitril/valsartan, 97/103 mg b.i.d. |
| **Beta-blockers**Bisoprolol, 10 mg o.d.Carvedilol, 25 mg b.i.d.eMetoprolol succinate (CR/XL), 200 mg o.d.Nebivolol, 10 mg o.d. |
| **MRA**Eplerenone, 50 mg o.d.Spironolactone, 50 mg o.d. |

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| Supplementary Table 2. Use of GDMT in the subgroup of patients fulfilling the 2018 HFA-ESC criteria for advanced HF (n = 152) |
|  | **Beta blockers** | **ACEi/ARB/ARNI** | **MRA** |
| Treated patients | 116 (76.8) | 76 (50.3) | 101 (66.9) |
| Dose ≥50% of the target dose | 50 (33.1) | 34 (22.5) | 98 (64.9) |
| Fractional dose, % | 43.6 ± 33.6 | 48.9 ± 31.0 | 97.8 ± 72.9 |
| Reasons for lack of treatment |
| Low blood pressure | 14 (40.0) | 24 (32.0) | 3 (6.0) |
| Bradycardia | 3 (8.6) | - | - |
| Chronic kidney disease | 1 (2.7) | 22 (29.3) | 12 (24.0) |
| Hyperkalaemia | - | 2 (2.7) | 8 (16.0) |
| Other side effects | 3 (8.6) | 2 (2.7) | - |
| Unknown reasons | 13 (37.1) | 25 (33.3) | 27 (54.0) |
| Reason for underdosing (<50% target dose) |
| Low blood pressure | 42 (41.6) | 51 (43.6) | 3 (5.7) |
| Bradycardia | 5 (5.0) | - | - |
| Chronic kidney disease | 3 (3.0) | 23 (19.7) | 12 (22.6) |
| Hyperkalaemia | - | 2 (1.7) | 9 (17.0) |
| Other side effects | 8 (7.9) | 3 (2.6) | - |
| Unknown reasons | 42 (41.6) | 38 (32.5) | 29 (54.7) |

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| **Supplementary Table 3** **Univariable and Multivariable Models for All-cause Death** |
|  | **Univariate** | **Multivariate\*** |
|  | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| Beta-blocker use (any dose) | 0.42 (0.30-0.58) | **<0.001** | 0.50 (0.36-0.71) | **<0.001** |
| Fractional dose beta blocker (%) | 0.34 (0.21-0.55) | **<0.001** | 0.52 (0.31-0.88) | **0.015** |
| Beta-blockers dose ≥50% target dose vs. no therapy or <50% target dose | 0.54 (0.39-0.74) | **<0.001** | 0.73 (0.51-1.03) | 0.073 |
| *Beta-blockers dose categories* ≥50% target dose vs. no therapy 1-49% target dose vs. no therapy | 0.34 (0.23-0.50)0.50 (0.35-0.72) | **<0.001****<0.001** | 0.48 (0.32-0.72)0.52 (0.36-0.76) | **<0.001****0.001** |
| ACE-I/ARB/ARNI use (any dose) | 0.45 (0.33-0.61) | **<0.001** | 0.66 (0.47-0.93) | **0.016** |
| Fractional dose ACE-I/ARB/ARNI (%) | 0.34 (0.19-0.62) | **<0.001** | 0.62 (0.35-1.12) | 0.114 |
| ACE-I/ARB/ARNI dose ≥50% target dose vs. no therapy or <50% target dose | 0.60 (0.39-0.90) | **0.015** | 0.79 (0.50-1.24) | 0.301 |
| *ACE-I/ARB/ARNI dose categories* ≥50% target dose vs. no therapy 1-49% target dose vs. no therapy | 0.45 (0.29-0.69)0.45 (0.31-0.65) | **<0.001****<0.001** | 0.68 (0.42-1.08)0.65 (0.43-0.96) | 0.106**0.032** |
| MRA use (any dose) | 0.76 (0.56-1.02) | 0.070 | 0.80 (0.59-1.10) | 0.168 |
| Fractional dose MRA (%) | 0.97 (0.75-1.24) | 0.795 | 1.06 (0.81-1.38) | 0.677 |
| MRA dose ≥50% target dose vs. no therapy or <50% target dose | 0.81 (0.60-1.09) | 0.161 | 0.83 (0.61-1.14) | 0.246 |
| *MRA dose categories* ≥50% target dose vs. no therapy 1-49% target dose vs. no therapy | 0.77 (0.57-1.04)0.52 (0.19-1.43) | 0.0970.208 | 0.81 (0.59-1.12)0.66 (0.24-1.83) | 0.1990.426 |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist

\*Adjusted for age, sex, inpatient versus outpatient status, peripheral artery disease, prior stroke or transient ischaemic attack, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, New York Heart Association class III–IV, systolic blood pressure, heart rate and estimated glomerular filtration rate (as in the previously published model of the original HELP-HF study)

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| **Supplementary Table 4** **Multivariable Models for the primary endpoint and for all-cause death including natriuretic peptides among covariates.** |
|  | **All-cause death or HF hospitalization\*** | **All-cause death#** |
|  | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| Beta-blocker use (any dose) | 0.72 (0.53-0.99) | **0.046** | 0.62 (0.42-0.92) | **0.017** |
| Beta-blockers dose ≥50% target dose vs. no therapy or <50% target dose | 0.69 (0.52-0.91) | **0.008** | 0.77 (0.53-1.11) | 0.158 |
| *Beta-blockers dose categories* ≥50% target dose vs. no therapy 1-49% target dose vs. no therapy | 0.60 (0.42-0.86) 0.83 (0.59-1.16) | **0.006**0.273 | 0.58 (0.37-0.91)0.66 (0.43-1.01) | **0.019**0.053 |
| ACE-I/ARB/ARNI use (any dose) | 0.79 (0.61-1.04)  | 0.094 | 0.76 (0.52-1.10) | 0.145 |
| ACE-I/ARB/ARNI dose ≥50% target dose vs. no therapy or <50% target dose | 0.80 (0.57-1.12) | 0.200 | 0.85 (0.53-1.36) | 0.493 |
| *ACE-I/ARB/ARNI dose categories* ≥50% target dose vs. no therapy 1-49% target dose vs. no therapy | 0.75 (0.52-1.07)0.83 (0.61-1.13) | 0.1070.241 | 0.77 (0.47-1.26)0.75 (0.48-1.17) | 0.2930.203 |
| MRA use (any dose) | 0.92 (0.70-1.19) | 0.516 | 0.80 (0.56-1.12) | 0.191 |
| MRA dose ≥50% target dose vs. no therapy or <50% target dose | 0.93 (0.71-1.20) | 0.563 | 0.80 (0.57-1.13) | 0.209 |
| *MRA dose categories* ≥50% target dose vs. no therapy 1-49% target dose vs. no therapy | 0.92 (0.70-1.20)0.89 (0.41-1.93) | 0.763 | 0.79 (0.56-1.13)0.83 (0.30-2.32) | 0.1940.724 |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist

\*Adjusted for age, sex, inpatient versus outpatient status, peripheral artery disease, prior stroke or transient ischaemic attack, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, New York Heart Association class III–IV, systolic blood pressure, estimated glomerular filtration rate and natriuretic peptides (< vs >= median value)

# Adjusted for age, sex, inpatient versus outpatient status, peripheral artery disease, prior stroke or transient ischaemic attack, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, New York Heart Association class III–IV, systolic blood pressure, heart rate, estimated glomerular filtration rate and natriuretic peptides (< vs >= median value)

**Supplementary Figure 1.** Kaplan Meier curves for 1-year all-cause death according to beta-blockers use and dose (not prescribed vs prescribed at <50% of the target dose vs prescribed at ≥50% of the target dose).



**Supplementary Figure 2**. Kaplan Meier curves for 1-year all-cause death according to ACEi/ARB/ARNI use and dose (not prescribed vs prescribed at <50% of the target dose vs prescribed at ≥50% of the target dose).



**Supplementary Figure 3**. Kaplan Meier curves for 1-year all-cause death according to MRA use and dose (not prescribed vs prescribed at <50% of the target dose vs prescribed at ≥50% of the target dose)



**References**

1. Authors/Task Force M, McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022;24(1):4-131.