# Orchestra BioMed

# AVIM Therapy R&D DAY

June 11, 2024

*Bringing medical innovation to life*

# Forward-Looking Statements

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# Agenda and Speakers

## Agenda

- Introduction and Orchestra BioMed Overview, David Hochman
- Unmet Hypertension Treatment Need in Older High-Risk Patients, David Kandzari, M.D.
- Evidence Supporting AVIM Therapy Mechanism of Action, Vivek Reddy, M.D.
- Clinical Data from the MODERATO I and II Studies, Vivek Reddy, M.D.
- Rationale and Design of the BACKBEAT Global Pivotal Study, David Kandzari, M.D.
- Closing Remarks and Q&A, David Hochman

## Presenters

**David Hochman**
CEO, Chairman, Founder
Orchestra BioMed

**David Kandzari, M.D.**
BACKBEAT Study Co-PI,
Piedmont Heart Institute

**Vivek Reddy, M.D.**
BACKBEAT Study Advisor,
Mount Sinai Hospital

## Q&A

**Darren Sherman**
COO, President, Founder
Orchestra BioMed

**Avi Fischer, M.D.**
SVP, Medical Affairs and Innovation
Orchestra BioMed

# Orchestra BioMed Overview

**David Hochman**

*Chief Executive Officer, Founder*
*Chairman, Orchestra BioMed*

# Orchestra BioMed Executive Overview

**Partnership-enabled business model designed to:**

***Accelerate innovation to patients & yield exceptional future profitability***

*Lead Program*

## Atrioventricular Interval Modulation (AVIM) Therapy

- **Targets >$10B** annual hypertension markets
- Statistically significant efficacy data from double-blind, randomized pilot study
- BACKBEAT global pivotal study ***now enrolling***


**Strategic collaboration**

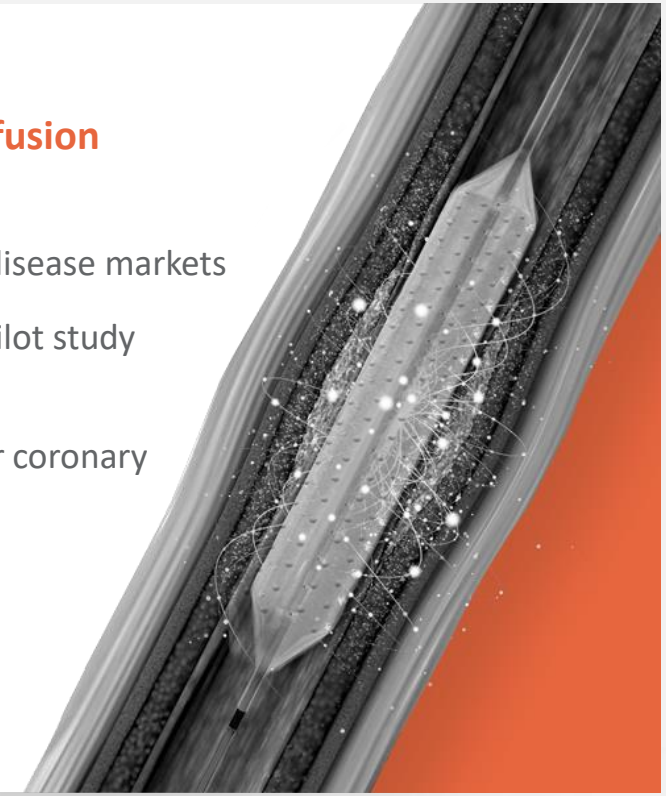
Medtronic

Double-digit revenue share

*Pipeline Program*

## Virtue® Sirolimus AngioInfusion Balloon (SAB)

- **Targets >$4B** annual artery disease markets
- Strong 3-year multi-center pilot study efficacy data
- Conditional IDE approved for coronary pivotal study



**Strategic collaboration**

TERUMO

Double-digit revenue share



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# Orchestra BioMed's Partnership-Enabled Model Benefits All

## Orchestra BioMed
*Development*

- Secure substantial long-term royalties
- Outsource commercialization
- Enable multiple pipeline opportunities

## Shared Benefits
*Innovation*

- Improve patient lives
- Accelerate development
- Leverage expertise & resources

## Strategic Partners
*Commercialization*

- Enable new growth opportunities
- Outsource development
- Minimize P&L dilution



# A Renaissance is Happening Now…

## Renaissance (n):

A **revival or renewed interest** in something; learning from the past to create something better for the future

- Art
- Architecture
- Science
- **Music**
- **Device innovation?**

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# The Renaissance of Orchestra

## *orchḗstra*

**Ancient Greece:** the circular space in front of the stage where ***the chorus performed***

## *Orchestra*

**Renaissance Italy**: a group of musicians performing a composition with pre-specified instrumentation

The chorus in Classical Greek drama was a group of actors who *described and commented upon the main action of a play with song, dance, and recitation*

## **Claudio Monteverdi** (1567-1643)

*The "Father" of the Symphony Orchestra*

In order for his music to be replicated ***exactly*** as he composed it; he required it be played with specific instrumentation:

*15 viols of different sizes; 2 violins; 4 flutes, 2 large and 2 medium; 2 oboes, 2 cornetts, 4 trumpets, 5 trombones, a harp, 2 harpsichords, and 3 small organs.*

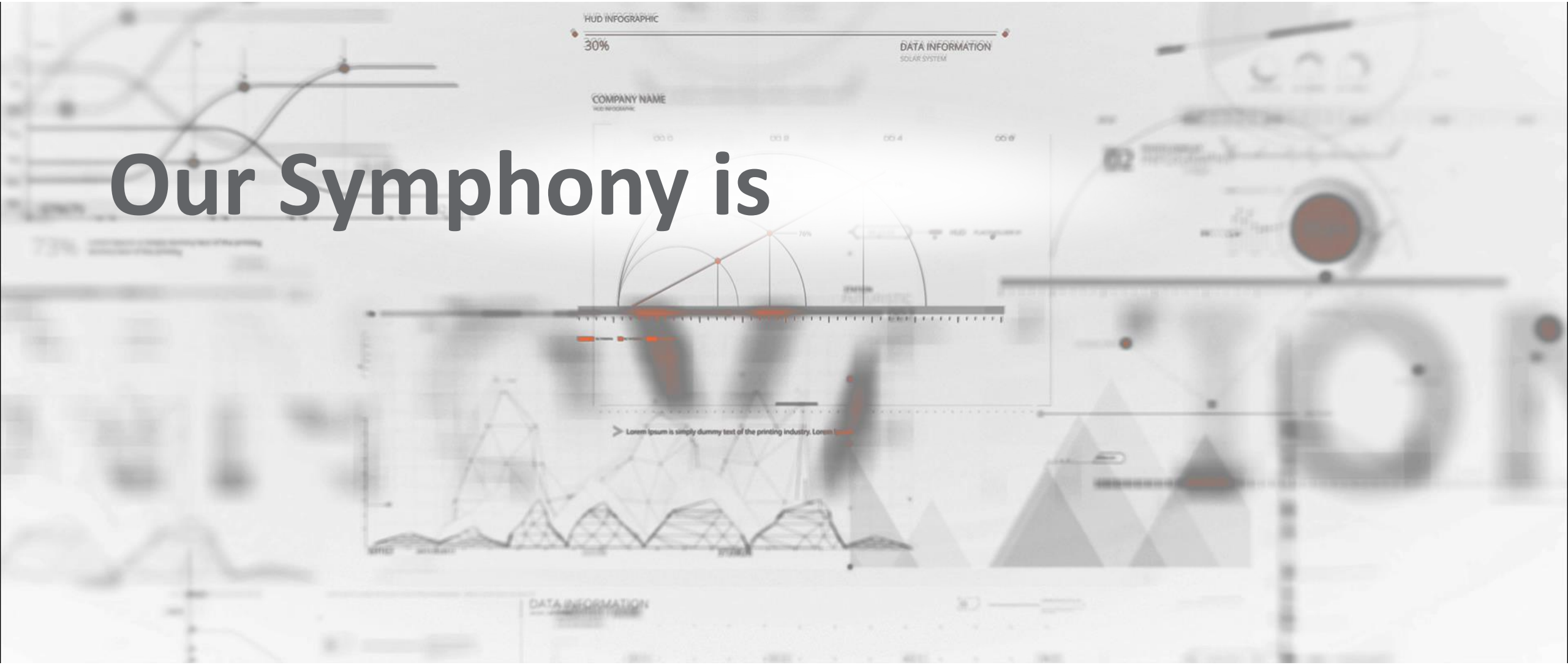
*"In the history of Western musical tradition, the evolution of **symphony orchestra** to its modern form can be seen as an apotheosis of instrumental music."*

# An Orchestra Succeeds Through Collaboration

*What more miraculous creation of mankind is there than the symphony orchestra — a hundred musicians* ***collaborating flawlessly*** *in the creation of a single sonority from moment to moment… We tend to take for granted the skill and sensitivity of such a performing organism, and* ***we should take time to marvel afresh that such a joint effort is possible for human beings, so rich in communication, beauty and meaning.***

Klaus George Roy

# Our Symphony is



# The Current Renaissance in Cardiac Pacing and Balloon Angioplasty

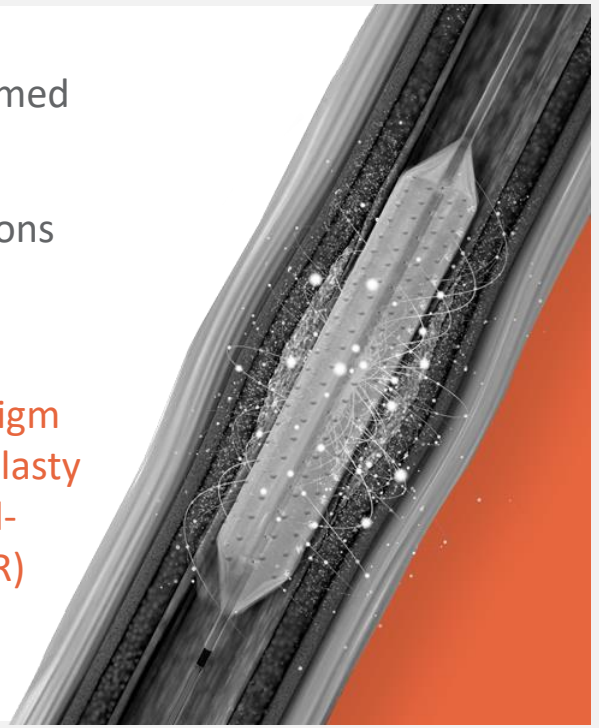
**Our large, established target markets, built on foundational technologies introduced 50+ years ago, are experiencing a *RENAISSANCE*, enhancing the opportunity for our innovative technologies**

## AVIM Therapy

- 1st pacemaker implanted in **1958** by Senning
- Leadless and conduction system pacing opening potential for expanded clinical use
- **AVIM therapy** driving potential use of pacemakers for treatment of **hypertension** and possible expanded indications


## Virtue® SAB

- 1st balloon angioplasty performed in **1977** by Grüntzig
- Drug-coated angioplasty balloons are becoming the preferred treatment for artery disease
- **Virtue SAB** expands the paradigm as the only non-coated angioplasty balloon that delivers extended-release sirolimus (SirolimusEFR)





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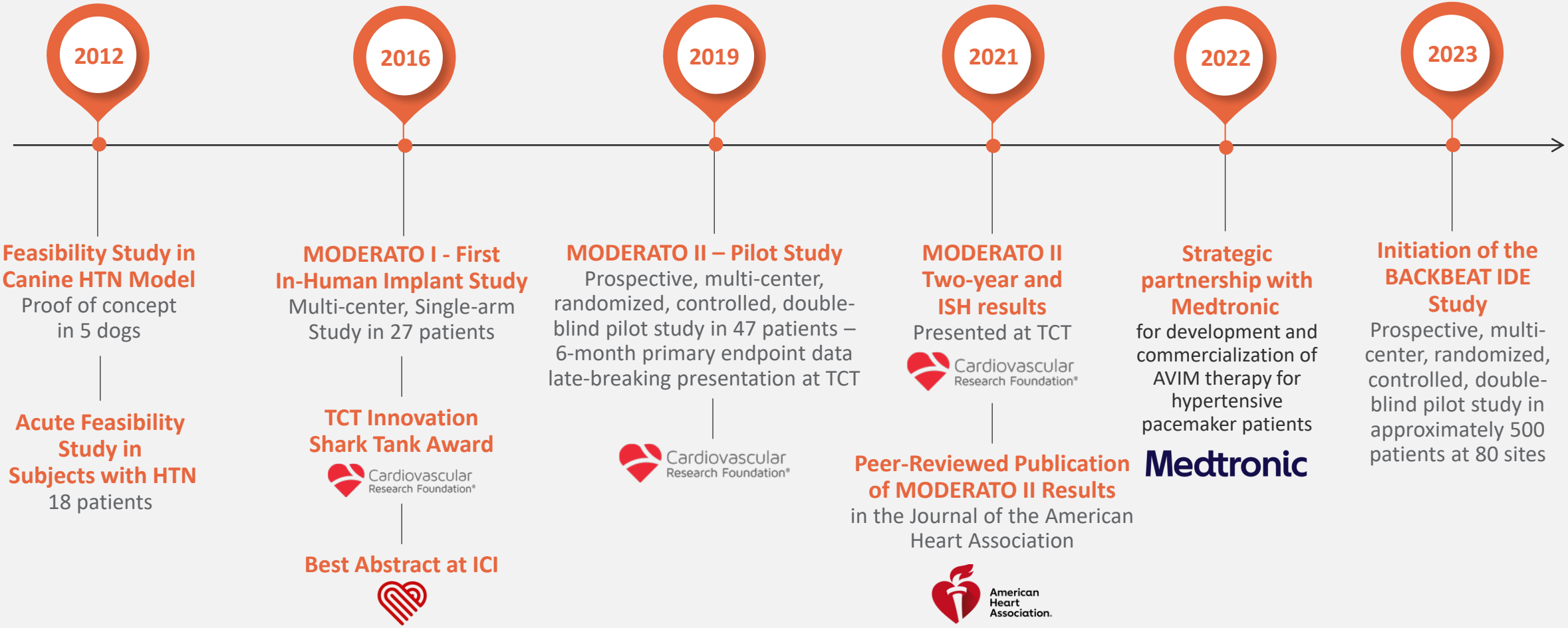
# Existing Body of Clinical Data Supporting Efficacy and Safety



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# AVIM Therapy Strategic Collaboration with Medtronic

- Developed BackBeat CNT (AVIM therapy) from concept stage; owns all related IP
- Conducted all prior development and the MODERATO I & II clinical studies
- Partnered with Medtronic for global regulatory approval and commercialization
- Sponsor for the BACKBEAT Global Pivotal Study
- **$500 - $1,600 revenue share** per AVIM-enabled device assuming existing reimbursement structures[1]

- Global market leader in cardiac pacing therapy: **>$1.5B in annual revenues**
- Pivotal trial utilizing premium commercial devices
- Providing clinical & regulatory resources
- Exclusive global commercial rights for AVIM therapy in pacemaker-indicated patients with HTN
- Right of first negotiation to expand global rights for the treatment of non-pacemaker patients with HTN
- **$50M equity investment** in Orchestra BioMed

[1] Amount is based on higher of (1) a fixed dollar amount per device (amount varies materially on a country-by-county basis) or (2) a percentage of sales.

# Large Global Opportunity for Treating Hypertension in Target Populations

**HTN + Pacemaker**

**750,000 patients**

~70% of pacemaker patients[1]

**>$2 Billion***


**High Risk HTN**

**2,400,000 patients**

~0.2% of HTN patients

**>$8 Billion***

- Same patients, device implant, and treating physicians
- Leverages existing reimbursement structures

- Older patients with uncontrolled hypertension and other significant comorbidities
- Similar demographics to pacemaker patients, high-risk, difficult-to-treat



*Total addressable market in 2025 based on company estimates; [1]Company estimates based on published sources, including National Inpatient Survey (NIS) and National Health and Nutrition Examination Survey (NHANES); Definition: Hypertension (HTN)

# The Unmet Treatment Need for Hypertension in Older High-Risk Patients

**David Kandzari, M.D., FACC, FSCAI**
*Chief, Piedmont Heart Institute and Cardiovascular Services*
*Chief Scientific Officer, Piedmont Healthcare*
*Director, Interventional Cardiology, Piedmont Heart Institute*
*Co-principal investigator of the BACKBEAT Study*

# Hypertension is a Common and Serious Global Health Problem[1]

Hypertension (HTN) is the **leading risk factor for death globally**,
and a significant portion of U.S. adults with HTN remain uncontrolled

**~120 million (48%)** of U.S. adults have HTN

**~25 million (21%)** are prescribed only lifestyle modification

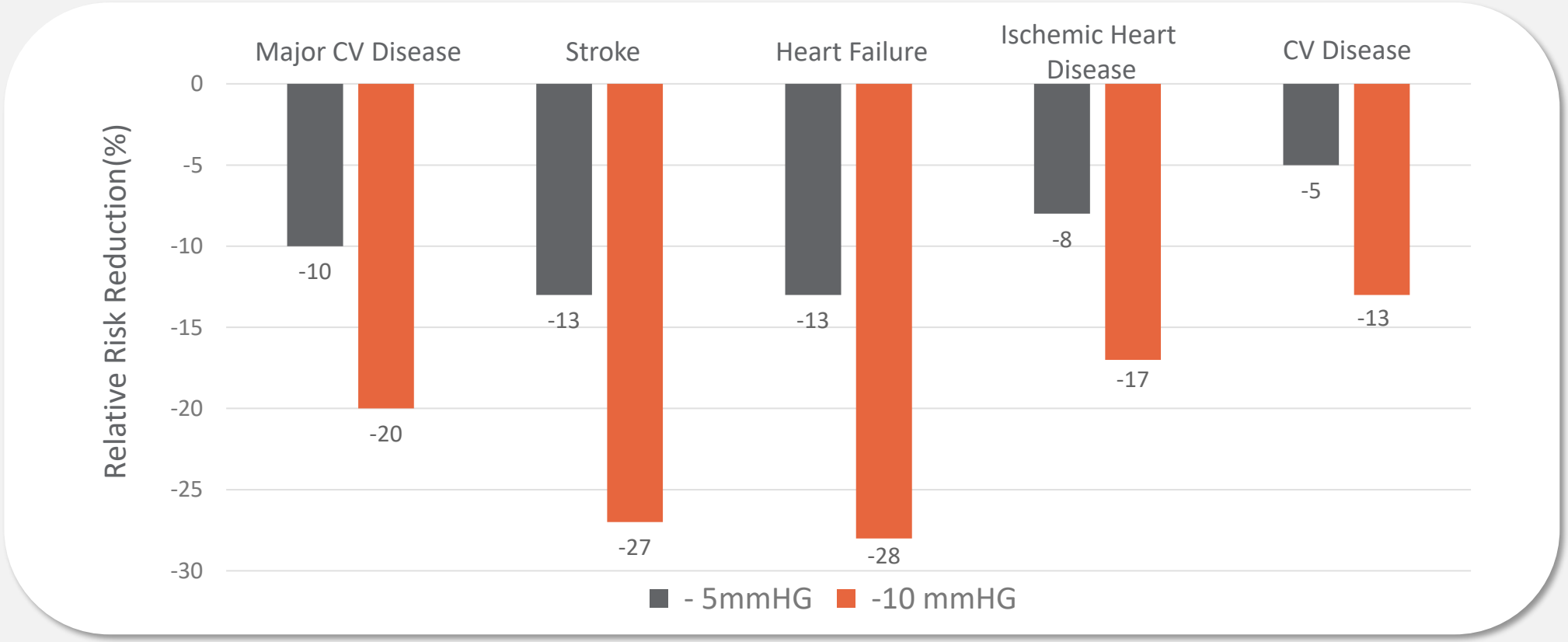
**~95 million (79%)** are prescribed lifestyle modification and medication

**~93 million (78%) remain uncontrolled**

[1]Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria From the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2017–2020. CDC. May 12, 2023. https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html.

# Modest Reductions in Blood Pressure (BP) Have Significant Clinical Benefit

Reductions as low as 5mmHg in office systolic blood pressure (oSBP)
**substantially decrease the Relative Risk (%) of common cardiovascular conditions**






[1] Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2021;397(10285):1625-36.
[2]Ettehad D, et al. *Lancet*. 2016;387(10022):957-67.

# Challenges with Pharmacotherapy for Hypertension

## While pharmacologic therapy is often effective, many patients experience insufficient BP control[1]

### Patient compliance is particularly difficult in HTN

- HTN is the "silent killer," and most patients are asymptomatic
- Medications often have significant side effects that feel worse than the disease itself
- ~50% of patients adhere to prescribed medications

### Many pharmacotherapies provide insufficient BP control

- > 40% of HTN patients remain uncontrolled despite pharmacotherapy
- Isolated systolic hypertension (ISH), emerges as the predominant form of HTN as patients age

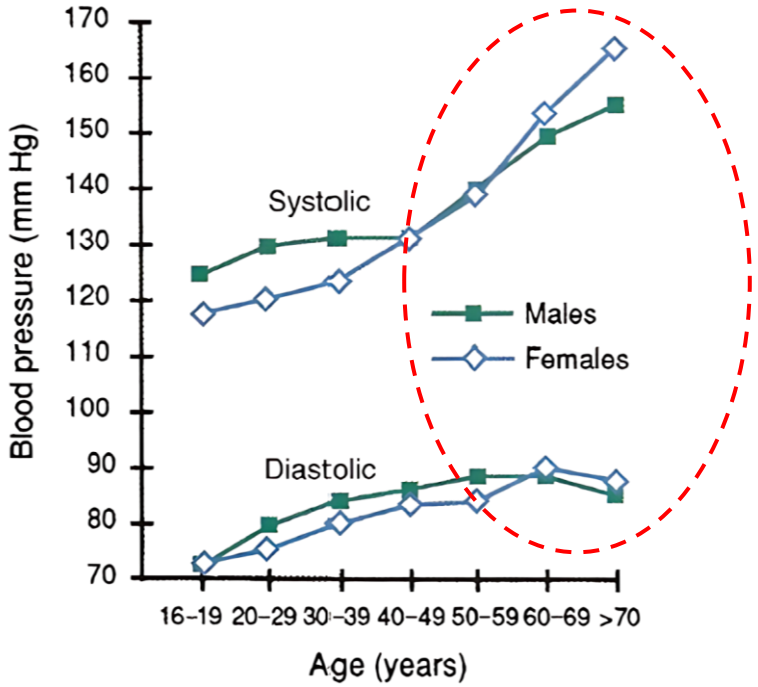


[1]Burnier M, et al., Adherence in hypertension. *Circ Res*. 2019 Mar;124(7): Whelton et al., 1124-1140; 2018https://doi.org/10.1161/CIR.0000000000000596Circulation. 2018;138:e484–e594

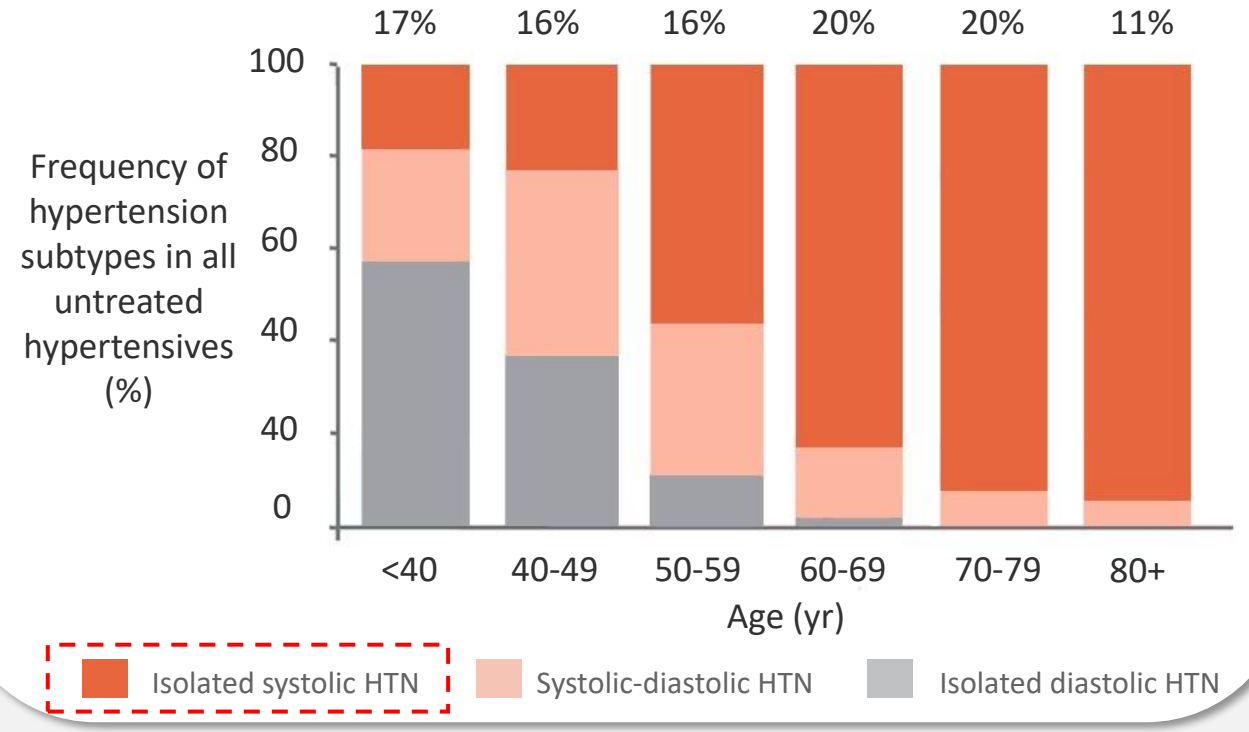
# The Nature of Hypertension Changes with Age

**Due to arterial stiffening, older patients have higher prevalence of ISH leading to substantially greater risk of CV complications (CAD, CHF, stroke, mortality)[1]**

### Variation of SBP & DBP with age




### ISH is the predominant hypertension subtype in patients over 60






[1]Lilly L, 2021, Wolters Kluwer; Franklin SS, *J Clin Hypertens*. 2006;8:444-449; ***Definitions***: NHANES: National Health and Nutrition Examination Survey; CAD: Coronary Artery Disease; CHF: Coronary Heart Failure

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# Older Patients with Hypertension Frequently Have Significant Comorbidities[1]

**Common comorbidities in older hypertensive patients**

- ACS/MI
- Heart Failure
- Stroke
- AFib
- TAVR
- Diabetes
- CAD/PAD
- Cardiac Arrhythmia
- Kidney Disease

[1]Company estimates based on published sources; **Definitions**: Acute coronary syndrome (ACS); myocardial infarction (MI); transcatheter aortic valve replacement (TAVR); coronary artery disease (CAD); peripheral artery disease (PAD); atrial fibrillation (Afib)



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# Hypertensive Patients with Pacemakers: An Older, Higher Risk Population in Need of Better Treatment Options[1]

**73 years**
average age

**70%** of patients with pacemakers also have HTN

Over **750K new HTN + PPM patients annually worldwide**


Frequent additional comorbidities: **atherosclerosis, hyperlipidemia, diabetes mellitus, and chronic kidney disease**

**More likely to have ISH** – a type of HTN for which there are **limited therapeutic options**



[1]Company estimates based on published sources; **Definition**: Permanent pacemaker (PPM)

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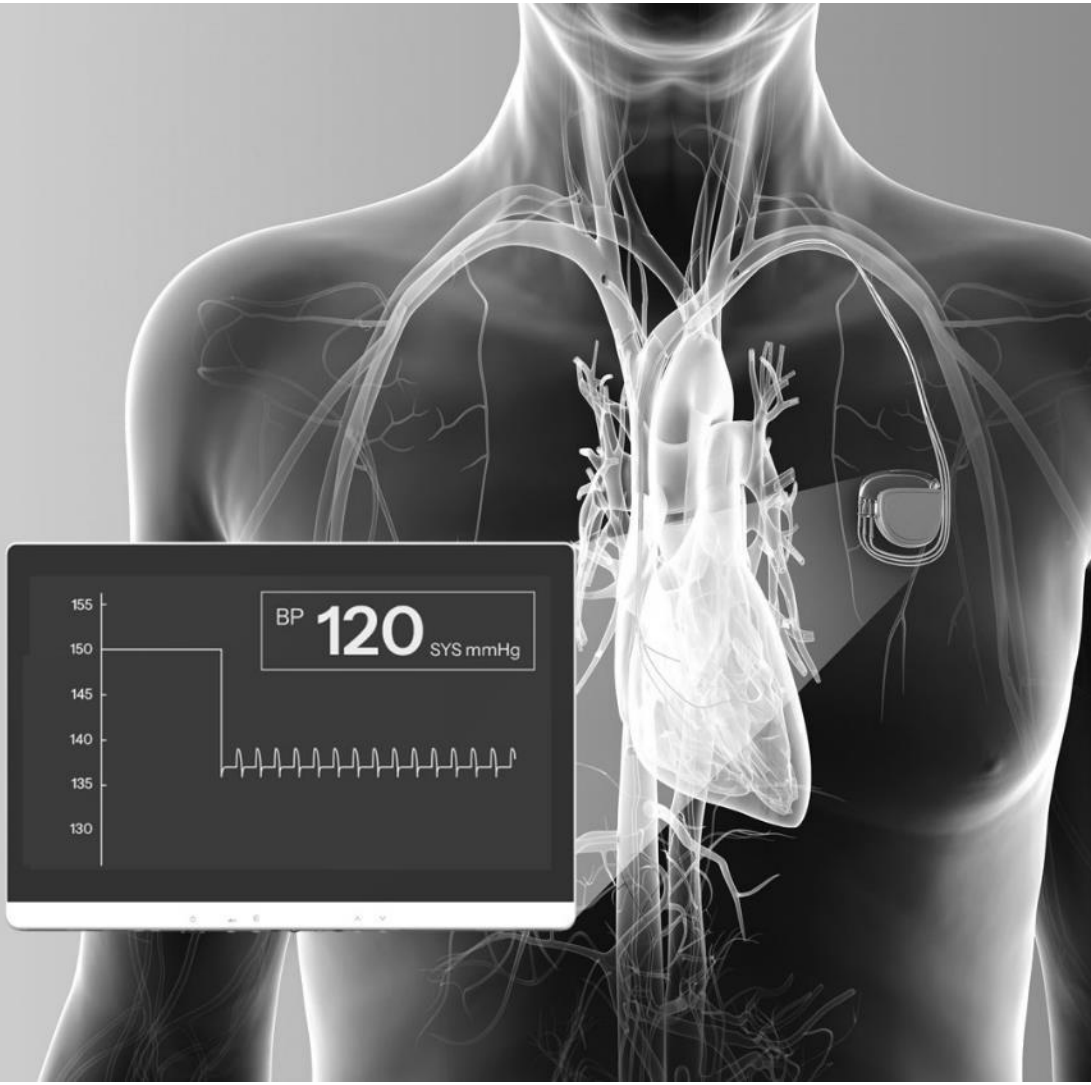
# Compelling Opportunity to Evaluate AVIM Therapy

## BACKBEAT IDE Pivotal study: currently enrolling

- Evaluating a novel investigational hypertension therapy that takes advantage of existing pacemaker
- Same device implant and treating physicians
- No additional daily compliance requirements for patients

Pilot study data show AVIM therapy drives **robust reduction in 24-hr aSBP in high-risk patient population with high rates of ISH, HFpEF, and other comorbidities**






**Definitions**: Heart failure with preserved ejection fraction (HFpEF)

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# Evidence in Support of AVIM Therapy Mechanism of Action

**Vivek Reddy, M.D.**

*Director, Cardiac Arrhythmia Services at Mount Sinai Hospital*

*Director, Electrophysiology at Mount Sinai Health System*

*Professor of Medicine, The Icahn School of Medicine at Mount Sinai*

*BACKBEAT Study Clinical Steering Committee Member*

# AVIM Therapy Summary*

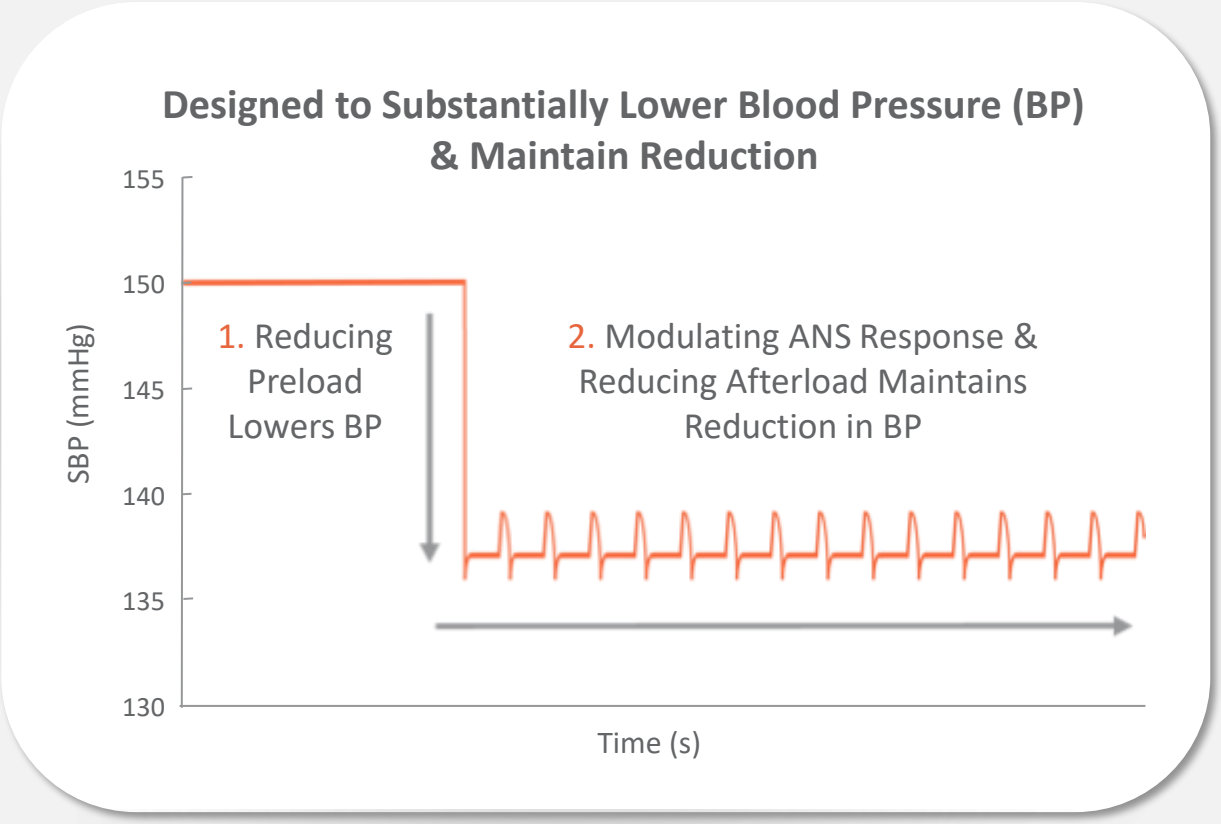
- Programmable and adjustable device-based HTN therapy designed to be delivered via dual-chamber pacemaker
  - Integrated for use with Medtronic Astra™ or Azure™ MRI-compatible pacemakers
  - Leverages previously completed or already indicated procedure
  - Can be activated, adjusted or deactivated, as needed
- Compatible with conduction system pacing (CSP) or right ventricular (RV) lead placement
- Data from previous preliminary clinical studies demonstrate an immediate, substantial, & persistent effect in reducing blood pressure




*AVIM therapy is investigational and not commercially approved. No claims can be made until regulatory approvals.

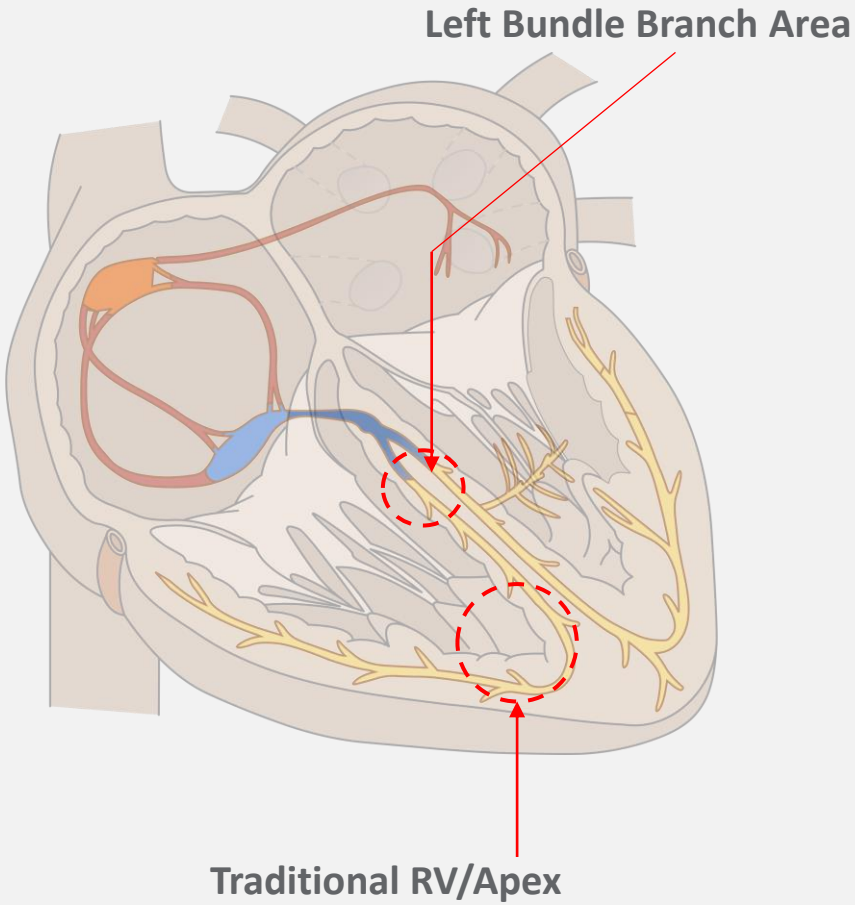
# Novel AVIM Therapy Mechanism of Action Designed to Substantially and Persistently Reduce Blood Pressure

- AVIM therapy uses a dual-chamber pacemaker to deliver programmed sequences of **short AV intervals** interspersed with **longer AV intervals** designed to reduce blood pressure by:
  - Reducing cardiac preload
  - Modulating autonomic nervous system (ANS) response
  - Reducing afterload
- Designed to utilize well characterized physiologic mechanisms, including the Frank-Starling law, to **improve circulatory hemodynamics**:
  - Reduced intra-cardiac volumes and pressures
  - Improved cardiovascular efficiency
  - No adverse impact on contractility
- Compatible with **conduction system pacing (CSP)** lead placements or traditional pacing lead locations



# Emerging Role of Conduction System Pacing in Cardiac Pacing Therapy

- Cardiac rhythm market **rapidly adopting CSP** via left bundle branch area pacing (LBBAP)
- LBBAP is a pacing approach that **taps into the heart's natural electrical system**, helping ensure pacing closely mimics physiologic contractions, **allowing the ventricles to work in coordination**
- Clinical data demonstrate **AVIM compatibility with CSP**



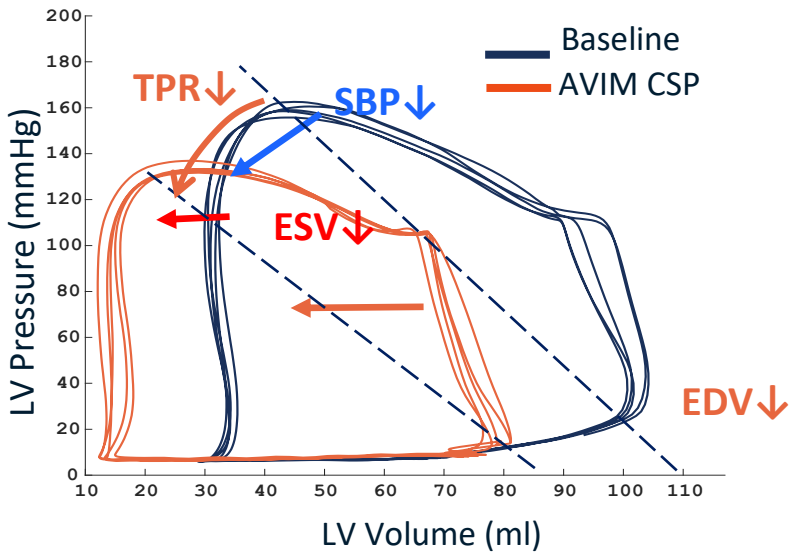
# Invasive Pressure Volume (PV) Loop Study Shows Favorable Acute Hemodynamics from AVIM Therapy[1]

**Decreases intra-cardiac volume & pressure**
**(↓ EDV, ↓ ESV, & ↓ SBP)**

**Decreases total peripheral resistance**
**(↓ TPR)**

**Decreases systolic blood pressure**
**(↓ SBP)**

**AVIM – CSP Lead Location**



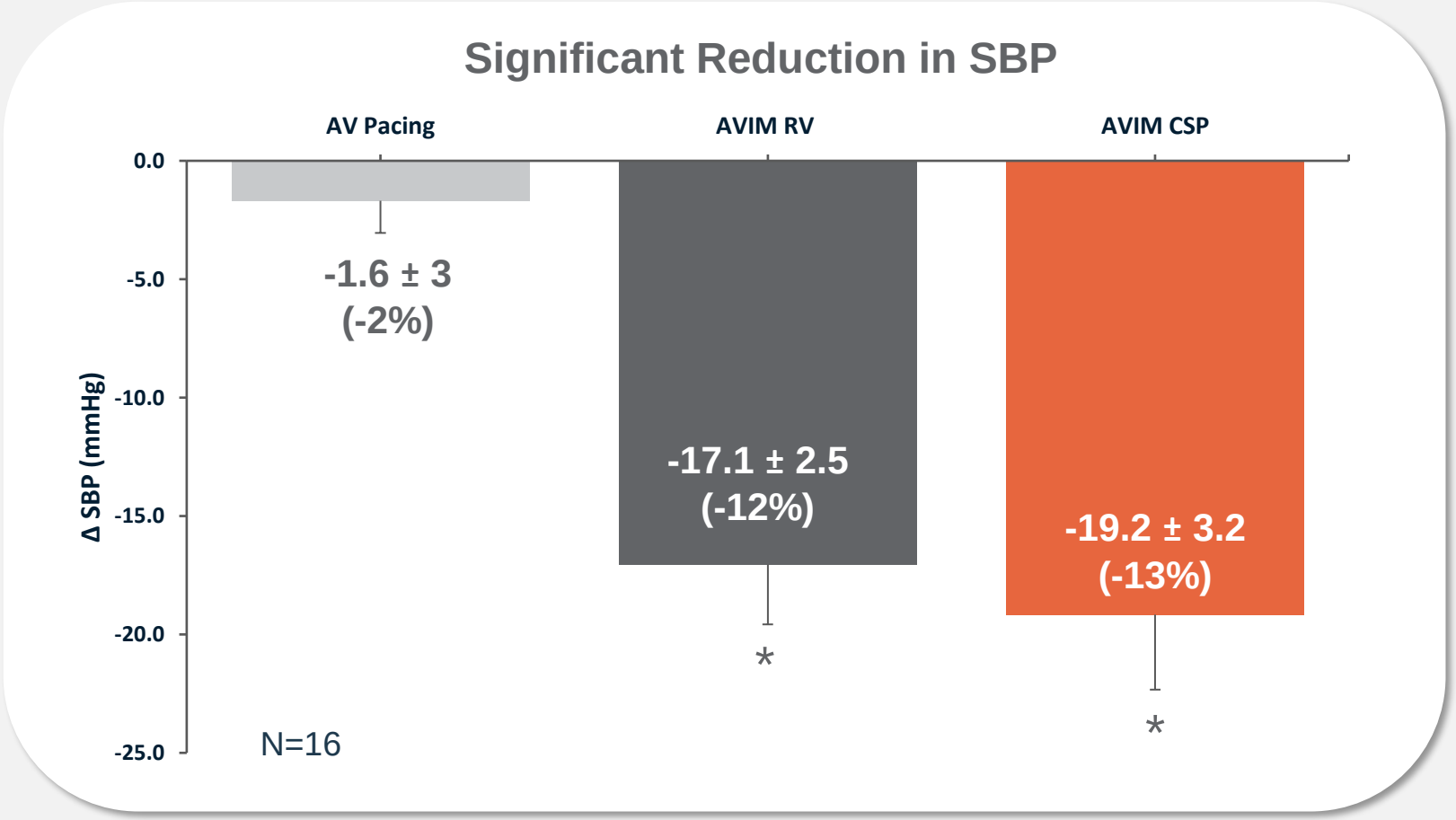

- N = 16 subjects indicated for a pacemaker with uncontrolled hypertension despite medical therapy
- Paired data (baseline vs. AV Sequential pacing or baseline vs. AVIM) reported



Data on file with Orchestra BioMed. [1]Kuck, Hemodynamics Effects of AVIM Therapy, THT'24.
**Definitions**: EDV (end-diastolic volume), ESV (end-systolic volume), LVP (left ventricular pressure).

# AVIM Therapy Reduces Systolic Blood Pressure[1]

Significant reduction in SBP with AVIM therapy and **no significant difference between right ventricular (RV) and conduction system pacing (CSP)** lead placement




*P < 0.05 (compared to baseline); no significant difference between AVIM RV & AVIM CSP

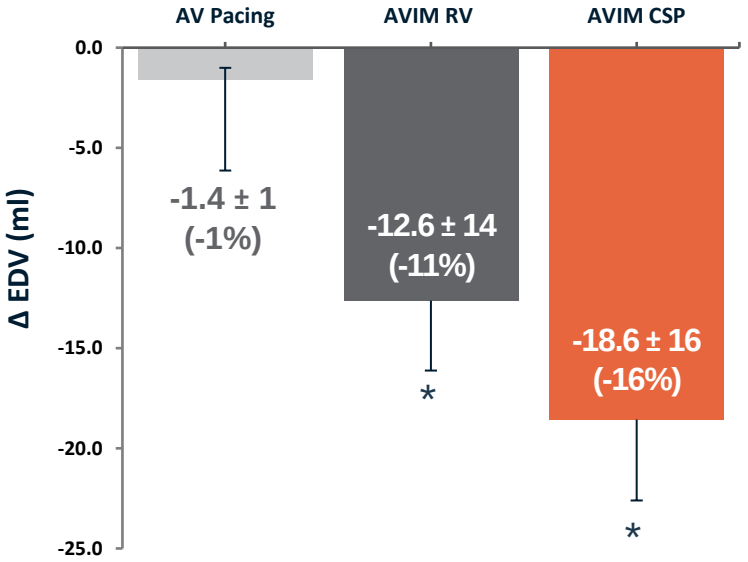


[1]Kuck, Hemodynamics Effects of AVIM Therapy, THT'24.

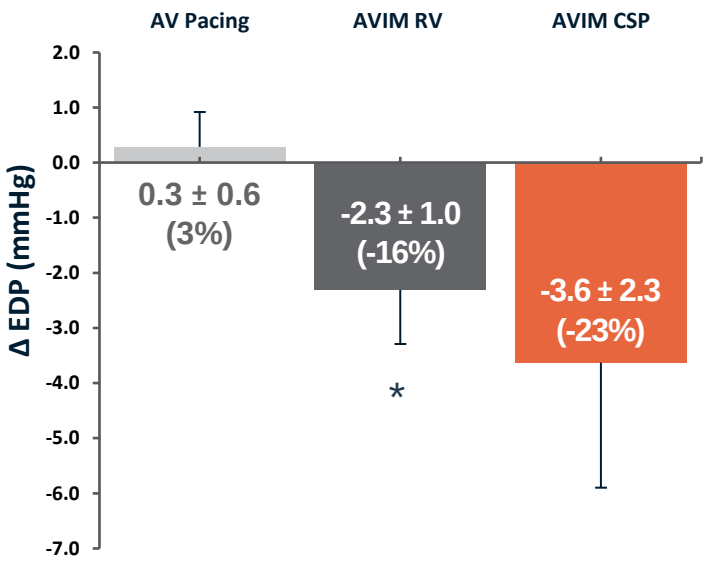
# AVIM Therapy has a Favorable Impact on Cardiac Hemodynamics[1]

## Significant reductions in EDV, $P_{ED}$ & ESV

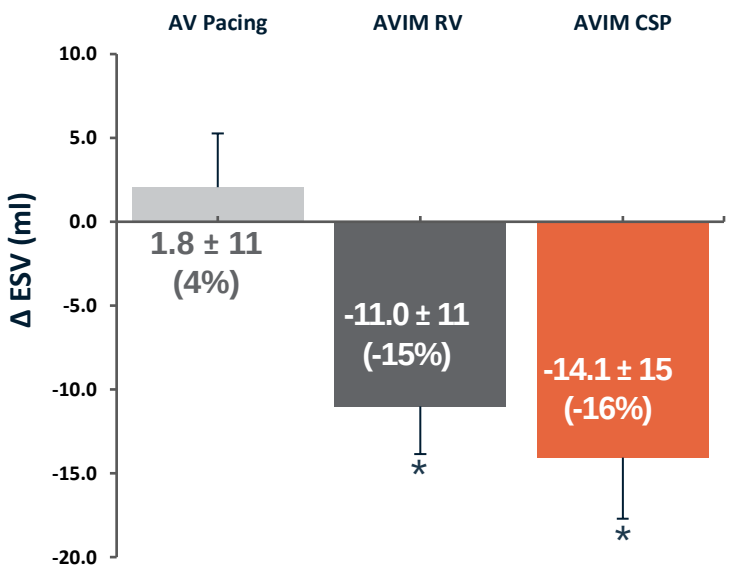
### Change in End-Diastolic Volume (EDV)




### Change in End-Diastolic Pressure ($P_{ED}$)




### Change in End-Systolic Volume (ESV)




N=16

*P < 0.05 (compared to baseline); no significant difference between AVIM RV & AVIM CSP

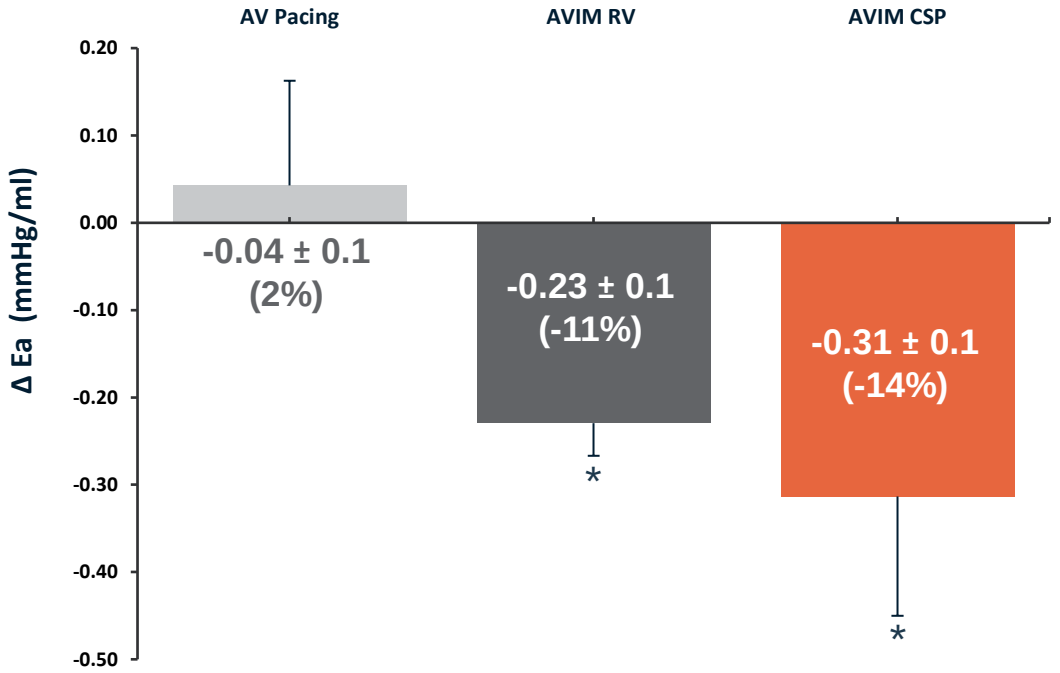


[1]Kuck, Hemodynamics Effects of AVIM Therapy, THT'24.

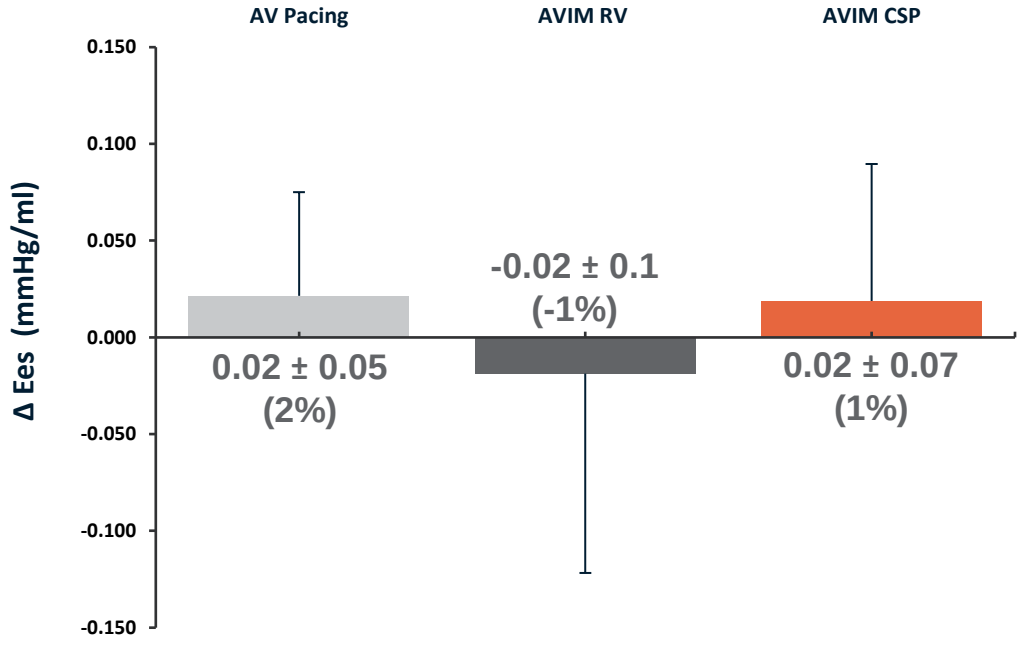
# AVIM Therapy has a Favorable Impact on Cardiac Hemodynamics[1]

## Reduction in total peripheral resistance (Ea) & no change in contractility (Ees)

### Change in Effective Arterial Elastance (Ea)




### Change in Contractility (Ees)




N=16 *P < 0.05 (compared to baseline); no significant difference between AVIM RV & AVIM CSP

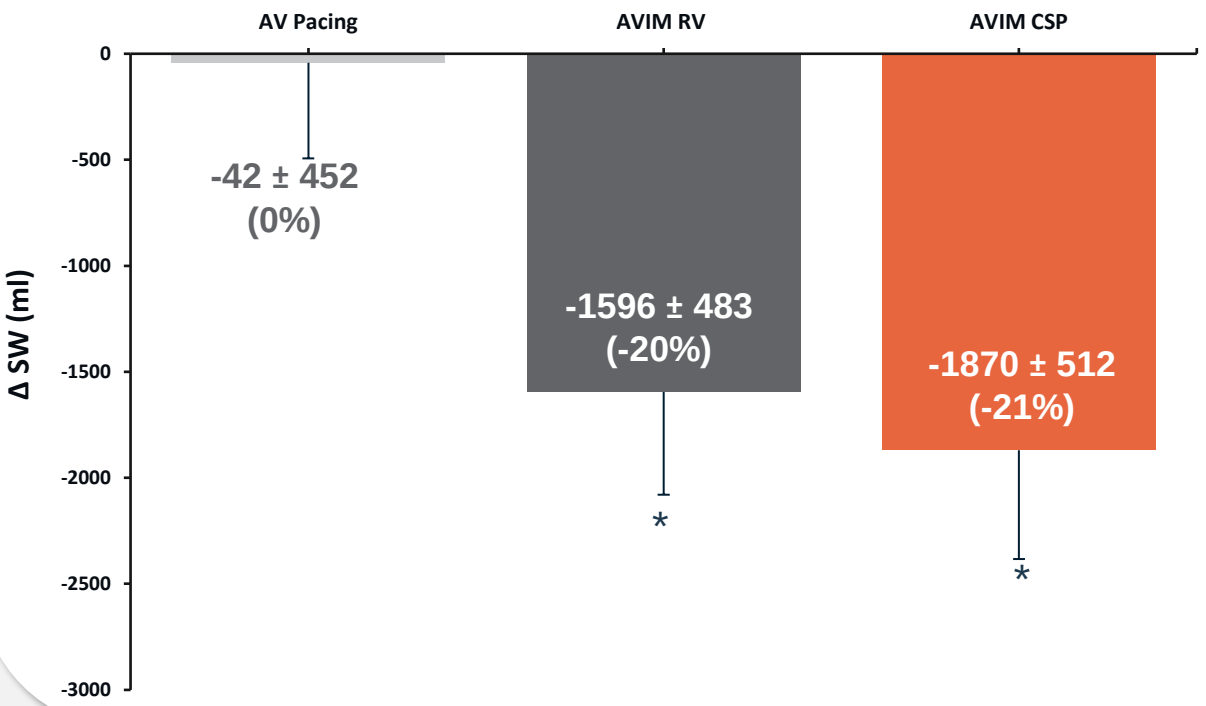


[1]Kuck, Hemodynamics Effects of AVIM Therapy, THT'24;
**Definitions**: Ea (arterial elastance) (Ees (end-systolic elastance, which is a measure of contractility)

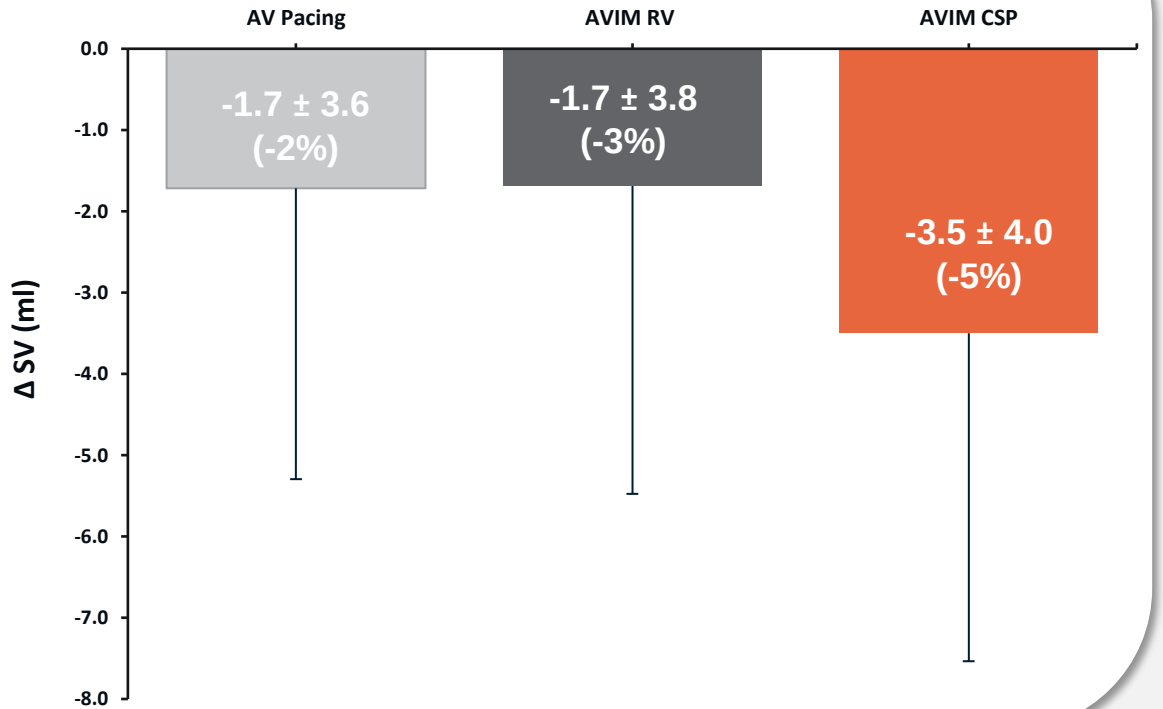
# AVIM Therapy has a Favorable Impact on Cardiac Hemodynamics[1]

## Significant reduction in stroke work (SW) without significant reduction in stroke volume (SV)

### Change in SW




### Change in SV




N=16

*P < 0.05 (compared to baseline); no significant difference between AVIM RV & AVIM CSP

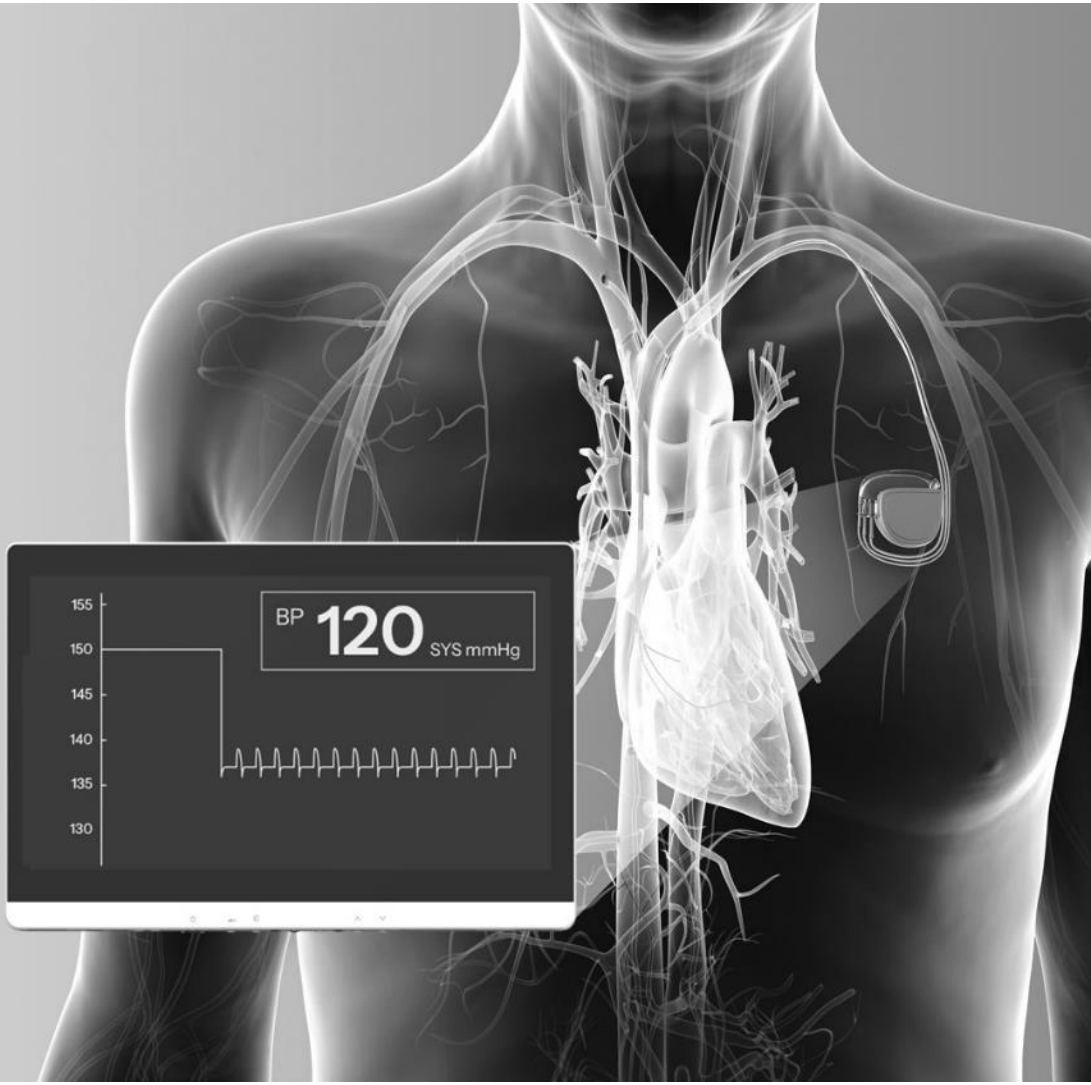


[1]Kuck, Hemodynamics Effects of AVIM Therapy, THT'24.

# AVIM Mechanism of Action Highlights

- AVIM therapy is designed to use a dual-chamber pacemaker to deliver programmed sequences of **short AV intervals interspersed with longer AV intervals to reduce blood pressure**

- Preliminary data support the mechanism of action and **demonstrated a favorable impact of AVIM therapy on cardiac hemodynamics**, independent of RV pacing lead location



# Clinical Data

*MODERATO I & II Pilot Studies*

**Vivek Reddy, M.D.**

*Director, Cardiac Arrhythmia Services at Mount Sinai Hospital*

*Director, Electrophysiology at Mount Sinai Health System*

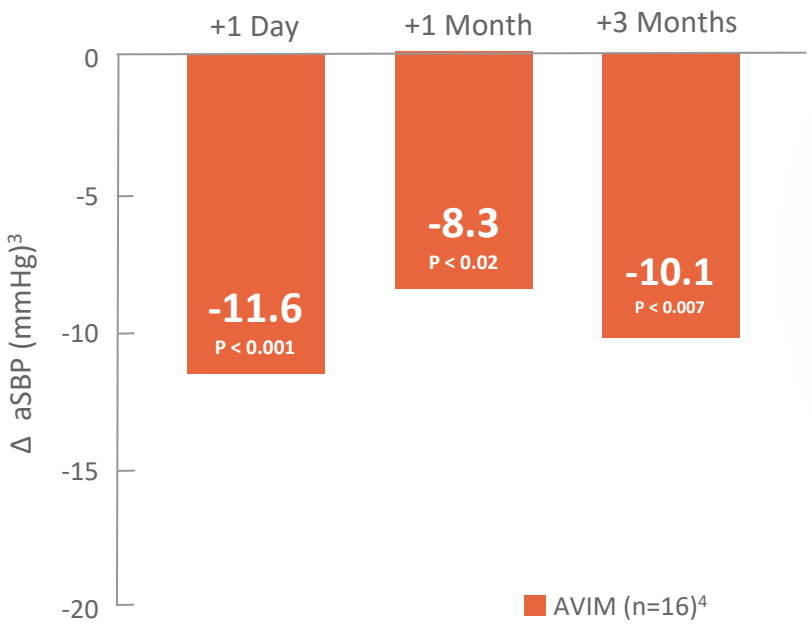
*Professor of Medicine, The Icahn School of Medicine at Mount Sinai*

*BACKBEAT study Clinical Steering Committee Member*

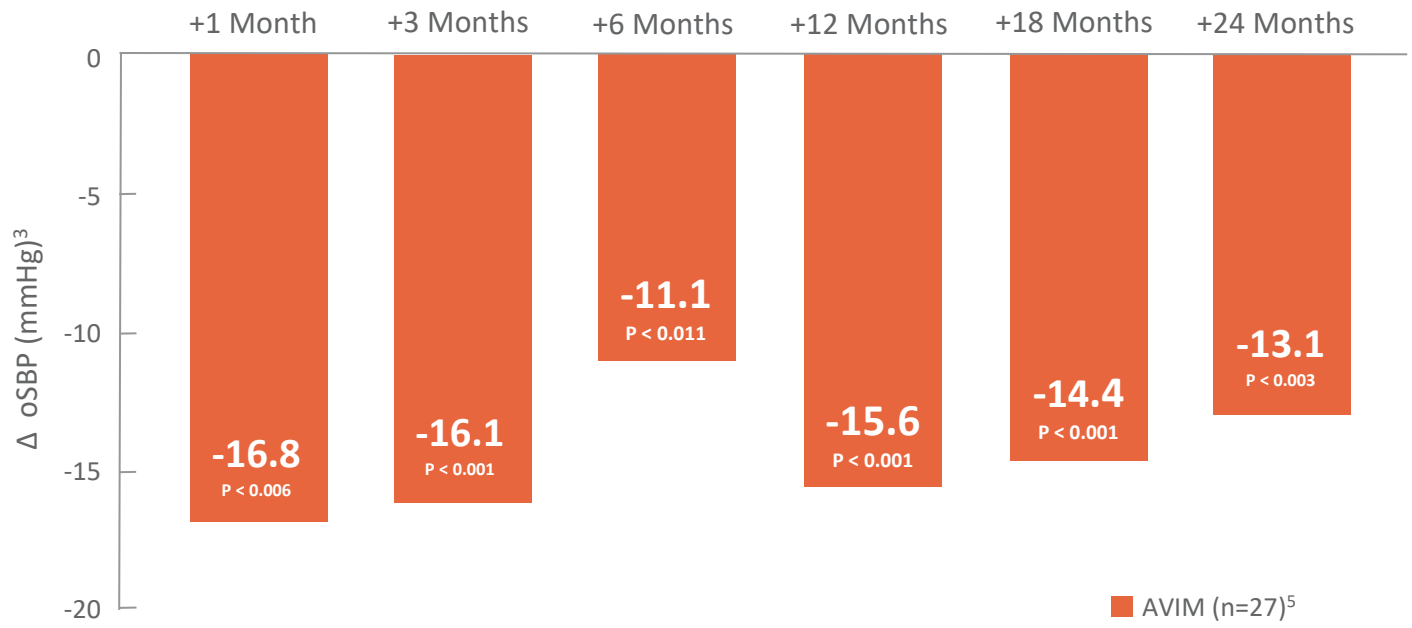
# MODERATO I Study Design & Results

- **Prospective, single-arm study** of 27 patients with persistent hypertension (office systolic blood pressure (oSBP) > 150mmHg) despite 2 or more anti-hypertensive medications & an indication for pacemaker
  - 1-month run-in to account for Hawthorne effect, followed by 3 months activation
- Primary safety & efficacy assessed at **3 months post AVIM therapy activation**; follow-up through 2 years[1,2]

## Significant Reduction in 24-Hour aSBP




## Significant Reduction in oSBP Through 24 Months






[1]Neuzil et al. *Journal of the Am Heart Assoc.* 2017;6:e006974. https://doi.org/10.1161/JAHA.117.006974. [2]Burkhoff MODERATO I Study 2-Year Results TCT 2018. [3]Compared to pre-activation. [4]aSBP (n=160 at pre-activation. [5]AVIM (n=21) continued after completion of study at 3 months to be followed for 2 years. ***Definitions:***, aSBP (Ambulatory Systolic Blood Pressure).

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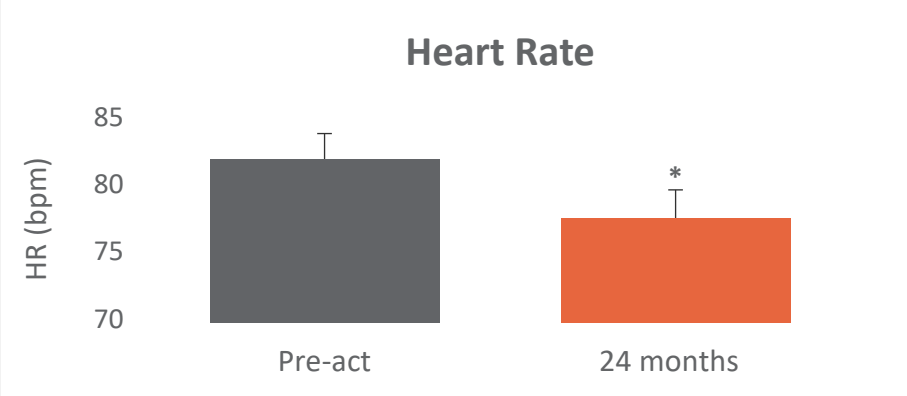
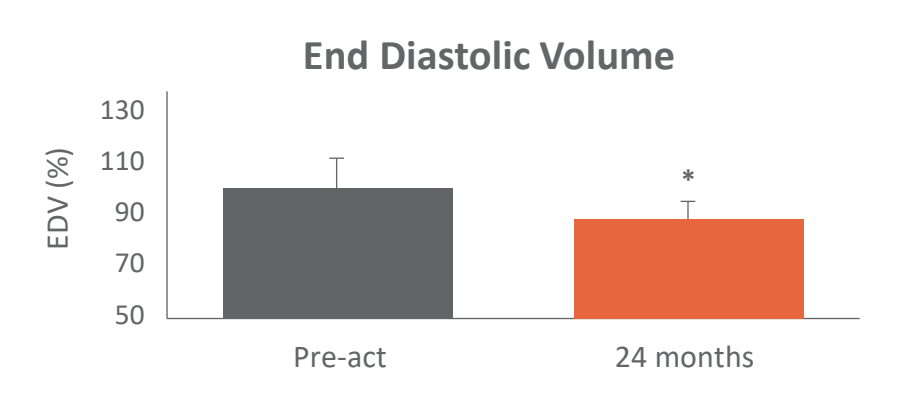
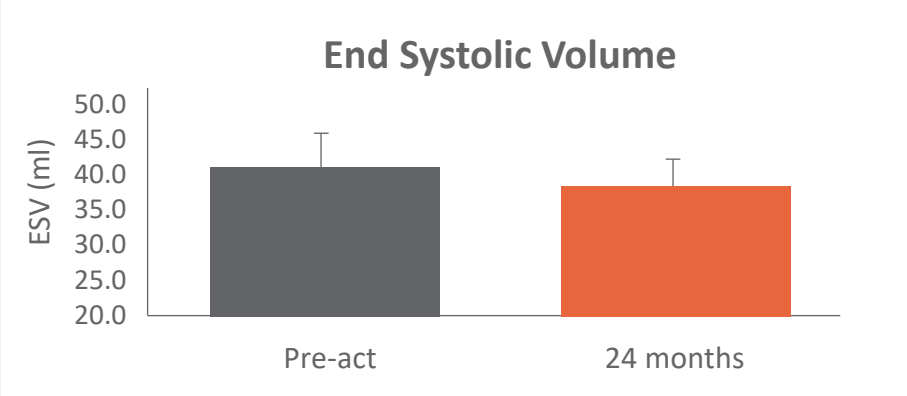
# MODERATO I: Safety Data at 24 Months

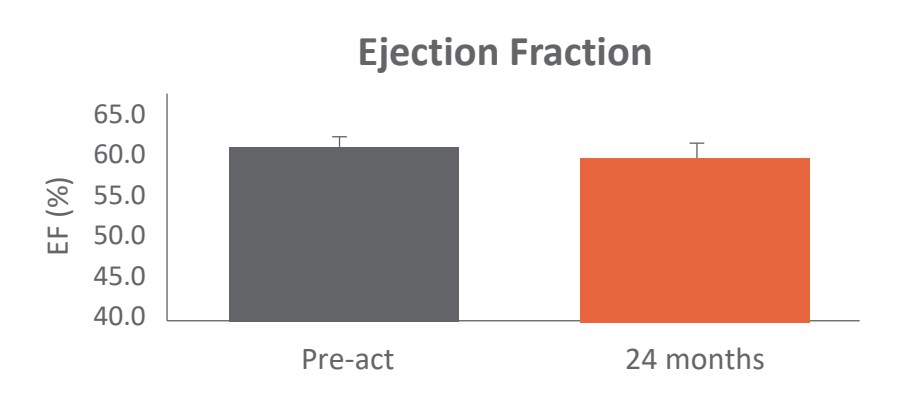
## Significant Reduction in End-Diastolic Volume & Heart Rate with No Significant Change in Ejection Fraction (EF)[1]




* P<0.05



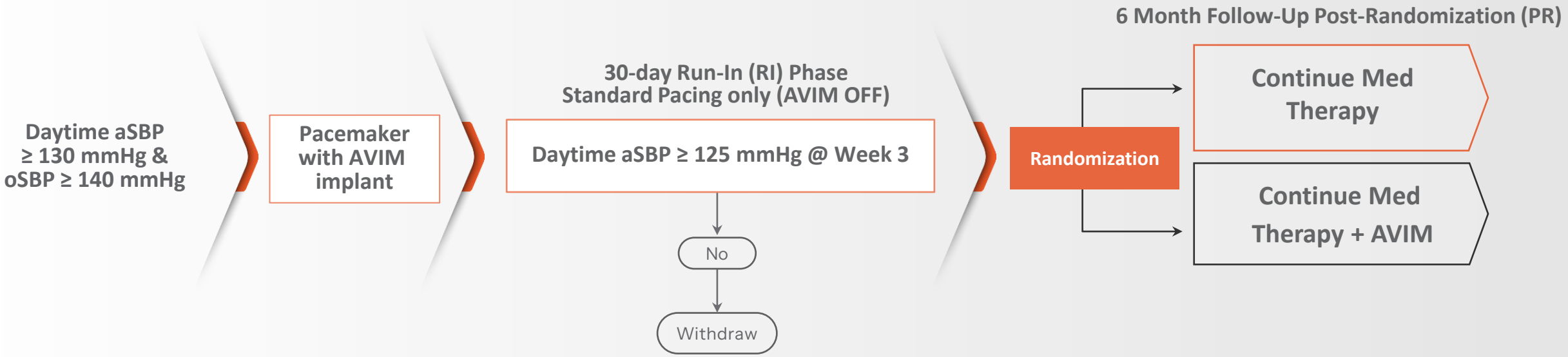



[1]Burkhoff MODERATO I Study 2-Year Results TCT 2018.

# MODERATO II Study Design[1]

**Prospective, multi-center, double-blind study** investigating the efficacy of AVIM therapy in patients with persistent hypertension and an indication for pacemaker

- Primary safety & efficacy assessed at **6 months post AVIM activation**; continued follow-up to 2 years






[1]Burkhoff MODERATO II Study 2-Year Results TCT 2021. **Definitions**: IPG (Implantable Pulse Generator).

# MODERATO II: Patient Demographics

## No significant differences between groups at baseline

| | Control (n=21) | AVIM Therapy (n=26) | p-value |
|---|---|---|---|
| Age | 74.9 ± 8.5 | 73.2± 9.0 | 0.518 |
| Gender | 15 M / 6 F | 15 M / 11F | 0.375 |
| LVEF (%) | 58.4±4.9 | 59.8±6.3 | 0.414 |
| Medical History | | | |
| Diabetes | 9 (42.9%) | 12 (46.2%) | 0.999 |
| Prior Atrial Fibrillation | 6 (28.6%) | 5 (19.2%) | 0.505 |
| Coronary Artery Disease | 9 (42.9%) | 10 (38.5%) | 0.775 |
| Stroke | 0 ( 0%) | 1 (3.8%) | 0.999 |
| Medications | 3.3±1.4 | 3.3±1.6 | 0.886 |
| Isolated Systolic Hypertension | 71.4% | 88.5% | 0.263 |
| 24-Hr aSBP | 136.3±12.5 | 136.3±9.2 | 0.995 |
| 24-Hr aDBP | 72.6±6.7 | 74.0±6.9 | 0.478 |
| Ambulatory Heart Rate (24-hour) | 68.4±8.5 | 69.6±9.5 | 0.670 |
| oSBP | 154.4±15.5 | 153.1±15.8 | 0.781 |
| oDBP | 81.6±12.4 | 83.0±10.8 | 0.693 |
| Office Heart Rate | 66.5±10.9 | 67.1±12.0 | 0.848 |

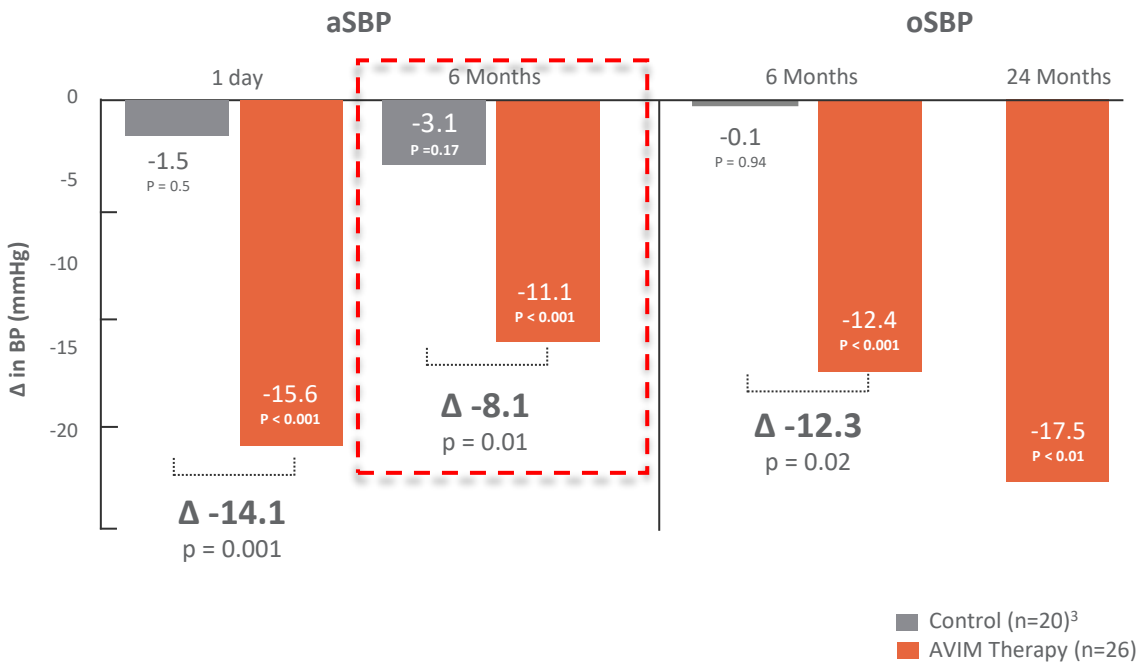


***Definitions***: LVEF (left ventricular ejection fraction), aDBP (ambulatory diastolic blood pressure), oDBP (office diastolic blood pressure).

# MODERATO II Randomized, Double-Blind Results

**AVIM therapy** showed encouraging results in MODERATO II, a prospective, multi-center, randomized (AVIM therapy + medical therapy vs. continued medical therapy), controlled, double-blind, pilot study of patients with pacemakers and persistent hypertension

## Significant Reduction in 24-Hr aSBP and oSBP[1,2]




**-11.1 mmHg**
in 24-Hour aSBP
at 6 months

**0%**
MACE vs. 14.3% in control group at 6 months

**-17.5 mmHg**
in oSBP
at 2 years

**85%**
of patients with reduction in aSBP



[1]Kalaras et al. *Journal of the Am Heart Assoc*. 2021;10:e020492 ahajournals.org/doi/10.1161/JAHA.120.020492; [2]Burkhoff MODERATO II Study 2-Year Results TCT 2021; [3]24-Hr aSBP Control (n=19),1 control patient could not be measured despite repeat measurement (patient had extremely high blood pressure); **Definitions**: Major Adverse Cardiac Events (MACE) included death, heart failure, clinically significant arrhythmias (i.e., persistent or increased atrial fibrillation, serious ventricular arrhythmias), myocardial infarction, stroke and renal failure in treatment group calculated per patient.

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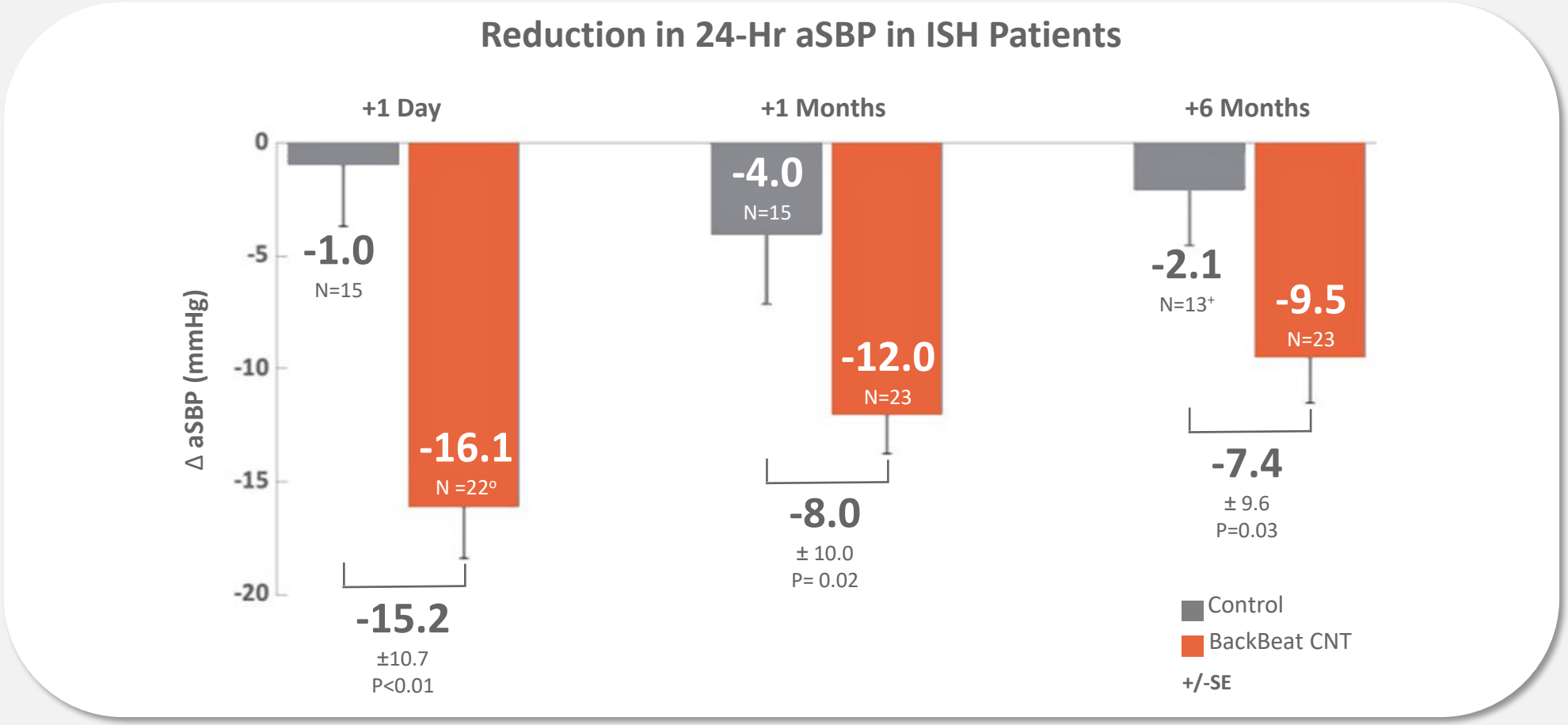
# MODERATO II: Significant aSBP Reduction in ISH Patients

**7.4 mmHg reduction in aSBP at 6 Months compared to control**

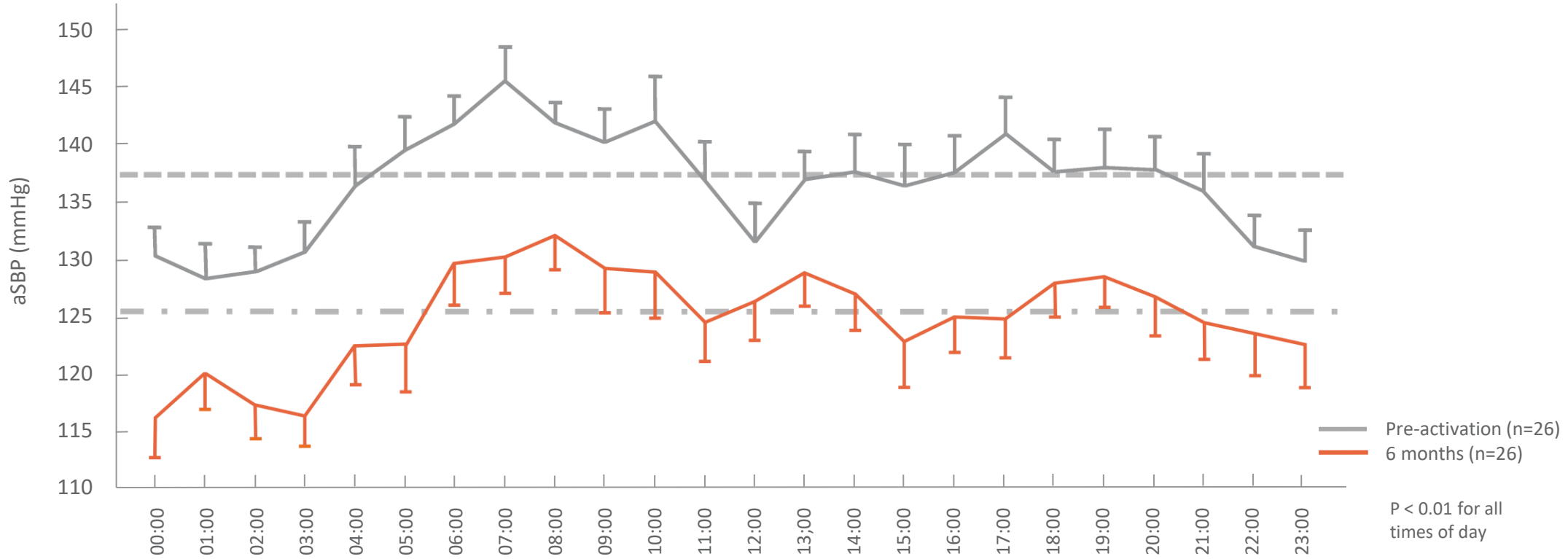





º aSBP could not be measured on 1 patient despite repeat measurement (patient had extremely high blood pressure);
⁺13 control had data at 6 months, one died of cancer, and one had unsuccessful recording

# MODERATO II: Significant Reduction in 24-hour aSBP[1]

**Paired average 24-hour aSBP profile after 6 months of AVIM therapy demonstrate reduction in SBP with preservation of normal daily blood pressure variations**






[1]Burkhoff MODERATO II Study 2-Year Results TCT 2021.

# MODERATO II: High Overall Response Rate to AVIM Therapy[1]

**6 Months Post-Randomization**

| | AVIM (n=26) | Control (n=19) |
|---|---|---|
| Isolated Systolic Hypertension (ISH) | **88.5%** | **71.4%** |
| % with Reduction in aSBP | **85%** | **53%** |
| % with > 5 mmHg Reduction in aSBP | **65%** | **42%** |
| % with > 10 mmHg Reduction in aSBP | **54%** | **21%** |



[1]Kalarus et al. *Journal of the Am Heart Assoc*. 2021;10:e020492 ahajournals.org/doi/10.1161/JAHA.120.020492.

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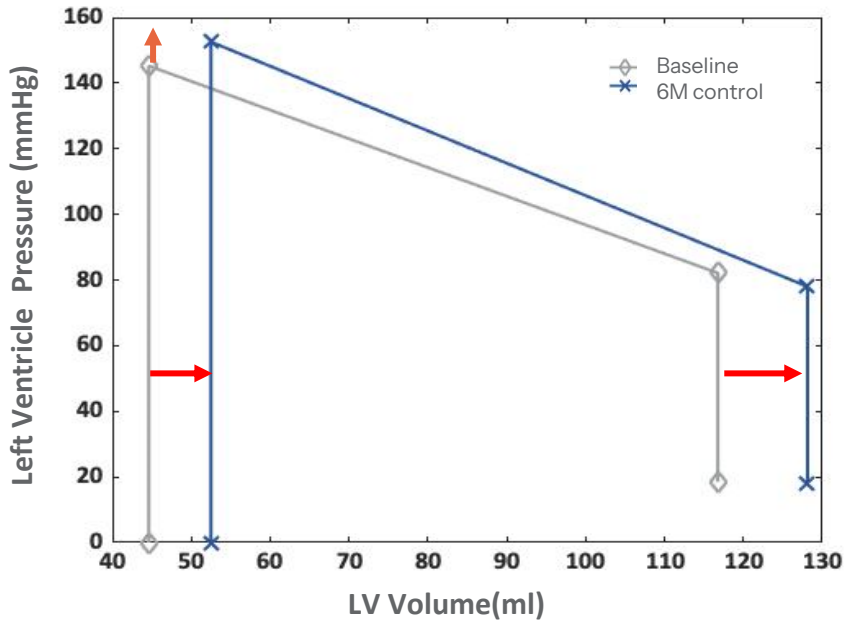
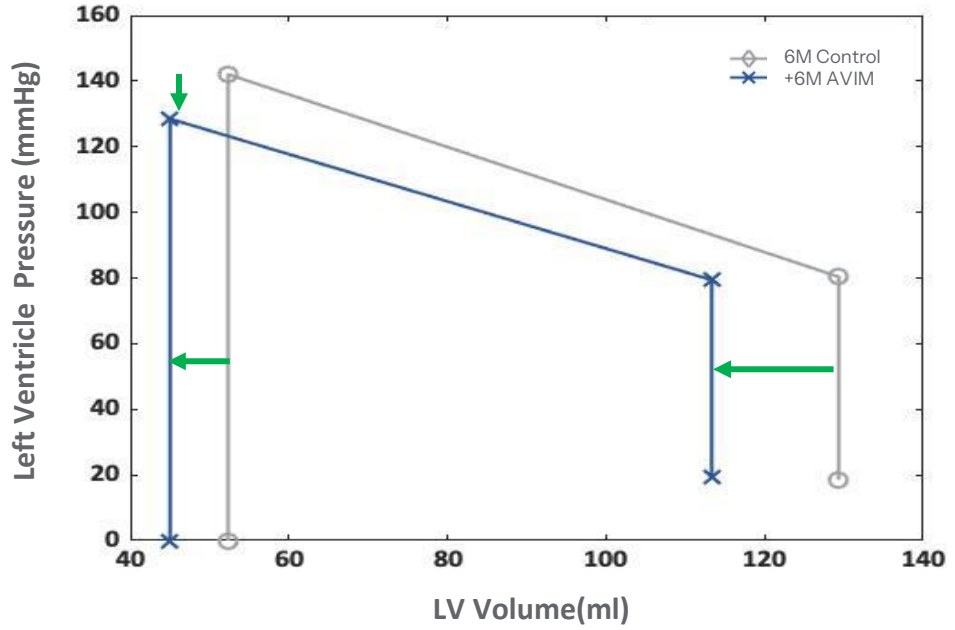
# MODERATO II: Chronic, Non-Invasive PV Loop Data Show Favorable Effects on Cardiac Remodeling[1]

## AVIM Therapy affects adverse remodeling

**Unfavorable remodeling in control patients after 6 months resulted in increases in ESV, EDV, & ESP**




**Favorable reverse remodeling 6 months after crossover to AVIM therapy demonstrated by reductions in ESV, EDV, & ESP[2]**






[1]Paired data (N=12, N=6); [2]6 months of control followed by 6 months of AVIM therapy after crossover (12 months from baseline). **Definition**: ESP (End-Systolic Pressure)

# MODERATO II: Long-Term SBP Reduction with AVIM Therapy

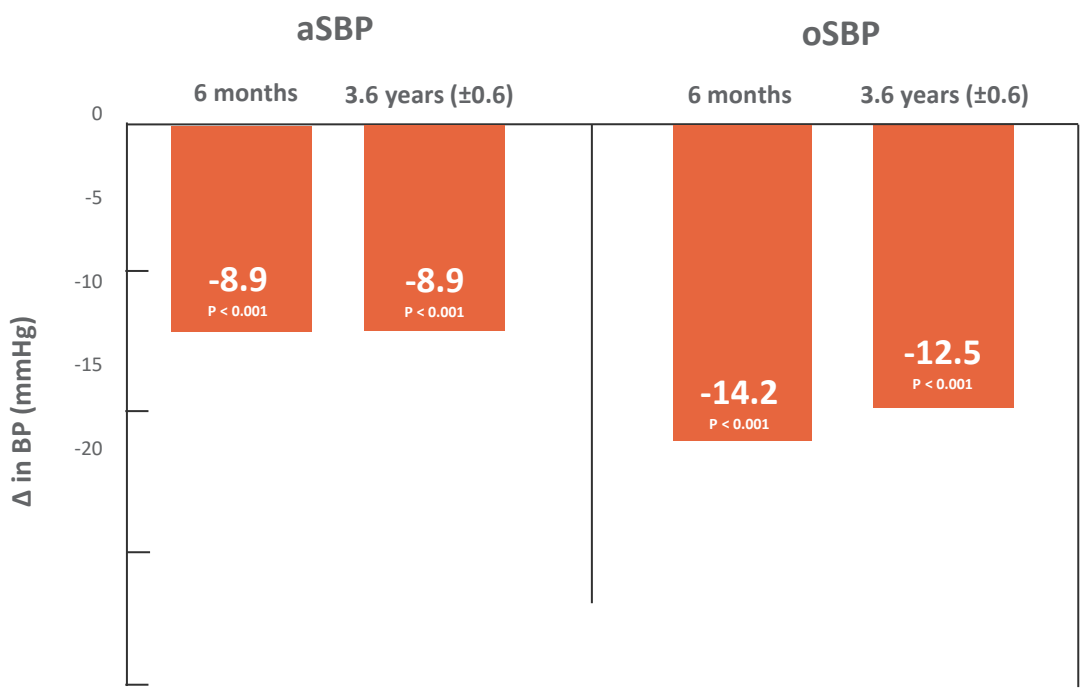
## AVIM therapy demonstrated sustained, long-term reduction in 24-Hr aSBP

**Long-term blood pressure from a follow-up study of 16 patients from MODERATO II***

- 8 AVIM & 8 control patients who crossed-over to AVIM therapy at the end of the 6-month double-blind phase of MODERATO II & agreed to be followed long-term
- Each patient had aSBP and oSBP measured at an average of **3.6 years** (±0.6) following initiation of AVIM therapy

*Patients were re-consented for long-term follow-up

### Significant Reduction in 24-Hr aSBP and oSBP[1,2,3]




P-value between 6 months & 3.6 years (±0.6) = non-significant

**-8.9 mmHg** in 24-Hour aSBP from baseline at **3.6 years** (±0.6)

**-12.5 mmHg** in oSBP at **3.6 years** (±0.6)

**100%** of patients with reduction in aSBP at **3.6 years** (±0.6)



[1]Kalaras et al. Journal of the American Heart Association. 2021;10:e020492 ahajournals.org/doi/10.1161/JAHA.120.020492; [2]Burkhoff MODERATO II Study 2-Year Results TCT 2021; [3]Fischer MODERATO Study Long-term Results ICI 2024;

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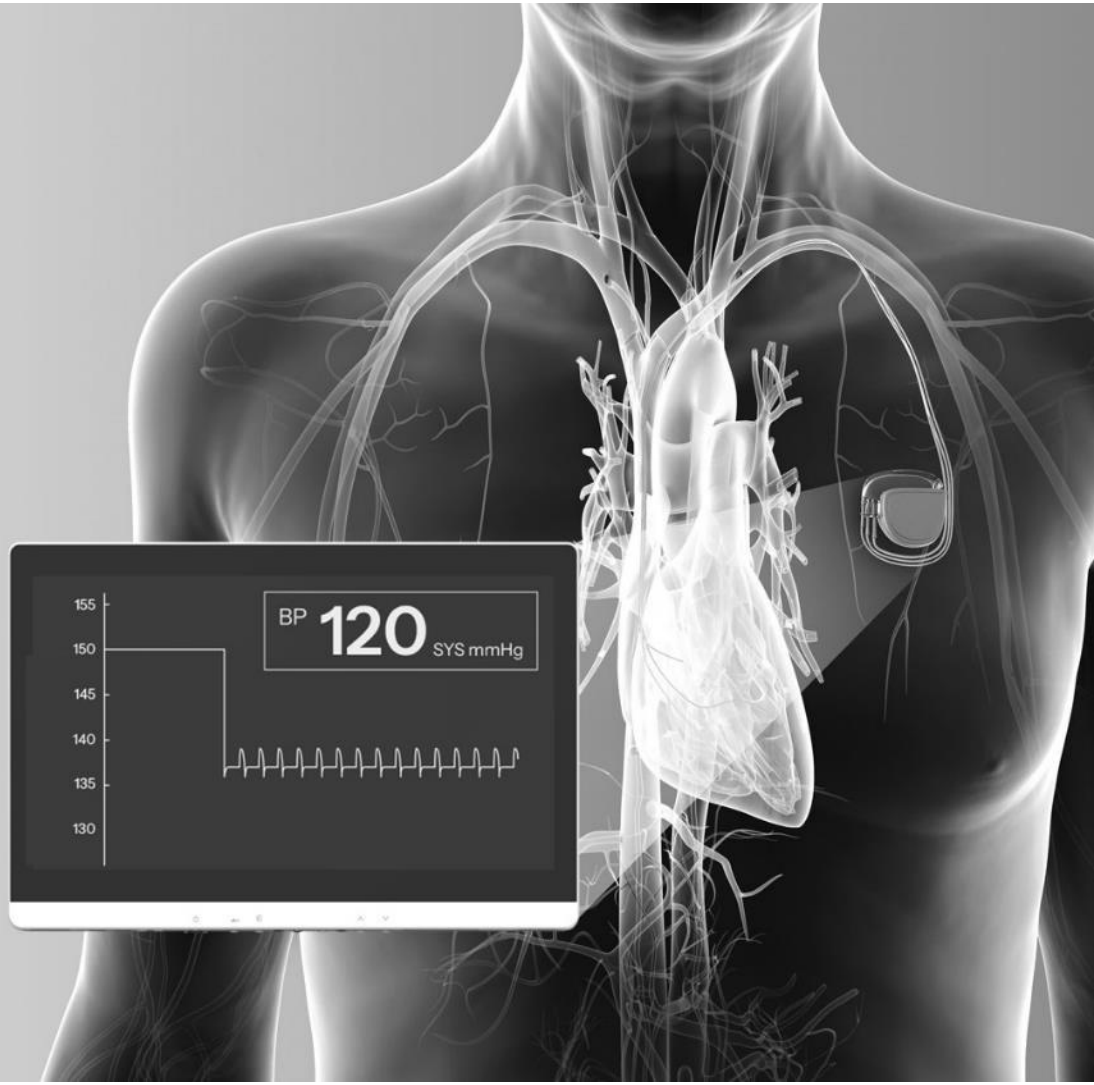
# AVIM Clinical Results Summary

AVIM therapy resulted in:

- **Significant reduction in mean aSBP & oSBP at 6 months, in a group where 88.5% were ISH patients**
  - 85% overall response rate to treatment with AVIM therapy
  - 54% experiencing > 10mmHg reduction in aSBP at 6 months
- Significant reduction in oSBP & aSBP **maintained through 3.6 years**
- **Low overall MACE** with no difference between groups

Chronic PV loop data support the mechanism of action and demonstrate a **favorable impact of AVIM therapy on cardiac hemodynamics**



# Rationale and Design of the BACKBEAT Global Pivotal Study

**David Kandzari, M.D., FACC, FSCAI**

*Chief, Piedmont Heart Institute and Cardiovascular Services*

*Chief Scientific Officer, Piedmont Healthcare*

*Director, Interventional Cardiology, Piedmont Heart Institute*

*Co-principal investigator for the BACKBEAT Study*



BACKBEAT STUDY

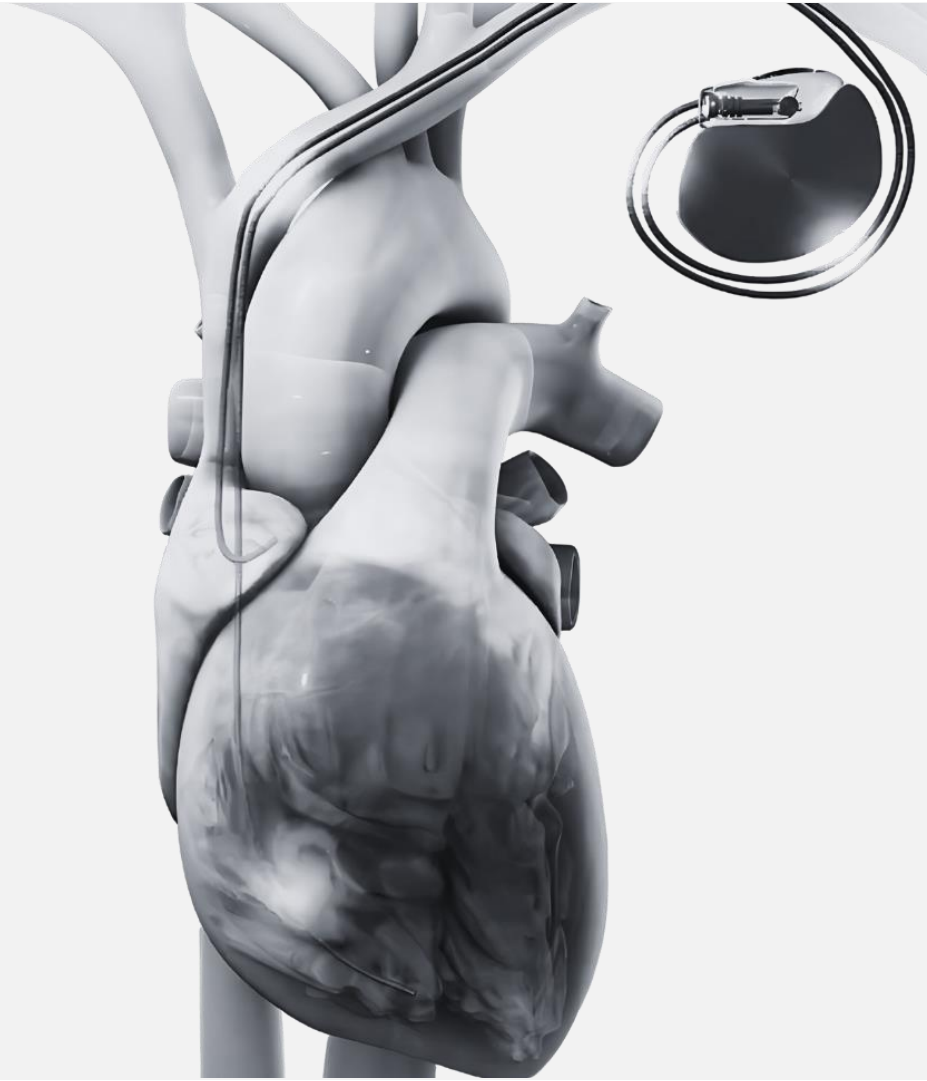
Orchestra BioMed™

# Novel Design for a Device-Based Therapy

BACKBEAT
GLOBAL PIVOTAL STUDY

**Global, pivotal randomized, controlled, double-blind study in which all patients:**

- Receive Medtronic dual-chamber pacemaker implant
- Have the investigational RAMware downloaded to their device
- Undergo follow-up testing with AVIM therapy ON and OFF
- Are managed by a blinded study team





BACKBEAT GLOBAL PIVOTAL STUDY
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# BACKBEAT Study Target Population

*Patients Indicated for a Dual-Chamber Pacemaker Who Also Have Uncontrolled Hypertension Despite Use of Antihypertensive Medications*

**Eligibility: recently received *de novo* implant of a dual-chamber pacemaker system (including leads)**

- All patients are indicated for a dual-chamber pacemaker
- Sinus node dysfunction & AV block patients are eligible
- Favorable risk/benefit profile with procedure independent of study
- Workflow & implant technique do not change
  - Leads can be placed in CSP or traditional RV locations




BACKBEAT GLOBAL PIVOTAL STUDY

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# Clinical Steering Committee Members

**Co-Principal Investigators**

Andrea M Russo
***Electrophysiology***

David Kandzari
***Interv. Cardiology, HTN***

**Steering Committee Members**

Vivek Reddy
***Electrophysiology***

Felix Mahfoud
***Interv. Cardiology, HTN***

Béla Merkely
***Electrophysiology***

JoAnn Lindenfeld
***Advanced Heart Failure***

Charles Love
***Electrophysiology***

Raymond Townsend
***Nephrology***



**Definitions**: Interv (Interventional)

BACKBEAT GLOBAL PIVOTAL STUDY

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# Approximately 50% of Patients Will be Enrolled Outside of the US

Study will randomize approximately 500 patients across ~80 study sites

**Participating countries include:**

- Belgium
- Czech Republic
- Germany
- Hungary
- Poland
- Spain
- Switzerland
- The Netherlands
- UK
- US



BACKBEAT GLOBAL PIVOTAL STUDY

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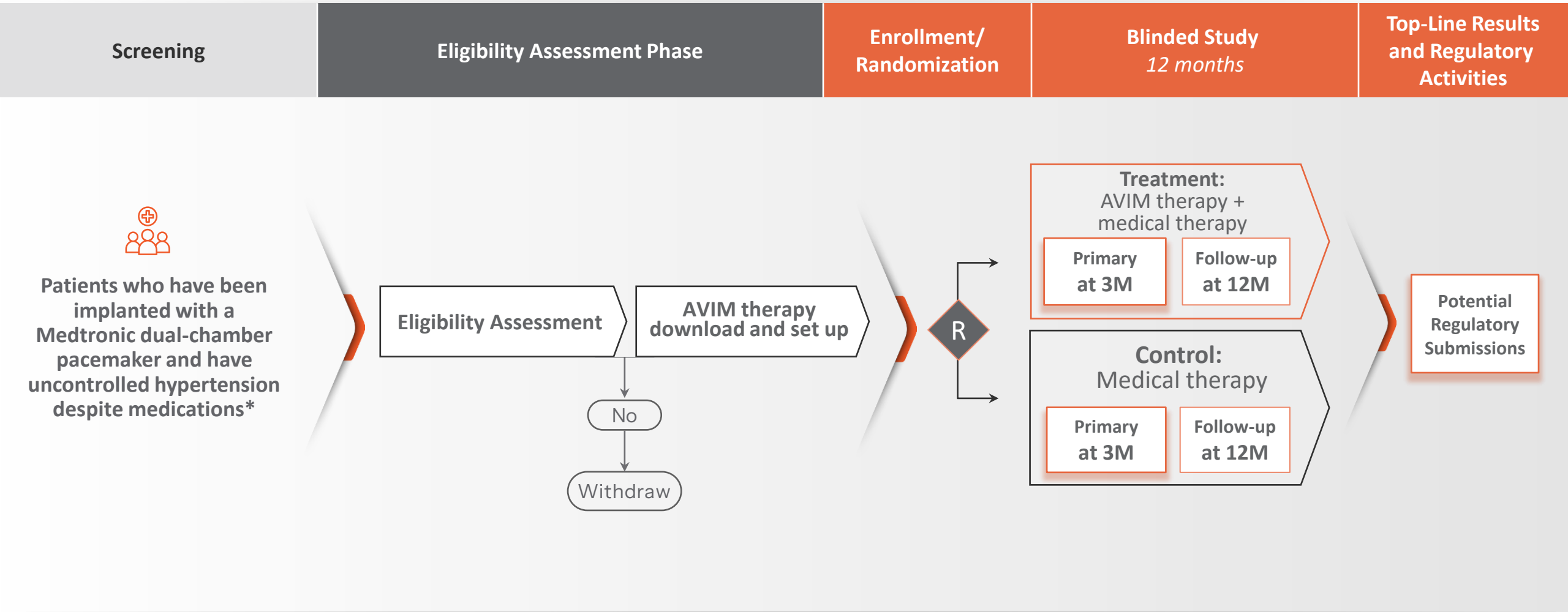
# BACKBEAT Study Design




*Implant is decoupled from study outcomes & endpoints.



BACKBEAT GLOBAL PIVOTAL STUDY

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# Key Inclusion and Exclusion Criteria

## Inclusion

- Recently received a **Medtronic Astra/Azure dual chamber pacemaker**
- On a stable anti-HTN treatment regimen of **1, 2 or 3 classes of anti-HTN drugs**
- oSBP **≥ 140 mmHg and < 180 mmHg**
- Average 24-Hour aSBP **≥ 130 mmHg and < 170 mmHg**

## Exclusion

- Presence of conditions that **limit effective delivery of AVIM therapy** (i.e., permanent or significant atrial fibrillation, severe valvular disease)
- **Left ventricular (LV) dysfunction** (reduced ejection fraction) and/or **symptomatic heart failure (HF)**
- Recent cardiovascular procedures, renal denervation, other active implantable devices and significant kidney impairment



BACKBEAT GLOBAL PIVOTAL STUDY

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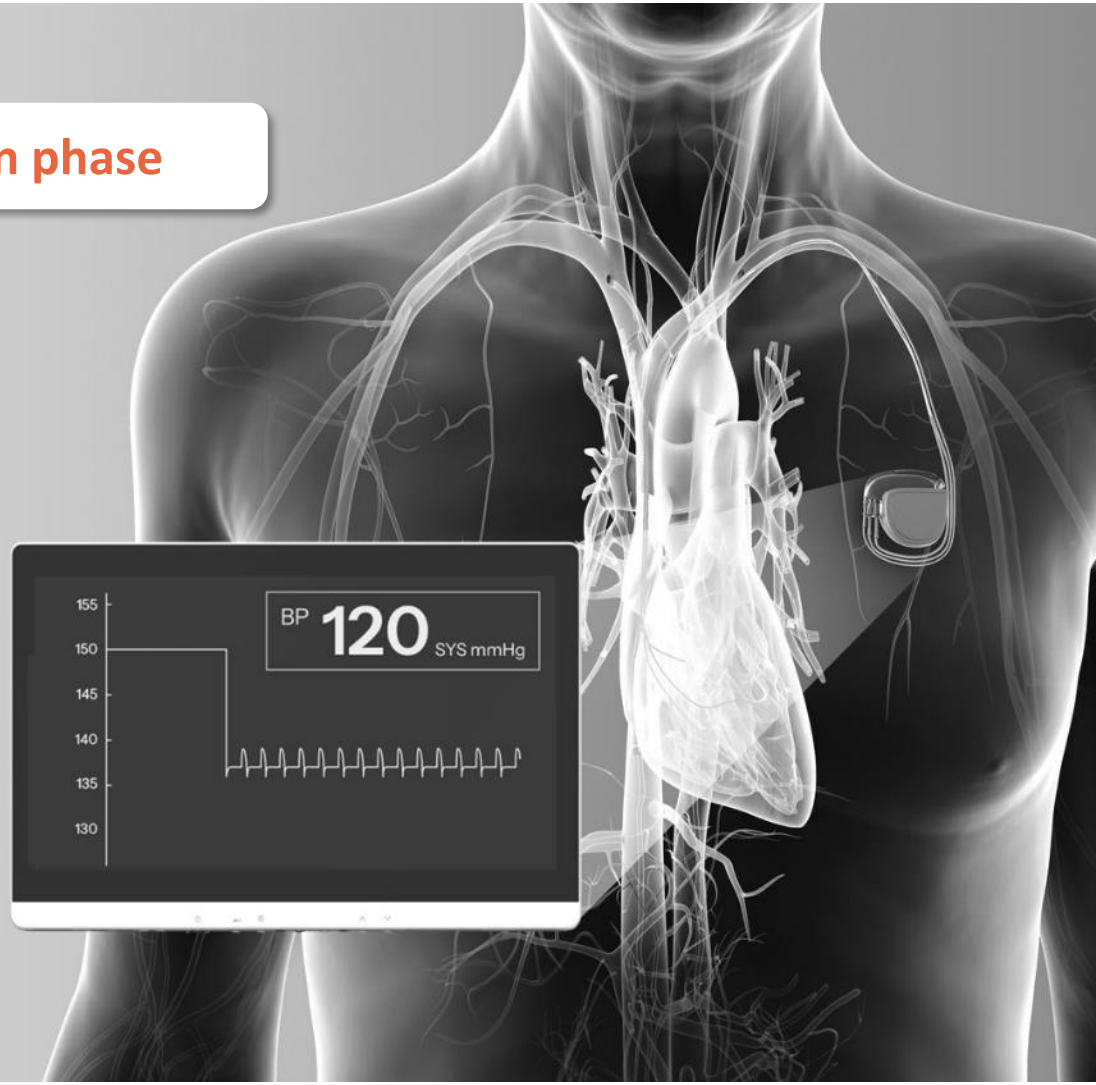
# Set-Up Procedure Determines Enrollment and Randomization

**≥ 5 mmHg reduction is required to proceed to randomization phase**

- **AVIM RAMware downloaded** onto previously implanted pacemaker **in all patients**
- Response to AVIM therapy activation assessed acutely:
  - Observe blood pressure reduction
  - Determine stability of reduction
  - Optimize therapy parameters for each patient



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# Double Blind Phase: Primary Endpoints

**Primary Efficacy Endpoint:**

Between group difference in the **change of mean 24-hour ambulatory systolic blood pressure (aSBP) at 3 months** post-randomization

- aSBP is the gold-standard measurement of blood pressure
- 3 months is the standard duration to demonstrate efficacy in HTN studies
- Balances time needed to demonstrate efficacy with ability to maintain medication regimens

**Primary Safety Endpoint**

Freedom from **unanticipated serious adverse device events at 3 months** post-randomization

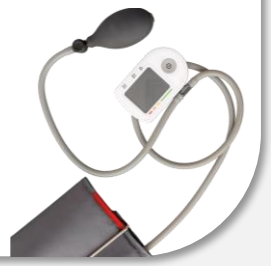
- Potential complications of pacemaker implant & follow-up are well-established
- Aims to identify unique & unexpected adverse events **directly related to AVIM therapy (treatment group only)**

# Double-Blind Follow-up Through 12-Months to Collect Additional Data

## Hypertension

*Between-group difference in:*

- Mean Change of 24-hour aSBP immediately after randomization
- Mean change in 24-hour ambulatory pulse pressure (aPP)
- Mean reduction of oSBP at 3 months post-randomization



## Adverse Events

*Between group comparison:*

- Freedom from the composite cardiovascular adverse events (CCAE) rate 12 months post-randomization
  - Including mortality, stroke, MI, HF, AFib, HTN crisis, decline in eGFR

## Medications

*Between group comparison:*

- Reduction in anti-hypertensive medication burden at 3-months
  - Medication dose, number, and/or class



**Definition:** Estimated glomerular filtration rate (eGFR)

# Key Takeaways and Q&A

# Key Takeaways

- **Hypertension is the leading risk factor for death** & most common comorbidity in patients with pacemakers globally
- AVIM therapy is an investigational, **programmable & adjustable treatment** developed by Orchestra BioMed
- AVIM therapy is designed to have an **immediate, substantial, & persistent effect in reducing blood pressure**
- Invasive PV loop studies support the mechanism of action and **demonstrate a favorable impact of AVIM therapy on cardiac hemodynamics, when pacing from traditional RV lead locations or left bundle branch area**
- Data from the MODERATO I & II studies demonstrated a **favorable efficacy and safety profile**
- BACKBEAT global pivotal study is being conducted in **collaboration with Medtronic, the global leader in cardiac pacing therapy**

# Q&A

## Moderator

**David Hochman**
CEO, Chairman, Founder
Orchestra BioMed

**Darren Sherman**
COO, President, Founder
Orchestra BioMed

**Avi Fischer, M.D.**
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