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Update on AVIM Therapy: A Pacemaker-Based Treatment for Hypertension

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest / arrangement or affiliation with the organization(s) listed below.

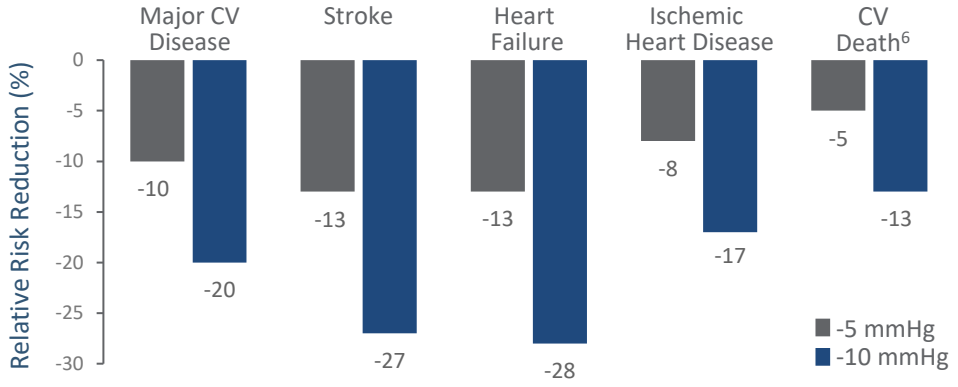
Affiliation/Financial Relationship	Company
Grant/Research Support	Abiomed Axon Therapies Ancora Edwards Lifesciences
Consulting Fees/Honoraria	Aquapass Axon Therapies Orchestra BioMed Corvia Edward Lifesciences IMPULSE Dynamics

High Risk Hypertension Patients Need Better Treatment Options: Pacemaker Patients Are Older & At Higher Risk

Hypertension: A Global Crisis Intensified in Older High-Risk Groups

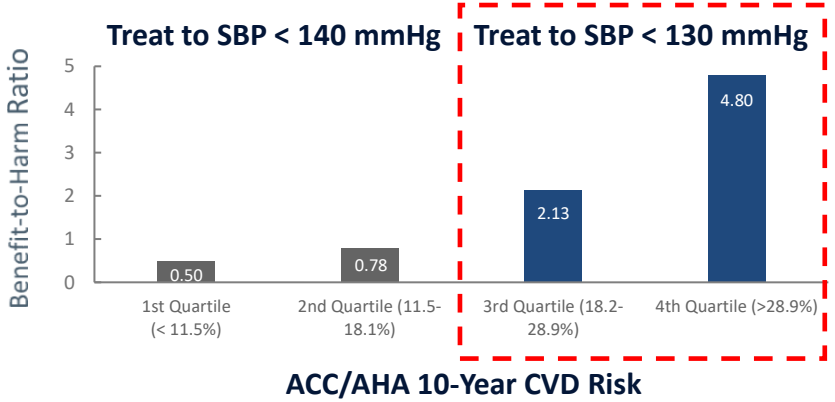
- Hypertension (HTN) is the **leading risk factor for death** and a leading risk factor for heart attack, stroke, and heart failure (HF)[1]
- **Older patients with HTN are at high risk** and predominantly have **isolated systolic hypertension (ISH)**
  - ISH is associated with **greater incidence** of CAD (34%), stroke (32%), and HF (26%)[2]
- HTN, especially ISH, can lead to **diastolic dysfunction** and **HFpEF**[3]
  - An estimated 1.4M+ US patients have HTN and HFpEF[8]

Significant Benefit From oSBP Reduction[4,5]



High CVD Risk Benefit From Intensive SBP Control[7]

SPRINT: Patients with ≥ 18.2% 10-Year CVD risk significantly benefited from SBP < 130 mmHg[7]



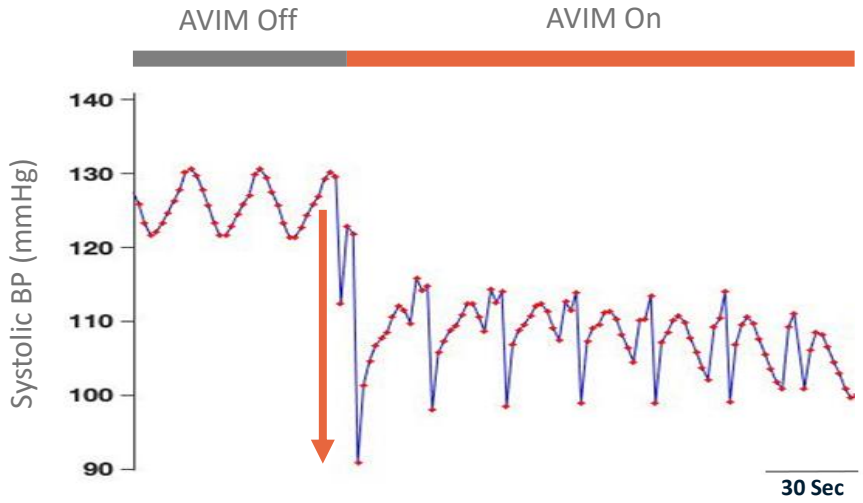
[1]Global Report on Hypertension. Geneva: World Health Organization; 2023. [2]Ekundayo et al. *Hypertension* 2009 Mar; 53(3):458-65. [3]Redfield et al. *JAMA* 329(10):827, 2023. [4]Rahimi, K., et al. *Lancet*. 2021 May 1;397(10285):1625-1636. [5]Ettehad D, et al. *Lancet*. 2016;387(10022):957-67. [6]All-cause mortality reported for -10 mmHg. [7]Philips et al., *J Am Coll Cardiol*. 2018;71:1601–10. [8]Orchestra BioMed company estimates. ***Definitions:*** SBP (Systolic Blood Pressure), oSBP (Office Systolic Blood Pressure), CVD (Cardiovascular Disease).

AVIM Therapy is a Novel Investigational Treatment to Reduce Blood Pressure

Designed to Have an Immediate, Substantial, and Sustained Effect[1]

- **Short AV intervals**: reduce cardiac preload, **immediately lowering BP**
- **Intermittent longer AV intervals**: modulate ANS response (baroreceptor reflex) and reduce afterload (TPR), sustaining BP reduction
- Delivered via Medtronic Astra™ or Azure™ dual-chamber pacemaker
- **No additional surgical procedure** and compatible with both RV pacing and conduction system pacing (CSP)
- **Programmable**, **adjustable**, and not dependent on **patient adherence**

Novel & Potent Mechanism[1]



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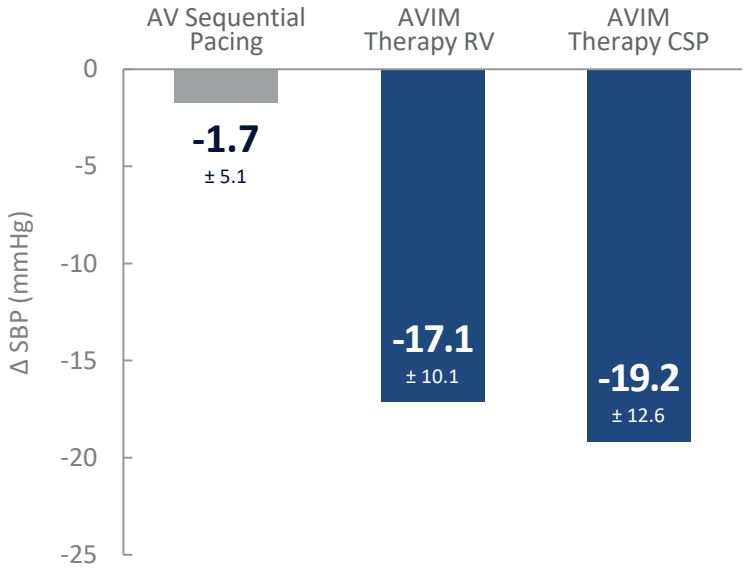
[1]Kalarus et al. *JAHA* 2021;10:e020492ahajournals.org/doi/10.1161/JAHA.120.020492. ***Definitions***: AV (Atrioventricular), AVIM (Atrioventricular Interval Modulation), BP (Blood Pressure), ANS (Autonomic Nervous System), TPR (Total Peripheral Resistance).

Benefit Shown in Acute Pressure-Volume Study

SBP Reduction (Independent of Lead Position) and Favorable Impact on Hemodynamics[1]

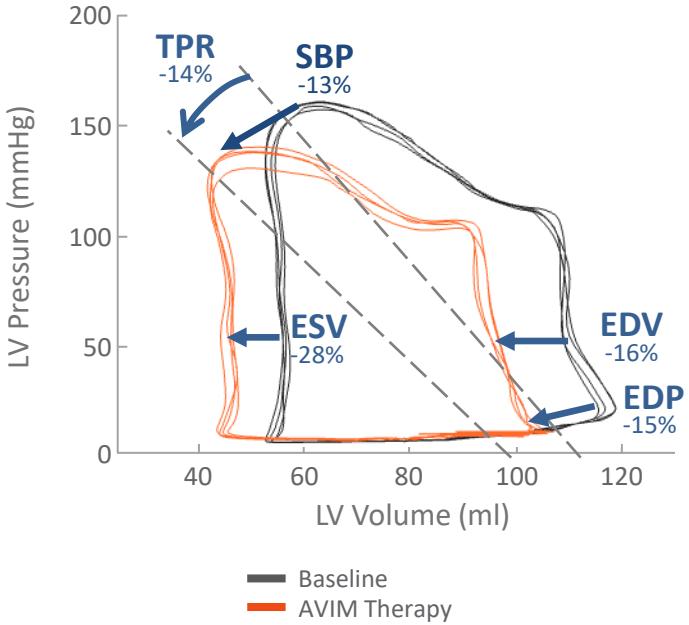
- **Significant reduction in pre-load and afterload** without change in contractility (± 1%)
- **Significant 21% reduction in stroke work** without significant reduction in stroke volume

SBP Reduction, N=16



P < 0.05 AVIM Therapy
P = NS between RV & CSP

PV Loops

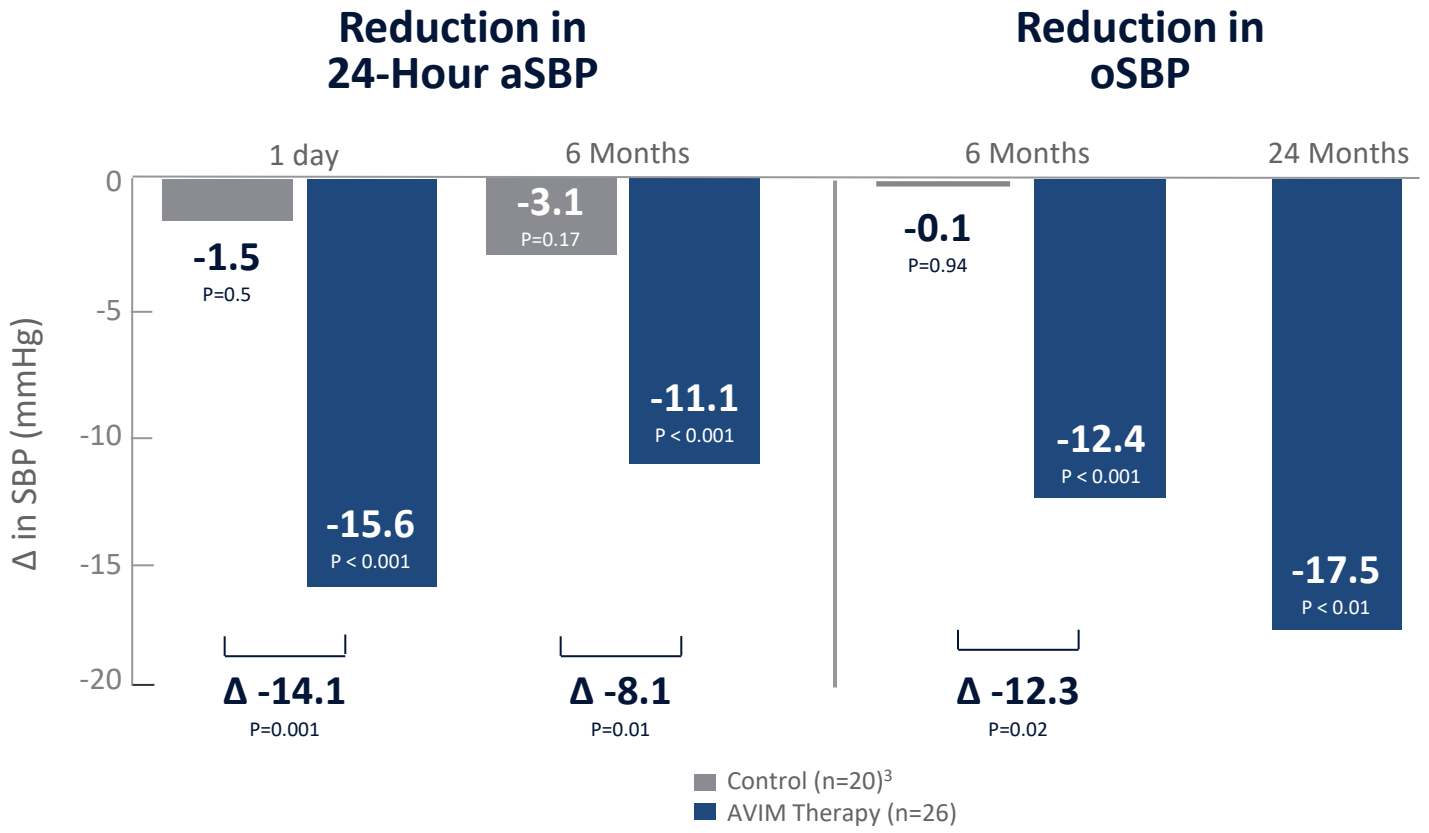


[1]Chovanec M, et al. *JACC Clin Electrophysiol*. 2025. n=16 for AVIM therapy in both lead positions. n=14 for AV sequential pacing. Baseline is atrial pacing with intrinsic conduction. CSP type is LBBA (Left Bundle Branch Area). ***Definitions***: ESV (End-Systolic Volume), EDV (End-Diastolic Volume), EDP (End-Diastolic Pressure).

AVIM Therapy Showed Encouraging Results in the MODERATO II Randomized, Double-Blind Pilot Study

Substantial and Sustained Reduction in aSBP and oSBP[1,2]

- Pacemaker patients with HTN despite medical therapy
- LVEF ≥ 50%
- **0% MACE** at 6 months[4]



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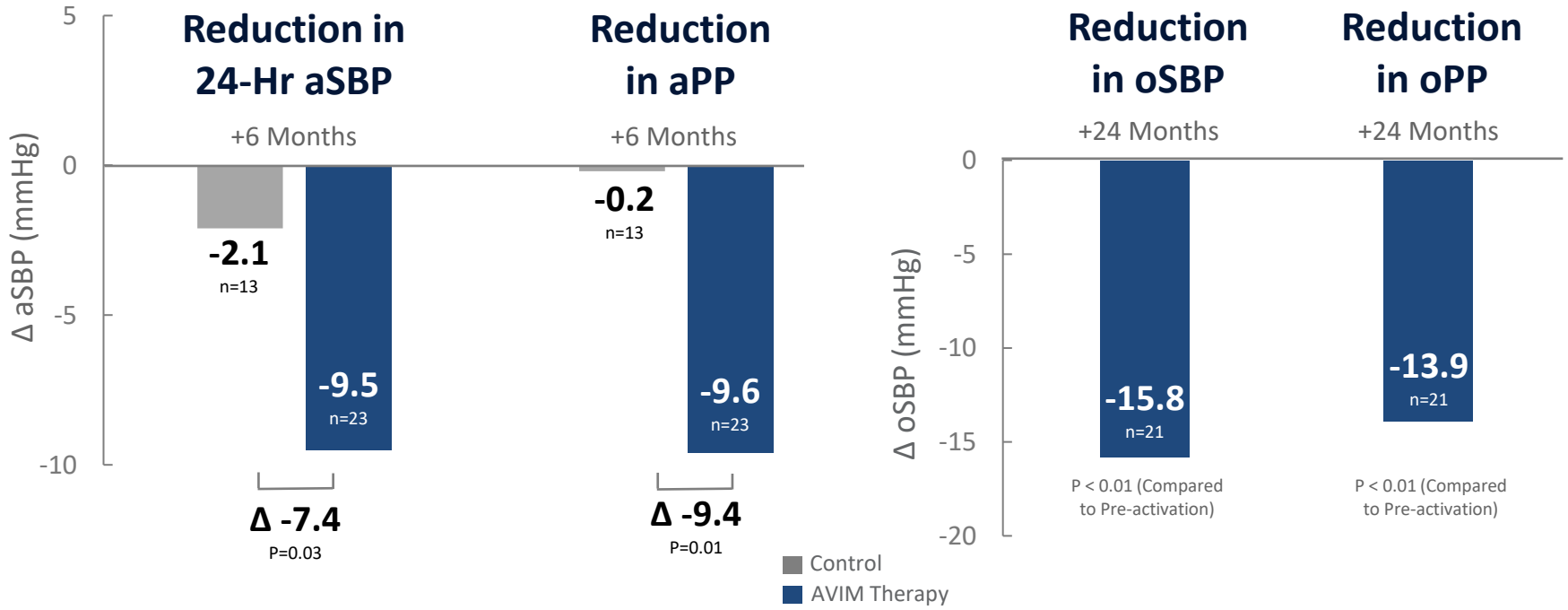
[1]Kalarus et al. *JAHA* 2021. [2]Burkhoff MODERATO II Study 2-Year Results TCT 2021. [3]24-Hr aSBP Control at 6 months (n=19): 1 control patient could not be measured despite repeat attempts (extremely high blood pressure) and another control patient died before the 6-month follow-up. [4]A blinded evaluation Data Safety Monitoring Board report for MODERATO II included a revised MACE rate, from 9.5% to 14.3%, in the control group to reflect a HF event after study result publication. ***Definitions:*** MACE (Major Adverse Cardiac Events included death, HF, clinically significant arrhythmias (i.e., persistent or increased AF, serious ventricular arrhythmias), myocardial infarction, stroke & renal failure in treatment group calculated per patient), aSBP (Ambulatory Systolic Blood Pressure), oSBP (Office Systolic Blood Pressure).

Significant Improvement in Challenging-to-Treat ISH Patients

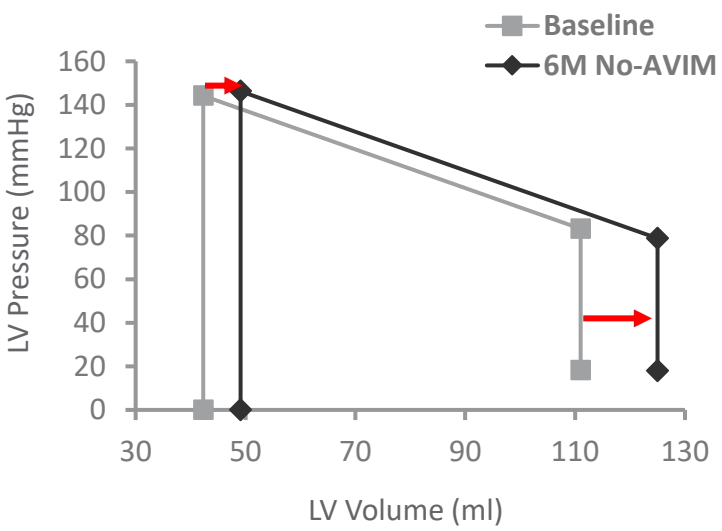
- 88% of AVIM therapy patients in MODERATO II had **ISH**[1]
- Increased pulse pressure (PP) is an **independent risk factor** for HF and stroke[2]



[1]Burkhoff MODERATO II Study 2-Year Results TCT 2021. [2]Vaccarino V, et al. *Am J Cardiol*. 2001. ***Definitions***: aPP (Ambulatory Pulse Pressure), oPP (Office Pulse Pressure).

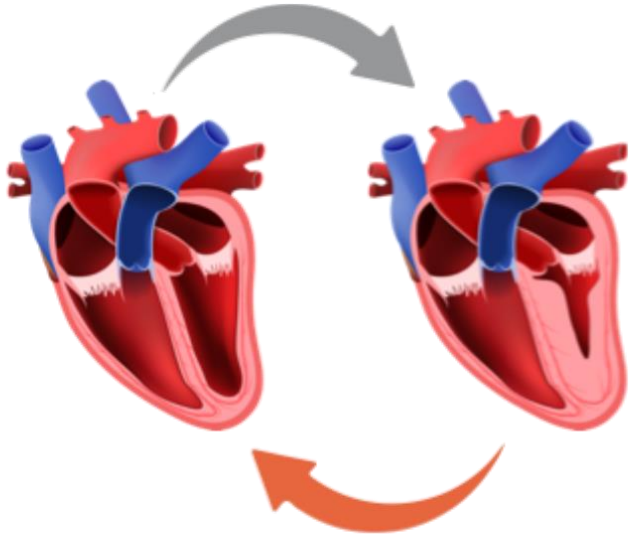
Induced Reverse Remodeling

Control Group Showed Progressive Ventricular Remodeling at 6 Months[1]



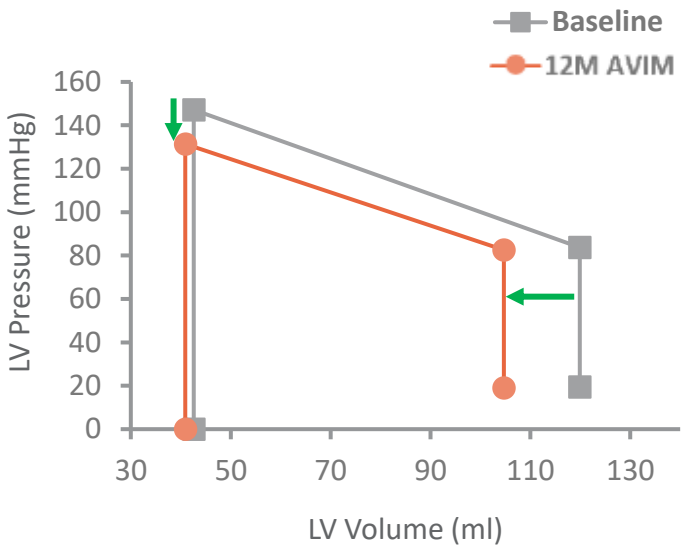
n=11

Control Group Developed Ventricular Remodeling



AVIM Therapy Induced Reverse Remodeling

AVIM Therapy Showed Reverse Remodeling at 12 months[1]

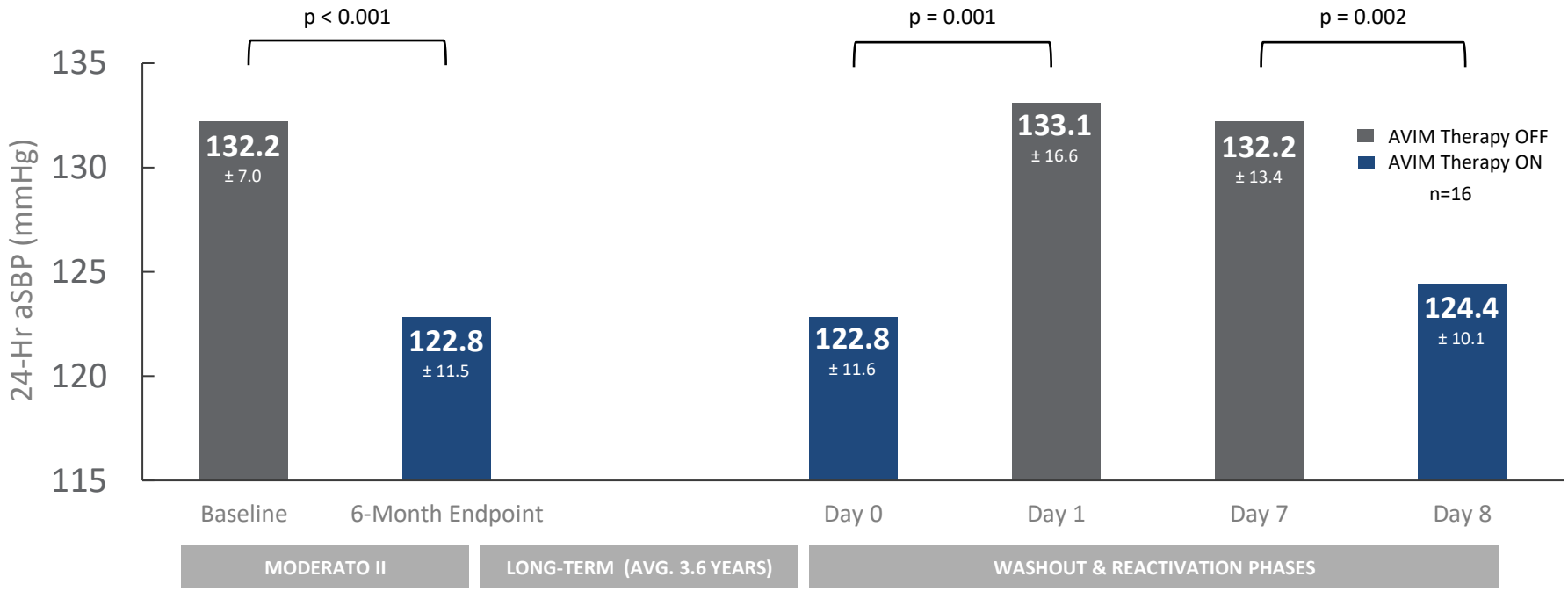


n=14

[1]Chovanec M, et al. *JACC Clin Electrophysiol*. 2025 Jul 22:S2405-500X(25)00518-3. doi:10.1016/j.jacep.2025.06.017 (article in press).

AVIM Therapy Demonstrates Sustained aSBP Reductions with Reproducible Effect & No Rebound Hypertension

- 16 MODERATO II patients with long-term follow-up & no increase in average number of meds had AVIM therapy de-activated & re-activated
- **Immediate, substantial, & sustained reduction in aSBP** seen across all study phases[1]
- **Potential to halt hypertensive heart disease progression**: aSBP returned to historical baseline after an average of 3.6 years[1]
- **No rebound HTN** observed during washout phase[1]



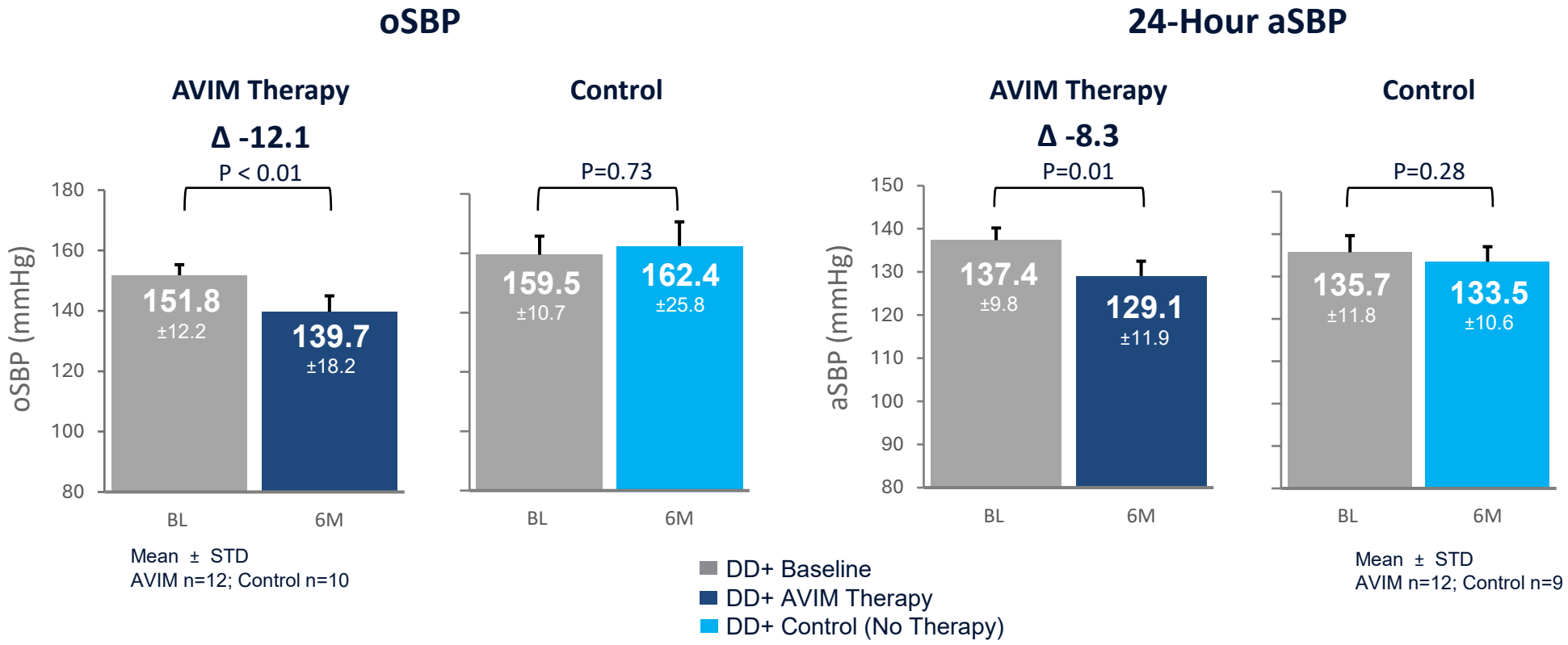
No significant differences between measurements with AVIM Therapy ON (6-Month, Day 0, & Day 8)
No significant differences between measurements with AVIM Therapy OFF (Baseline, Day 1, & Day 7)

[1]Kalarus et al., Time Course of Changes in Blood Pressure Upon Cessation of Chronic Atrioventricular Interval Modulation (AVIM) Therapy, HRX 2025 abstract.
Definition: AVG (Average).

Reduced SBP in Patients with Diastolic Dysfunction (DD)

Significantly Reduced oSBP & aSBP in Retrospective Treatment-Blinded Analysis

- HTN is the leading cause of DD. Both are common in the elderly and contribute to HF development.[1,2]
- Core lab echoes were assessed with independent blinded adjudication[3]
- 61% of AVIM therapy patients in MODERATO II had DD[3,4]

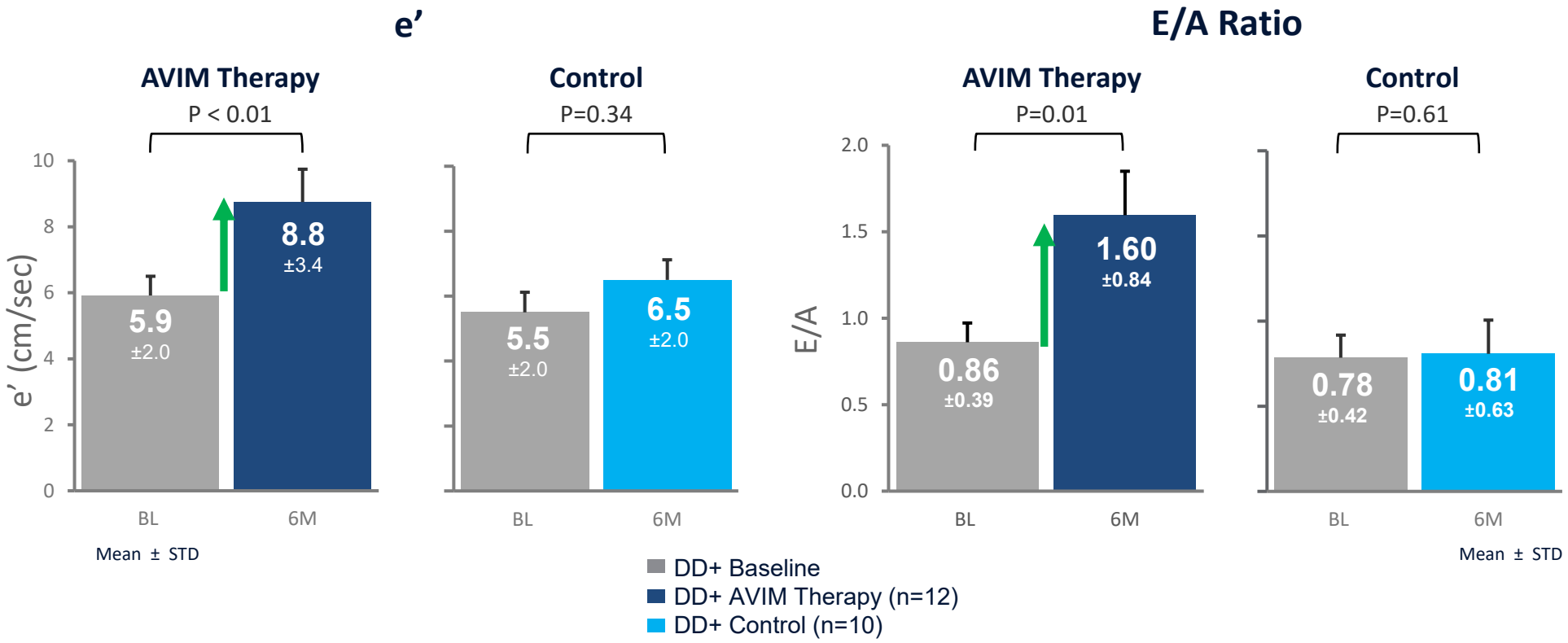


[1]Nadruz W, Shah AM, Solomon SD. Diastolic Dysfunction and Hypertension. *Med Clin North Am*. 2017 Jan;101(1):7-17. [2]Redfield et al. Heart Failure With Preserved Ejection Fraction: A Review *JAMA*. 2023;329(10):827-838. [3]Fudim M et al. Effects of Atrioventricular Interval Modulation Therapy in Subjects with Hypertension and Diastolic Dysfunction. *JACC: Advances*. Vol. 4, No. 7, July 2025:101896. [4]DD assessed via American Society of Echocardiography guidelines.

AVIM Therapy Improved Echocardiographic Markers of DD

Significantly Increased e' and E/A, Indicating Improved Myocardial Relaxation and Diastolic Compliance[1]

AVIM therapy increased the percentage of patients with normal values for e' (16% → 58%) and E/A (42% → 73%)[1]



[1]Fudim M et al. Effects of Atrioventricular Interval Modulation Therapy in Subjects with Hypertension and Diastolic Dysfunction. *JACC: Advances*. Vol. 4, No. 7, July 2025:101896.

The BACKBEAT Global Pivotal Trial

Designed to Secure Regulatory Approval and Demonstrate Novel Approach to BP Management

BACKBEAT
GLOBAL PIVOTAL STUDY

- Randomized, prospective, multi-center, double-blind, controlled trial
- Sponsored by Orchestra BioMed, conducted in partnership with Medtronic
- Actively enrolling up to 500 patients across 130 sites in US, Europe, and APAC
- NYHA I or II HF with LVEF ≥ 50% eligible
- Echocardiography and KCCQ at baseline, 3 months, and 12 months

Patients who **have or are scheduled to receive** a Medtronic Astra™ or Azure™ dual-chamber pacemaker and have **hypertension despite medication**

AVIM Therapy download & set-up

R

1:1

AVIM Therapy + Medical Therapy

Medical Therapy

Primary Efficacy Endpoint
Between group difference in the change in mean 24-hour aSBP at 3-months

Primary Safety Endpoint
Freedom from unanticipated serious device events at 3 months

Secondary Endpoints
Efficacy and safety endpoints after 12-month follow-up

Summary

- AVIM therapy is a novel investigational, pacemaker-delivered treatment designed to have an immediate, substantial, and sustained effect in reducing BP independent of lead position
  - MODERATO II feasibility study demonstrated efficacy in both isolated systolic and combined hypertension
  - “Always on” effect with sustained BP reduction
- AVIM therapy is associated with improved hemodynamics in parallel with BP reductions
  - Significant reductions in both preload and afterload without decrease in contractility
  - Ventricular remodeling at 6 months with decreases in LV pressure and volume
- In patients with diastolic dysfunction, AVIM therapy significantly reduced BP and improved echocardiographic markers of myocardial relaxation and diastolic compliance
- Ongoing BACKBEAT Global Pivotal Trial (NCT06059638) is intended to demonstrate safety and effectiveness of AVIM therapy in patients with hypertension despite medication