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

Coats AJS\*1, Abraham WT\*2, Zile MR3, Lindenfeld JA4, Weaver FA5, Fudim M6,7, Bauersachs J8, Duval S9, Galle E10, Zannad F11

1. University of Warwick, UK

2. Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA

3. Medical University of South Carolina, Charleston, South Carolina, USA

4. Vanderbilt Heart and Vascular Institute, Nashville, TN, USA

5. Division of Vascular Surgery and Endovascular Therapy, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

6. Duke University Medical Center, Durham, NC, USA

7. Duke Clinical Research Institute, Durham, NC, USA

8. Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany

9. Cardiovascular Division, University of Minnesota Medical School, Minneapolis, MN, USA

10. CVRx®, Inc., Minneapolis, MN, USA

11. Inserm Centre d'Investigation, CHU de Nancy, Institute Lorrain du Coeur et des Vaisseaux, Université de Lorraine, Nancy, France

\* = Joint First authors

Address for correspondence: Professor Andrew JS Coats, Faculty of Medicine, University of Warwick, Coventry, CV4 8UW, United Kingdom. Email: [ajscoats@aol.com](mailto:ajscoats@aol.com)

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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

1. Zile MR, Lindenfeld J, Weaver FA, Zannad F, Galle E, Rogers T, Abraham WT. Baroreflex Activation Therapy in Patients With Heart Failure With Reduced Ejection Fraction. J Am Coll Cardiol. 2020 Jul 7;76(1):1-13. doi: 10.1016/j.jacc.2020.05.015.  [↑](#endnote-ref-1)
2. Gold MR, Van Veldhuisen DJ, Hauptman PJ, Borggrefe M, Kubo SH, Lieberman RA, Milasinovic G, Berman BJ, Djordjevic S, Neelagaru S, Schwartz PJ, Starling RC, Mann DL. Vagus Nerve Stimulation for the Treatment of Heart Failure: The INOVATE-HF Trial. J Am Coll Cardiol. 2016 Jul 12;68(2):149-58. doi: 10.1016/j.jacc.2016.03.525. [↑](#endnote-ref-2)
3. Zannad F, De Ferrari GM, Tuinenburg AE, Wright D, Brugada J, Butter C, Klein H, Stolen C, Meyer S, Stein KM, Ramuzat A, Schubert B, Daum D, Neuzil P, Botman C, Castel MA, D'Onofrio A, Solomon SD, Wold N, Ruble SB. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. Eur Heart J. 2015 Feb 14;36(7):425-33. doi: 10.1093/eurheartj/ehu345. [↑](#endnote-ref-3)
4. Zipes DP, Neuzil P, Theres H, Caraway D, Mann DL, Mannheimer C, Van Buren P, Linde C, Linderoth B, Kueffer F, Sarazin SA, DeJongste MJL; DEFEAT-HF Trial Investigators. Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Systolic Heart Failure: The DEFEAT-HF Study. JACC Heart Fail. 2016 Feb;4(2):129-36. doi: 10.1016/j.jchf.2015.10.006. [↑](#endnote-ref-4)