TITLE:

Baroreflex activation therapy with the BAROSTIM™ DEVICE in patients with heart failure with reduced ejection fraction: A patient level meta-analysis of randomized controlled trials

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**Abbreviations**

BATTM: Baroreflex Activation Therapy; CRT: Cardiac Resynchronization Therapy; 6MHW: Six Minute Hall Walk; QoL: Minnesota Living with Heart Failure Quality of Life (MLWHF) questionnaire score; NT-proBNP/BNP: N-terminal pro-B-type natriuretic peptide; NYHA Class: New York Heart Class Association; CRT: Cardiac Resynchronization Therapy; OR: Odds Ratio; CI: Confidence Interval; GDMT Guideline Directed Medical Therapy; NCI: No CRT Indication

SUPPLEMENT

**Supplement Table 1: BASELINE DEMOGRAPHCS COMBINED ACROSS HOPE4HF AND BeAT\_HF**

| **Variable** | **HOPE4HF and BEAT-HF** |
| --- | --- |
| Demographics |  |
|   Sex: Women | 19% |
|   NYHA: Class III | 95% |
|   Age(years) | 64 ± 11 |
| Health Status |  |
|   BMI (kg/m2) | 30 ± 5 |
|   SBP (mmHg) | 119 ± 18 |
|   DBP (mmHg) | 73 ± 11 |
|   HR (bpm) | 75 ± 11 |
|   LVEF (%) | 26 ± 7 |
|   NT-proBNP (pg/mL)\* | 1092 (569, 2524) |
|   6 Minute Walk (m) | 297 ± 75 |
|   QOL | 51 ± 24 |
| Co-Morbidities |  |
|   Coronary Artery Disease | 66% |
|   Atrial Fibrillation | 41% |
|   Chronic Kidney Disease | 29% |
|   Diabetes Type II | 42% |
| HF Treatments |  |
|   ACE-I/ARB or ARNI | 83% |
|   Beta-Blocker | 92% |
|   Diuretics | 85% |
|   CRT | 10% |
|   ICD/CRT-D | 81% |
|  |

Results reported as Mean ± SD/or %
\*\*Results reported as median (IQR)

**Supplement Table 2: ENdpoint Results Across All PATIENTS BY TRIALS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Endpoint / Trial** | **Device** | **Control** | **Device - Control** |
| **n** | **Diff (95% CI)** | **n** | **Diff (95% CI)** | **Diff (95% CI)\*** | **p-value** |
| ***6MHW*** |  |  |  |  |  |  |
|  HOPE4HF | 56 | 60 (31,88) | 43 | 1.5 (-25,28) | 58 (20,96) | 0.003 |
|  BeAT-HF | 168 | 39 (27,50) | 182 | -6.4 (-19,6.5) | 47 (29,64) | <0.001 |
| ***QoL MLWHF*** |  |  |  |  |  |  |
|  HOPE4HF | 64 | -17 (-23,-12) | 54 | 2.1 (-4.2,8.4) | -13 (-21,-5.9) | <0.001 |
|  BeAT-HF | 170 | -22 (-26,-18) | 189 | -6.9 (-9.9,-3.9) | -13 (-18,-9.0) | <0.001 |
| ***NT-proBNP***†  |  |  |  |  |  |  |
|  HOPE4HF | 43 | -3.2% (-23,22) | 40 | 37% (0.5,88) | -30% (-51,1.4) | 0.06 |
|  BeAT-HF | 170 | -17% (-27,-6.2) | 186 | -9.8% (-19,1.1) | -9.6% (-23,6.6) | 0.23 |
| ***NT-proBNP / BNP\*\**** |  |  |  |  |   |
|  HOPE4HF | 59 | 2.4% (-14,23) | 48 | 31% (0.5,70) | -22% (-42,5.4) | 0.106 |
|  BeAT-HF | 170 | -17% (-27,-6.2) | 186 | -9.8% (-19,1.1) | -9.6% (-23,6.6) | 0.23 |
|  | **n** | **nimp (%)** | **n** | **nimp (%)** | **OR (95% CI)** | **p-value** |
| ***NYHA Class*** |  |  |  |  |  |  |
|  HOPE4HF | 64 | 35 (55%) | 54 | 13 (24%) | 3.81 (1.72,8.43) | 0.001 |
|  BeAT-HF | 170 | 100 (59%) | 190 | 58 (31%) | 3.25 (2.11,5.02) | <0.001 |

Abbreviations: BATTM: Barostim Therapy; 6MHW: 6-minute Hall Walk; QoL: Minnesota Living with Heart Failure Quality of Life; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Class Association; CRT: Cardiac Resynchronization Therapy; OR: Odds Ratio; CI: Confidence Interval

\* Adjusted mean difference from ANCOVA (95% CI)

\*\* Combined relative reduction of BNP and NT‐proBNP

**SUPPLEMENT Table 3: ENdpoint Results Across All PATIENTS BY TRIALS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Endpoint / Cohort** | **N** | **I2** | **Difference** **(95% CI)\*** |
| **HOPE4HF** | **BeAT-HF** |
| ***6MHW*** |  |  |  |  |
|  All patients | 99 | 350 | 0% | 48.5 (32.7, 64.2) |
|  NT-proBNP<1600 | 43 | 238 | 0% | 61.2 (42.1, 80.3) |
|  NT-proBNP<1600 or BNP<400 | 61 | 238 | 0% | 58.8 (40.3, 77.4) |
|  No CRT | 65 | 350 | 41% | 50.2 (33.8, 66.5) |
|  No CRT and NT-proBNP<1600 | 28 | 238 | 48% | 63.0 (43.7, 82.4) |
| ***QoL MLWHF*** |  |  |  |  |
|  All patients | 118 | 359 | 0% | -13.4 (-17.1, -9.6) |
|  NT-proBNP<1600 | 50 | 245 | 0% | -13.4 (-18.1, -8.8) |
|  NT-proBNP<1600 or BNP<400 | 69 | 245 | 53% | -12.3 (-16.8, -7.7) |
|  No CRT | 79 | 359 | 12% | -14.3 (-18.3, -10.4) |
|  No CRT and NT-proBNP<1600 | 34 | 245 | 0% | -13.9 (-18.7, -9.1) |
| ***NT-proBNP*** |  |  |  |  |
|  All patients | 83 | 356 | 33% | -13.3 (-25.4, 0.69) |
|  NT-proBNP<1600 | 48 | 243 | 0% | -25.4 (-37.6, -10.5) |
|  NT-proBNP<1600 or BNP<400 | 48 | 243 | 0% | -25.4 (-37.6, -10.5) |
|  No CRT | 58 | 356 | 54% | -13.7 (-25.9, 0.46) |
|  No CRT and NT-proBNP<1600 | 33 | 243 | 0% | -25.4 (-37.6, -10.7) |
| ***NT-proBNP / BNP\*\**** |  |  |  |  |
|  All patients | 107 | 356 | 0% | -12.7 (-24.3, 0.93) |
|  NT-proBNP<1600 | 48 | 243 | 0% | -25.4 (-37.6, -10.5) |
|  NT-proBNP<1600 or BNP<400 | 67 | 243 | 0% | -23.6 (-35.7, -9.22) |
|  No CRT | 73 | 356 | 0% | -12.5 (-24.5, 1.62) |
|  No CRT and NT-proBNP<1600 | 33 | 243 | 0% | -25.4 (-37.6, -10.7) |
| ***NYHA Class*** |  |  |  | **OR (95% CI)** |
|  All patients | 118 | 360 | 0% | 3.37 (2.30, 4.93) |
|  NT-proBNP<1600 | 50 | 245 | 0% | 3.51 (2.20, 5.62) |
|  NT-proBNP<1600 or BNP<400 | 69 | 345 | 29% | 3.27 (2.01, 5.30) |
|  No CRT | 79 | 360 | 0% | 3.09 (2.09, 4.59) |
|  No CRT and NT-proBNP<1600 | 34 | 245 | 36% | 3.62 (2.20, 5.95) |

Abbreviations: BAT: Barostim Therapy; 6MHW: 6-minute Hall Walk; QoL: Minnesota Living with Heart Failure Quality of Life; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Class Association; CRT: Cardiac Resynchronization Therapy; OR: Odds Ratio; CI: Confidence Interval

\* Adjusted mean difference from ANCOVA (95% CI)

\*\* Combined relative reduction of BNP and NT‐proBNP

**Supplement Table 4: SUMMARY OF PUBLISHED RANDOMIZED CONTROLLED TRIALS OF AUTONOMIC MODULATION DEVICES IN HFrEF**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trial** | **BeAT-HF[[1]](#endnote-1)** | **INNOVATE-HF[[2]](#endnote-2)** | **NECTAR-HF[[3]](#endnote-3)** | **DEFEAT-HF[[4]](#endnote-4)** |
| **Treatment** | **BAT + GDMT****vs GDMT alone** | **VNS + CMT****vs CMT alone** | **VNS ON** **vs VNS OFF**  | **SCS ON** **vs SCS OFF** |
| **Δ 6MHW (m)** | 60\* | 33\* | pVO2 +0.7 | 40 |
| **Δ QOL** | -14\* | +5 (KCCQ)\* | -8\* | -3 |
| **NYHA** **% improve** | 34\* | 13\* | 17\* | -5 |
| **NT-proBNP** **% change** | -25%\* | NA | +11% | -6% |

CRT: Cardiac Resynchronization Therapy; BAT: Baroreflex Activation Therapy; VNS: Vagus Nerve Stimulation; SCS: Spinal Cord Stimulation; GDMT: Guideline-Directed Medical Therapy;

CMT: Continued Medical Therapy

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