LBCT UPDATES: MOST RELEVENT IN SHOW

Wednesday, October 30, 2019

Martin C. Burke, DO
Chief Scientific Officer
CorVita Science Foundation

www.corvitascience.org

COI DISCLOSURES

- I have received lecture and proctoring honoraria from Spectranetics.
- I have been funded by and NIH/SBIR grant to AJ Medical Devices, Inc. (AJMD) and research grants from Boston Scientific, Medtronic, St. Jude Medical, Guidant, Inc. and Cameron Health, Inc.
- I am or have been a consultant to AJMD, Boston Scientific and Cameron Health.
- I have an equity stake in AtaCor Medical, Inc. and am Chief Medical Officer.

Results of a Large-scale, App-based Study to Identify Atrial Fibrillation Using a Smartwatch:

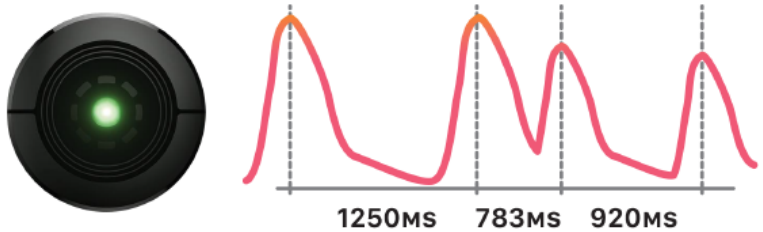
The Apple Heart Study

Mintu Turakhia MD MAS and Marco Perez MD
on behalf of the Apple Heart Study Investigators

NCT # 03335800

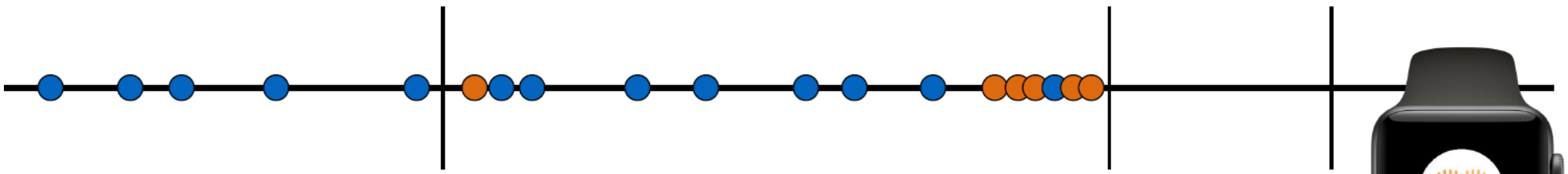
Stanford | MEDICINE

Irregular Pulse Notification Algorithm



Algorithm results

- Regular pulse
- Suggestive of Afib



Tachogram = Periodic, opportunistic measurements

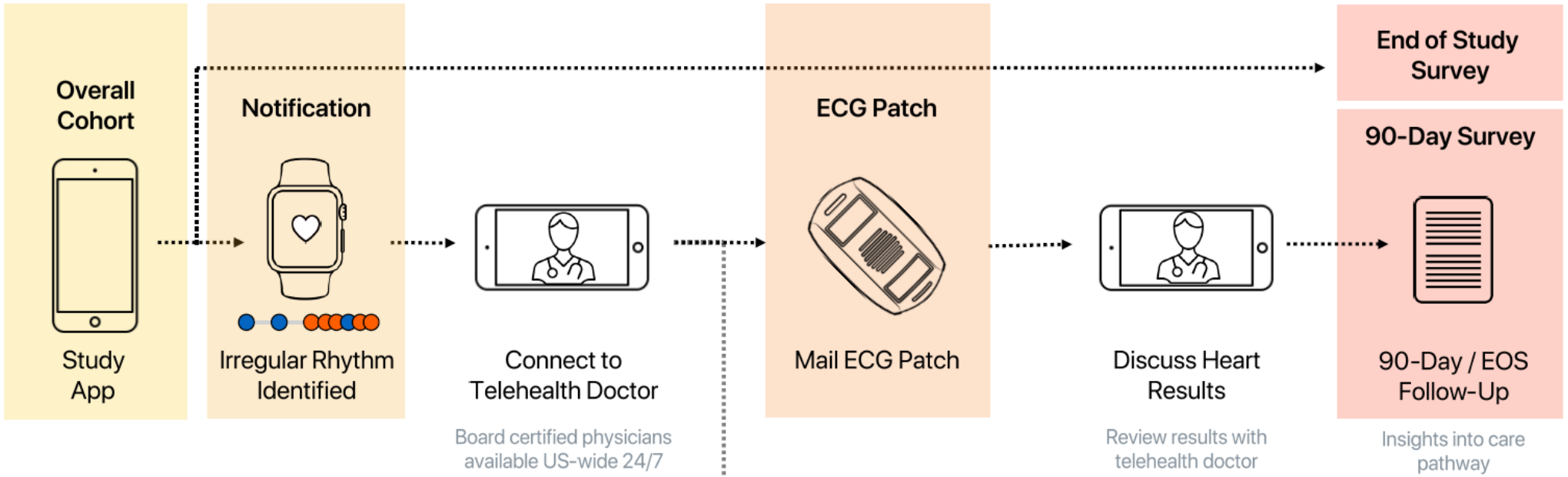
5 confirmations ⇒ notify user

Positive triggers frequent measurements

Not confirmed ⇒ return to usual sampling

The algorithm does not use the watch ECG feature

Prospective, Single Arm, Open Label Study



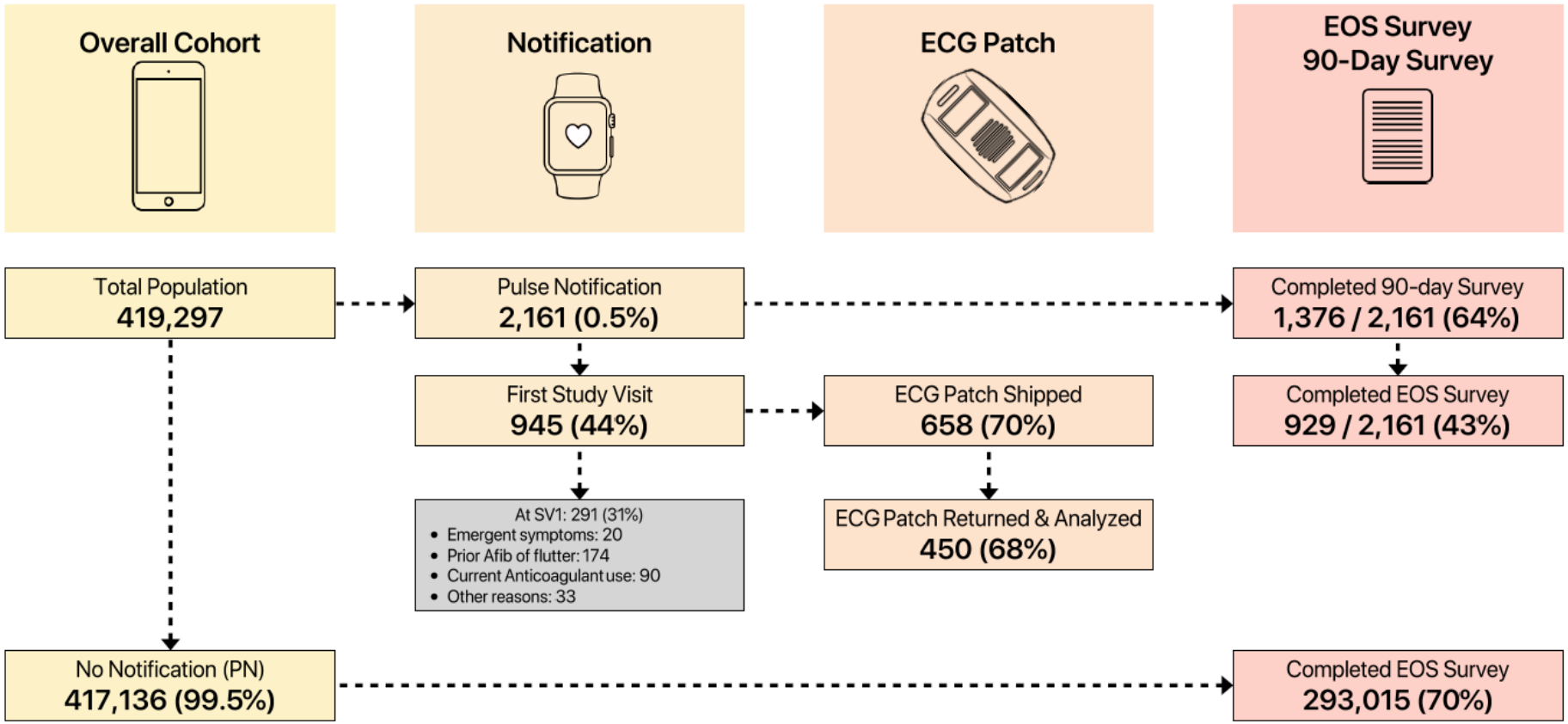
Inclusion criteria

- Age ≥ 22; U.S. Resident
- iPhone (5S or higher) + Watch (Series 1-3)

Exclusion criteria

- Atrial fibrillation or atrial flutter
- Current use of anticoagulation

Consort Diagram



Baseline Demographics

		Overall Cohort 	Notification 	ECG Patch 
	N	419,297	2,161	450
	Female (%)	177,087 (42)	461 (21)	102 (23)
Age	Age, mean (sd)	41 (13)	57 (15)	59 (14)
	≥ 65	24,626 (6)	775 (36)	181 (40)
	55–64	42,633 (10)	556 (26)	114 (25)
	40–54	132,696 (32)	488 (23)	106 (24)
	22–39	219,179 (52)	341 (16)	49 (11)
Race	White	286,190 (68)	1,747 (81)	379 (84)
	Hispanic	48,775 (12)	104 (5)	20 (4)
	African American	32,275 (8)	106 (5)	16 (4)
	Asian	26,156 (6)	87 (4)	8 (2)
	Other Mixed Ethnicity	7,958 (2)	32 (1)	6 (1)

Baseline Demographics *(continued)*

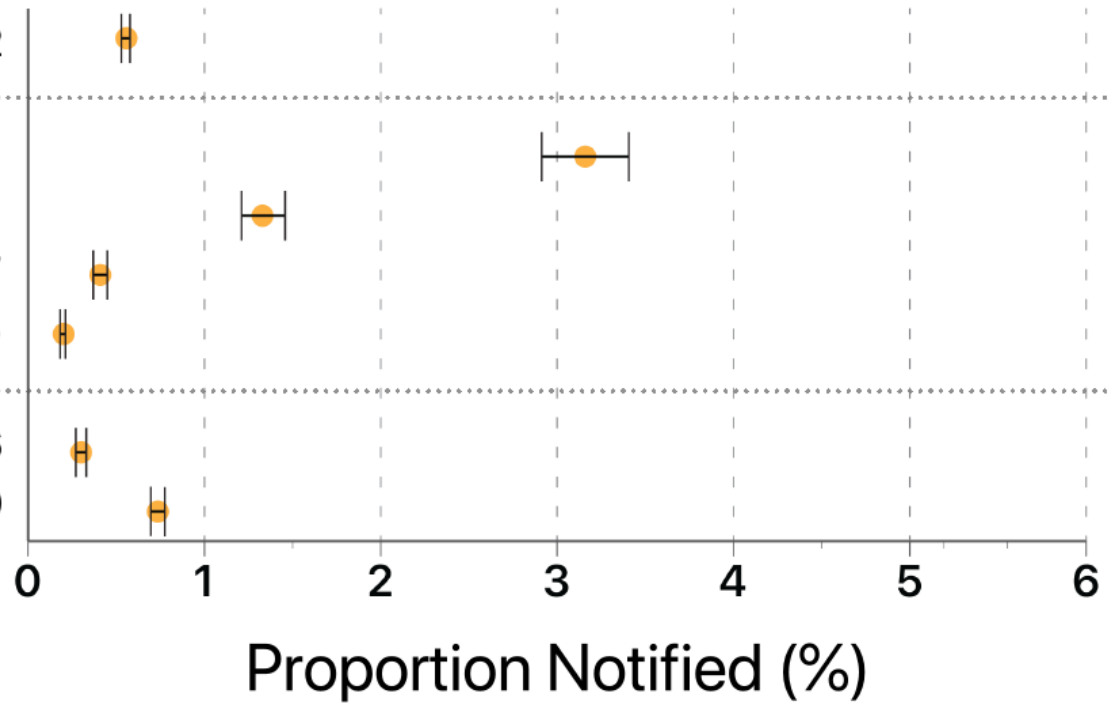
	Overall Cohort 	Notification 	ECG Patch 
N	419,297	2,161	450
$CHA_2DS_2VASc \geq 2$	55,277 (13)	713 (33)	171 (38)
Obesity (%)	160,197 (38)	984 (46)	192 (43)
Hypertension (%)	86,338 (21)	917 (42)	200 (44)
Diabetes (%)	20,443 (5)	255 (12)	53 (12)
Heart failure (%)	2,511 (0.6)	72 (3)	10 (2)
Stroke (%)	4,153 (1)	66 (3)	10 (2)
Peripheral Arterial Disease (%)	2,596 (0.6)	52 (2)	10 (2)
Smoking (any)	25,458 (6)	88 (4)	10 (2)
Alcohol (≥ 1 drink/week)	190,463 (45)	1,092 (51)	227 (50)

Initial Irregular Pulse Notifications

Overall Cohort

~ 8 Months Monitoring

Grouping		Notified / Total	%
	Overall	2,161 / 419,297	0.52
Age	≥ 65	775 / 24,626	3.2
	55–64	556 / 42,633	1.3
	40–54	488 / 132,696	0.37
	22–39	341 / 219,179	0.16
Sex	Female	461 / 177,087	0.26
	Male	1,672 / 238,700	0.70

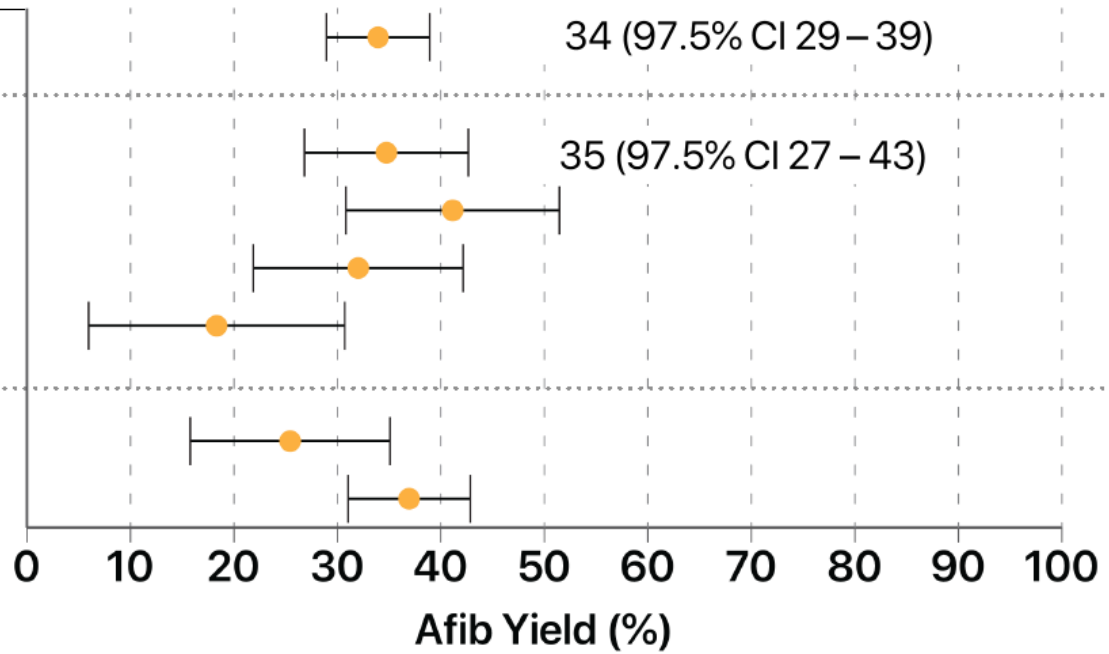


Afib Yield on ECG Patch

ECG Patch 450

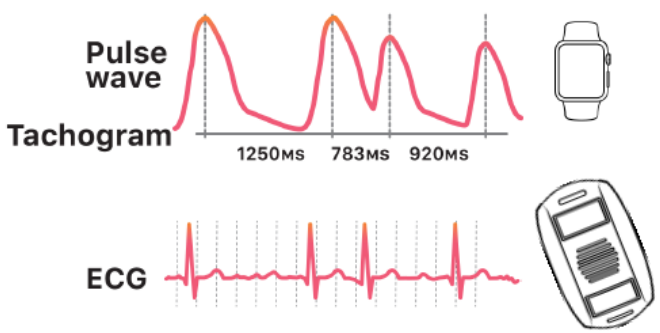
Mean time to hookup: 13 days
Mean wear time: 6.3 days

	Grouping	Observed AF / Total	%
	Overall	153 / 450	34
Age	≥ 65	63 / 181	35
	55–64	47 / 114	41
	40–54	34 / 106	32
	22–39	9 / 49	18
Sex	Female	26 / 102	26
	Male	124 / 335	37

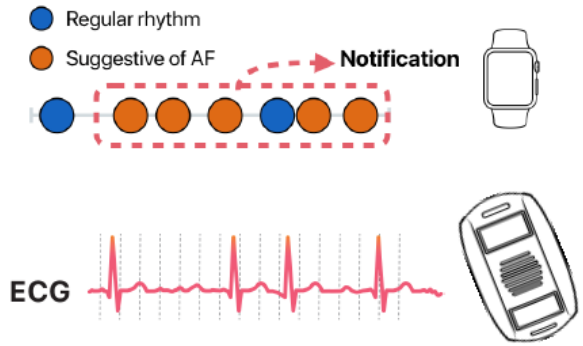


Positive Predictive Values

Irregular Tachograms



Irregular Pulse Notifications



	Afib on ECG Patch	Positive Tachograms	PPV* (97.5% CI)
Overall	1,489	2,089	0.71 (0.69–0.74)
Age ≥ 65	548	914	0.60 (0.56 – 0.64)

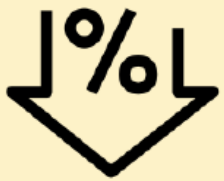
Afib on ECG Patch	Positive Notifications	PPV (95% CI)
72	86	0.84 (0.76–0.92)
25	32	0.78 (0.64 – 0.92)

90-Day Survey

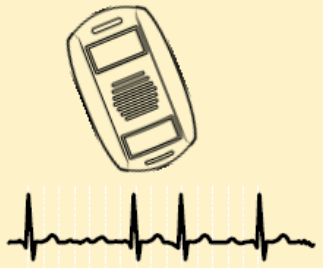
Notification	90-Day Survey	Contacted Non-Study Provider
		
2,161 (0.5%)	1,376 / 2,161 (64%)	787 / 1,376 (57%)
	161 (15%) Afib before study enrollment	218 (28%) Start new medication
		262 (33%) Referral to specialist
		287 (36%) Additional testing

Conclusions

Study w/ Novel Virtual Design
419,297 in 8 months



Proportion Notified low
Overall: 0.52% (0.49-0.54)



ECG patch 13 days after
34% had Afib

Positive predictive value
Tachogram: 0.71 (0.69-0.74)
Notification: 0.84 (0.76-0.92)

57% Notified (surveyed)
Contacted Non-Study Provider

Exposure to the
app was safe

Clinical Implications

- In the AHS, we found a low proportion of notifications across a diverse population
- Notification PPV of 0.84 supports ability to correctly identify Afib among those notified
- Findings may inform further clinical evaluation after notification (with history, exam)
- Future Direction: Rigorous investigation of this technology and its potential use in clinical setting.
- AHS provides solid foundation upon which further research in digital health can be conducted.

ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

DOI: 10.1056/NEJMoa1607887

Andexanet alfa in Factor Xa Inhibitor-Associated Acute Major Bleeding

- Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., Mark Crowther, M.D.
- on behalf of the ANNEXA-4 investigators

PORTOLA® PHARMACEUTICALS

McMaster University

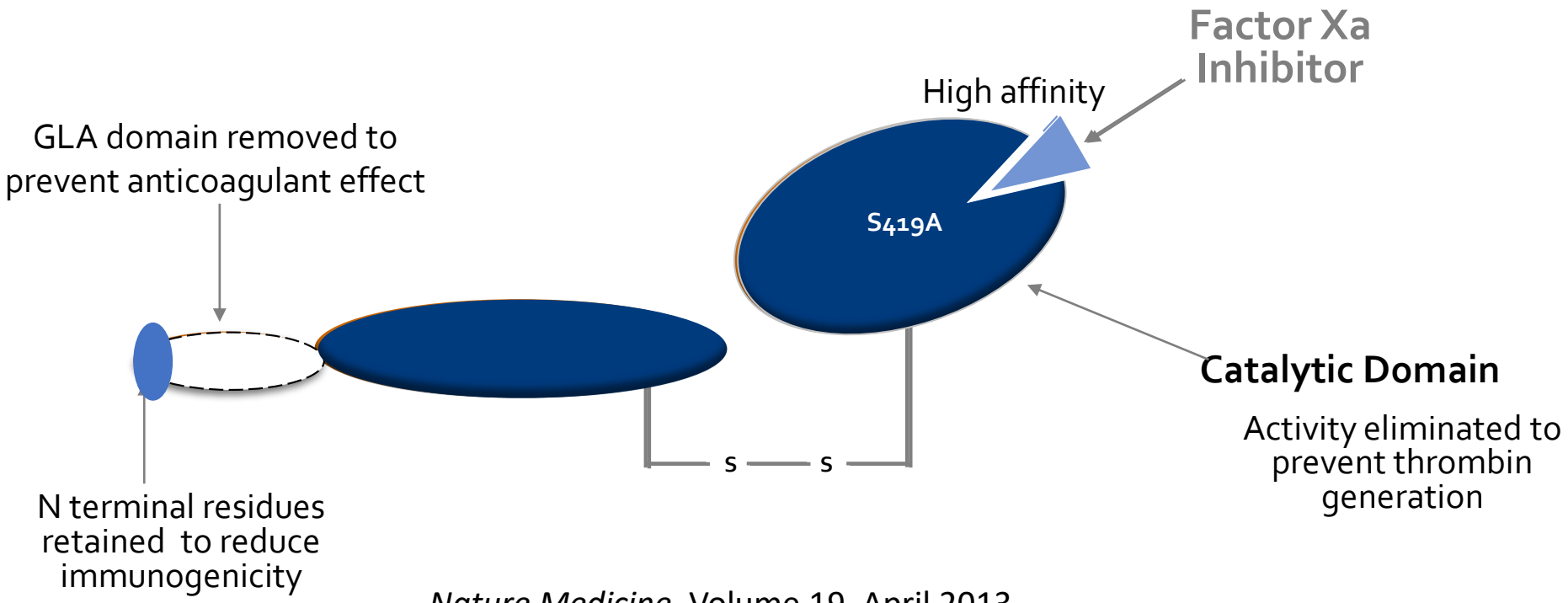
Health Through Knowledge PHRI

Background

- Factor Xa (fXa) inhibitors are effective, but can cause serious bleeding
- No available specific reversal agent available fXa inhibitors
- Andexanet alfa developed as a specific reversal agent for both direct and indirect fXa inhibitors,
- It rapidly and safely reversed anti-fXa activity in healthy volunteers

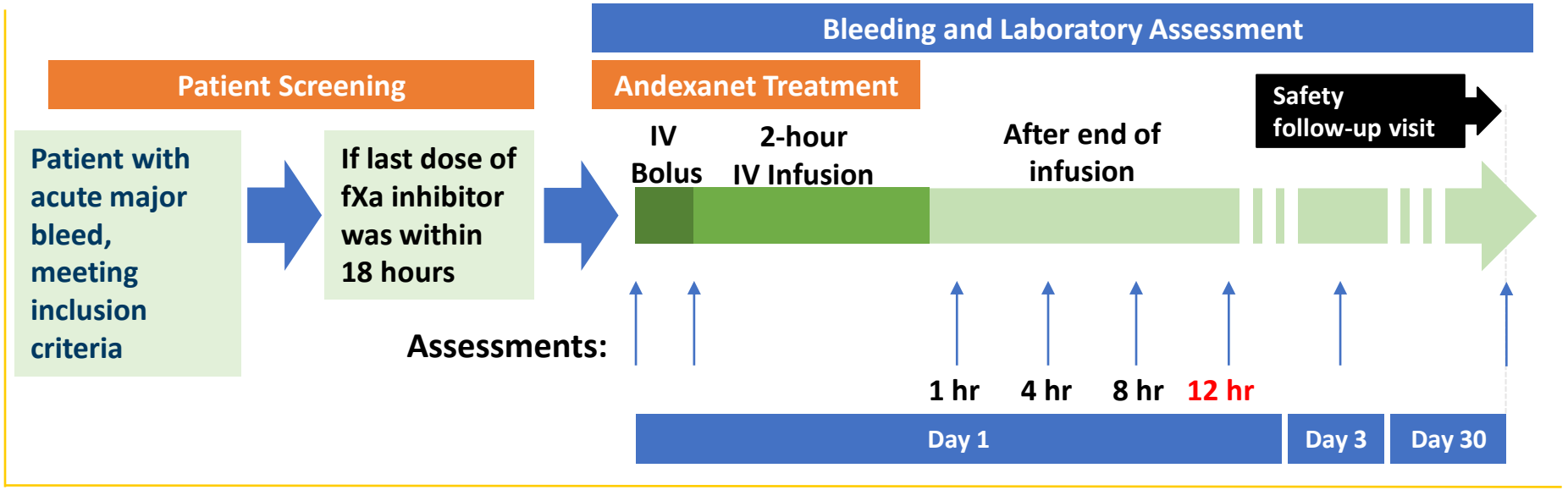
Andexanet alfa: Recombinant Modified Human Factor Xa

- Specifically designed to reverse anticoagulant effects of fXa inhibitors
- Acts as a fXa decoy to bind molecules that target and inhibit fXa



Nature Medicine, Volume 19, April 2013

ANNEXA-4 Study Design



Efficacy Measurements

- Change in anti-FXa activity
- Clinical hemostatic efficacy through 12 hours

Safety Measurements

- Thrombotic events
- Antibodies to FX, FXa, andexanet
- 30-day mortality

ANNEXA-4 Dose Selection

Acute major bleeding ≤ 18 hours of last dose of apixaban, edoxaban, rivaroxaban, or enoxaparin

Andexanet IV bolus and 2 hour infusion

Pts on apixaban or >7 h from last rivaroxaban dose	Pts on enoxaparin, edoxaban or ≤7 h from last rivaroxaban dose
Bolus 400 mg + Infusion 480 mg @ 4 mg/min	**Bolus 800 mg + Infusion 960 mg @ 8 mg/min**

ANNEXA-4: Design and Analysis Plan

- **Criteria for Major Acute Bleeding**
  - Life-threatening bleeding with hemodynamic compromise
  - Bleeding with hemoglobin drop of >2 gm/dl, or falling below 8 gm/dl
  - Critical organ bleeding, such as intra-cranial, intra-spinal, etc.
- **Analysis Populations**
  - **Safety** population included all patients receiving andexanet
  - **Efficacy** population excluded patients with baseline anti-fXa activity <75 ng/ml (<0.5 IU/ml for enoxaparin)
- **Preliminary analysis**
  - Includes all patients with complete data on June 17, 2016
  - ANNEXA-4 study is ongoing

Assessment of Clinical Hemostatic Efficacy

- All cases assessed by independent committee
- Specific efficacy criteria for each type of bleed
- Independent Core Lab interpreted brain CT and MRI
  - Cases rated as excellent/good vs. poor/none
  - Based on method developed for assessment of PCC in warfarin bleeding, where efficacy reported was 71%*

**Sarode et al, Circulation 2013; 128, 1234-43*

Baseline Characteristics

	Safety Population N=67	Efficacy Population N=47
Age (yr), mean ± SD	77.1 (10.00)	77.1 (10.08)
Male, n (%)	35 (52.2)	24 (51.1)
White race, n (%)	54 (80.6)	36 (76.6)
Time from presentation until andexanet bolus (hrs), mean ± SD	4.8 ± 1.93	4.8 ± 1.82
Estimated creatinine clearance < 30 mL/min, n (%)	6 (9.0)	4 (8.5)
Indication for anticoagulation		
Atrial fibrillation, n (%)	47 (70.1)	32 (68.1)
VTE , n (%)	15 (22.4)	12 (25.5)
Atrial fibrillation and VTE , n (%)	5 (7.5)	3 (6.4)
Medical History		
Myocardial infarction, n (%)	13 (19.4)	7 (14.9)
Stroke, n (%)	17 (25.4)	15 (31.9)
Deep vein thrombosis, n (%)	20 (29.9)	16 (34.0)
Pulmonary embolism, n (%)	6 (9.0)	4 (8.5)
Atrial Fibrillation, n (%)	49 (73.1)	34 (72.3)
Heart Failure, n (%)	23 (34.3)	19 (40.4)
Diabetes mellitus, n (%)	23 (34.3)	17 (36.2)

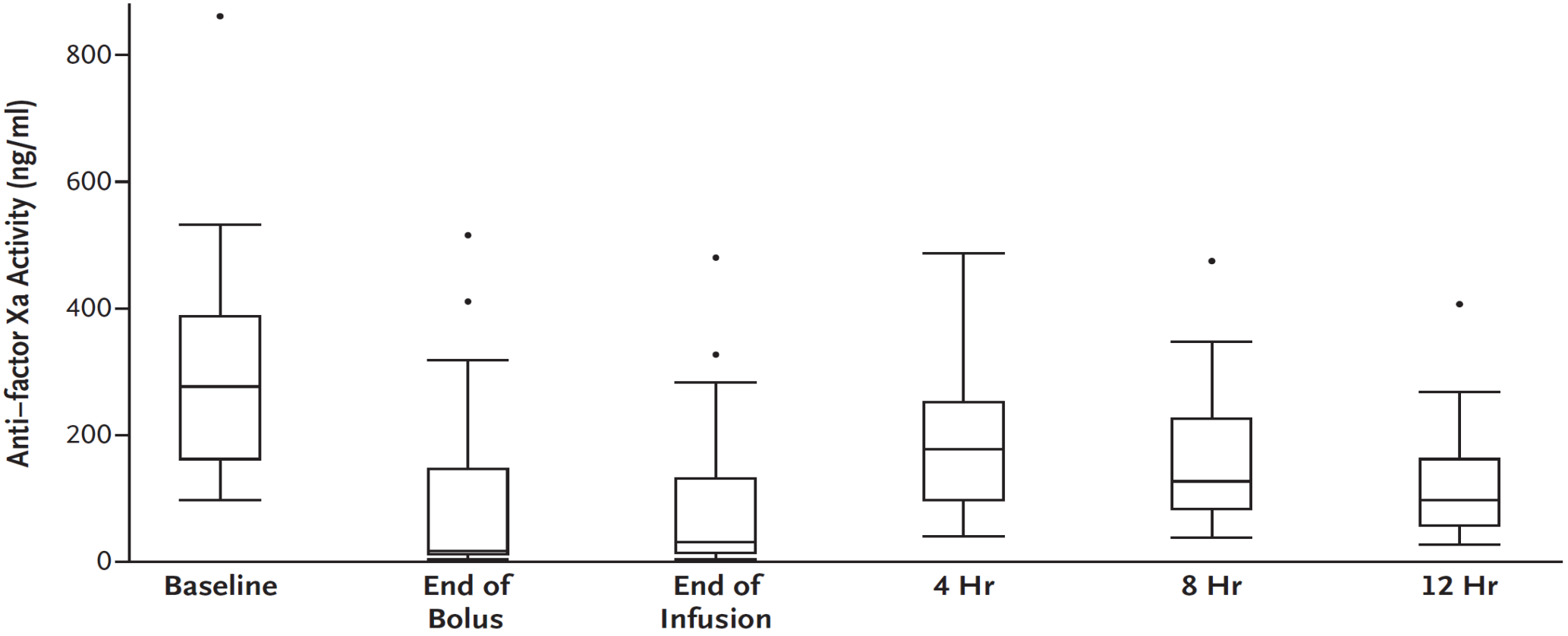
Factor Xa Inhibitors Received

	Safety Population N=67	Efficacy Population N=47
Rivaroxaban, N	**32**	**26**
Daily dose, median (IQR)	20 (15-20)	20 (20-20)
Time from last dose to andexanet (hrs), mean ± SD	12.8 ± 4.21	12.0 ± 4.12
Baseline anti fXa activity (ng/mL), mean ± SD	247.4 ± 185.98	297.0 ± 171.00
Unbound plasma concentration (ng/mL), median (IQR)	16.7 (10.2-25.5)	19.3 (12.0-26.9)
Apixaban, N	**31**	**20**
Daily dose, median (IQR)	5 (5-10)	5 (5-10)
Time from last dose to andexanet (hrs), mean ± SD	12.1 ± 4.70	11.0 ± 4.74
Baseline anti fXa activity (ng/mL), mean ± SD	137.7 ± 102.25	174.5 ± 97.02
Unbound plasma concentration (ng/mL), median (IQR)	9.4 (6.0-19.2)	10.5 (8.1-19.2)
Enoxaparin, N	**4**	**1**
Daily dose, median (IQR)	90 (80-150)	200
Time from last dose to andexanet (hrs), mean ± SD	10.8 ± 3.49	13.1
Anti fXa activity (IU/mL), mean ± SD	0.4 ± 0.22	0.6

Site of Bleeding

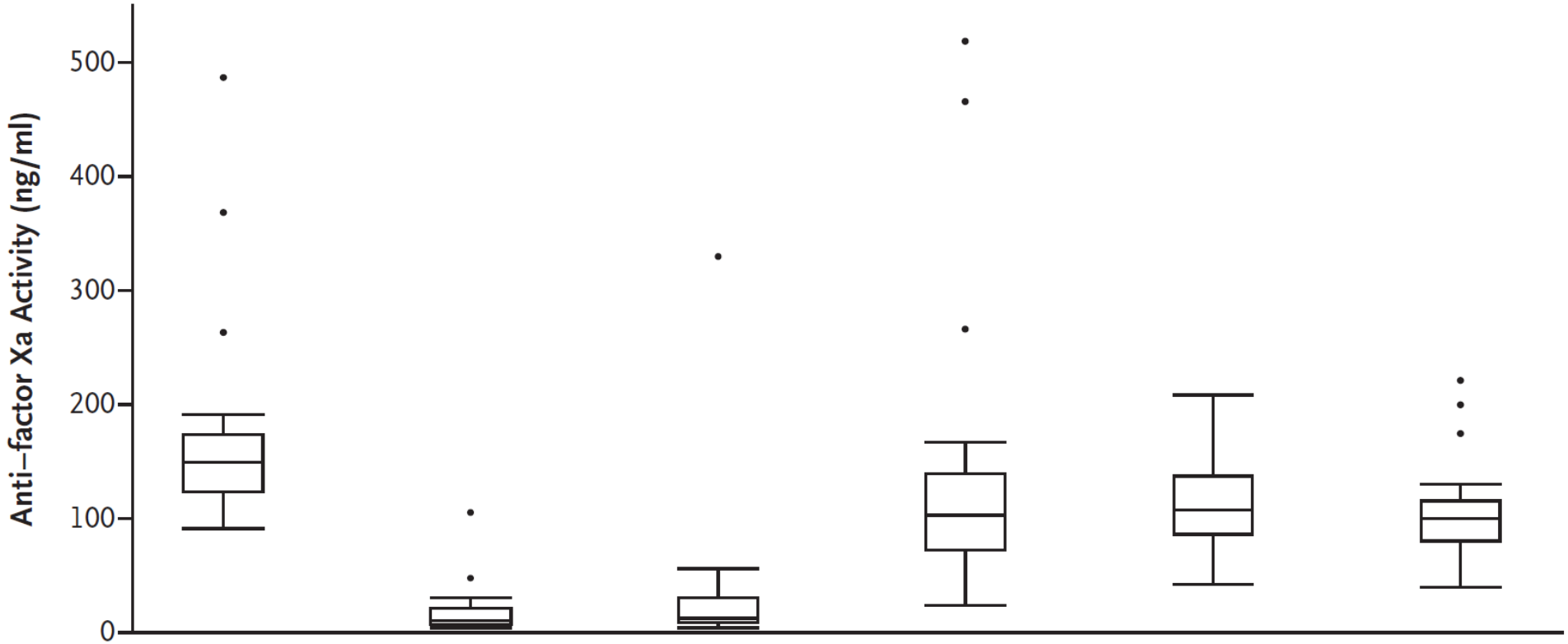
	Safety Population N=67	Efficacy Population N=47
Gastrointestinal Bleeding, n (%)	**33 (49.3)**	**25 (53.2)**
Upper, n (%)	9 (27.3)	7 (28.0)
Lower, n (%)	10 (30.3)	8 (32.0)
Unknown, n (%)	14 (42.4)	10 (40.0)
Intracranial Bleeding, n (%)	**28 (41.8)**	**20 (42.6)**
Glasgow Coma Scale, mean ± SD	14.1 ± 1.69	14.1 ± 1.72
Intracerebral site, n (%)	14 (50.0)	12 (60.0)
Sub-dural site, n (%)	11 (39.3)	7 (35.0)
Subarachnoid site, n (%)	3 (10.7)	1 (5.0)
Other Bleeding site, n (%)	**6 (9.0)**	**2 (4.3)**
Nasal, n (%)	1 (16.7)	0 (0.0)
Pericardial/pleural/retroperitoneal, n (%)	3 (50.0)	1 (50.0)
Genital/urinary, n (%)	1 (16.7)	1 (50.0)
Articular, n (%)	1 (16.7)	0 (0.0)

Anti-factor Xa Activity: Rivaroxaban n= 26



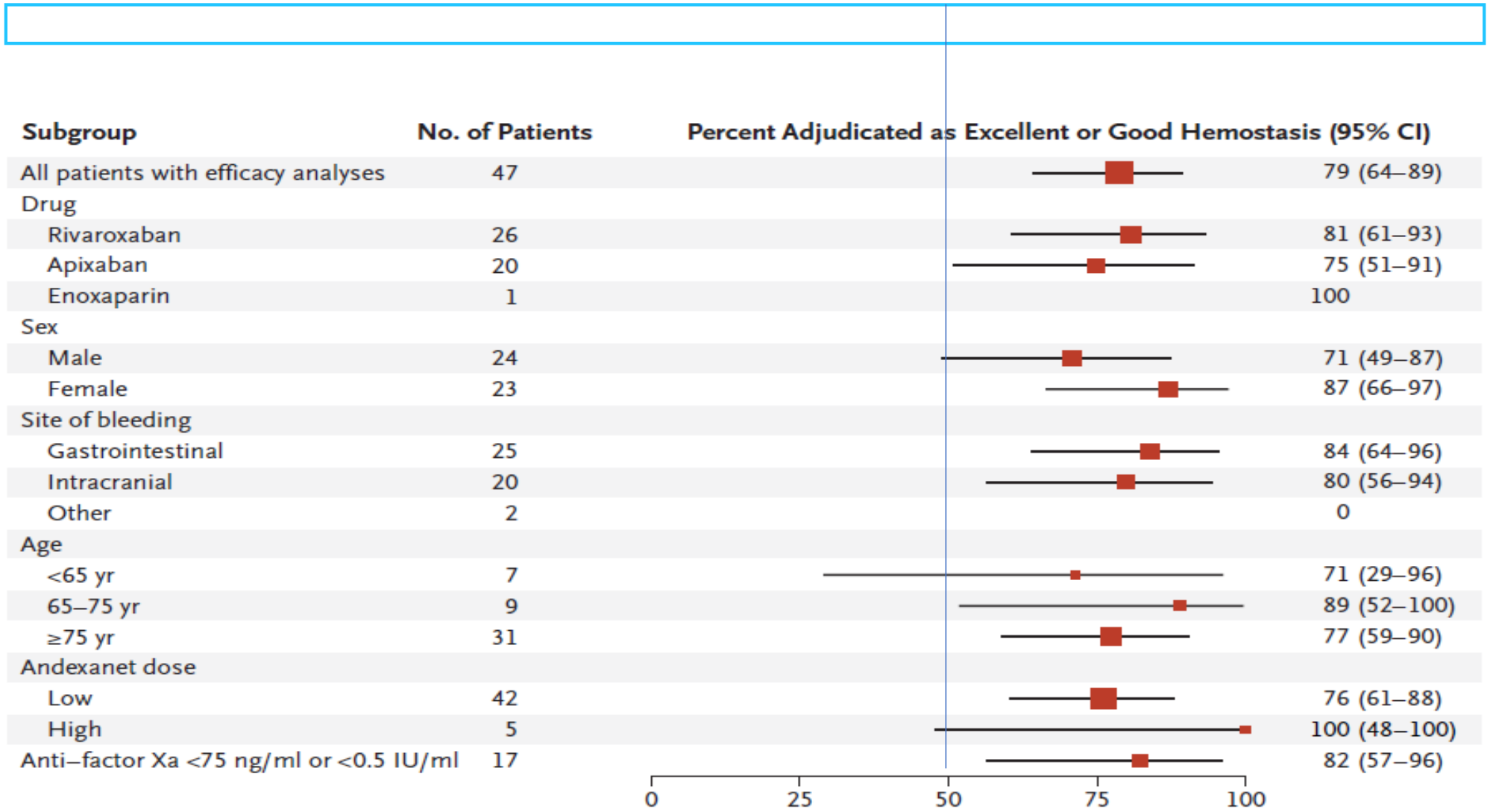
Median Percent Change (95% CI)	277.0	16.8 –89 (–58 to –94)	30.6 –86 (–55 to –93)	177.7 –39 (–27 to –45)	127.1 –49 (–43 to –57)	97.9 –64 (–51 to –70)

Anti-factor Xa Activity: Apixaban n=20



Median Percent Change (95% CI)	149.7	10.3 –93 (–87 to –94)	12.5 –92 (–85 to –94)	103.0 –30 (–23 to –46)	107.1 –28 (–19 to –38)	100.2 –31 (–27 to –41)

Clinical Hemostatic Efficacy



Safety Assessment

- Anticoagulation re-started in 18 patients (27%) by 30 days
- Thrombotic events occurred within 3 days of andexanet in 4 (6%) patients and by 30 days in 12 (18%)
- Therapeutic anticoagulation was re-started in only 1 patient before a thrombotic event occurred
- 10 deaths occurred by 30 days (15%), of which 6 were cardiovascular

Conclusions

- Andexanet bolus plus 2 hour infusion rapidly reversed anti-fXa activity
- Effective hemostasis observed in 79% of patients
- Thrombotic events occurred at rates consistent with the high risk profile of the patients

Safety and Efficacy of BackBeat™ Cardiac Neuromodulation Therapy (CNT™) in Patients with Hypertension: Final Results of a Double-Blind Randomized Trial

- Karl-Heinz Kuck, MD

- On behalf of coauthors:

- Z. Kalarus, B. Merkely, P. Neuzil, M. Grabowski, G. Marinskis, A. Erglis, J. Kazmierczak, P. Mitkowski, T. Sturmberger, F. Malek, A. Kolodzinska, D. Burkhoff, A. Sokal, L. Geller *and the Moderato 2 Study Investigators*

- Study Sponsored By: BackBeat Medical, Inc. a subsidiary of Orchestra BioMed, Inc.

BackBeat™ Cardiac Neuromodulation Therapy (CNT™)

- **Cardiac pacing to reduce blood pressure through two mechanisms:**
  - Reduction in LV Filling (preload) to provide an acute effect
  - Neuromodulation to maintain effect chronically (afterload)

- **Delivered via implantable pulse generator (IPG) using standard lead positions**
  - IPG also provides standard pacemaker functionality

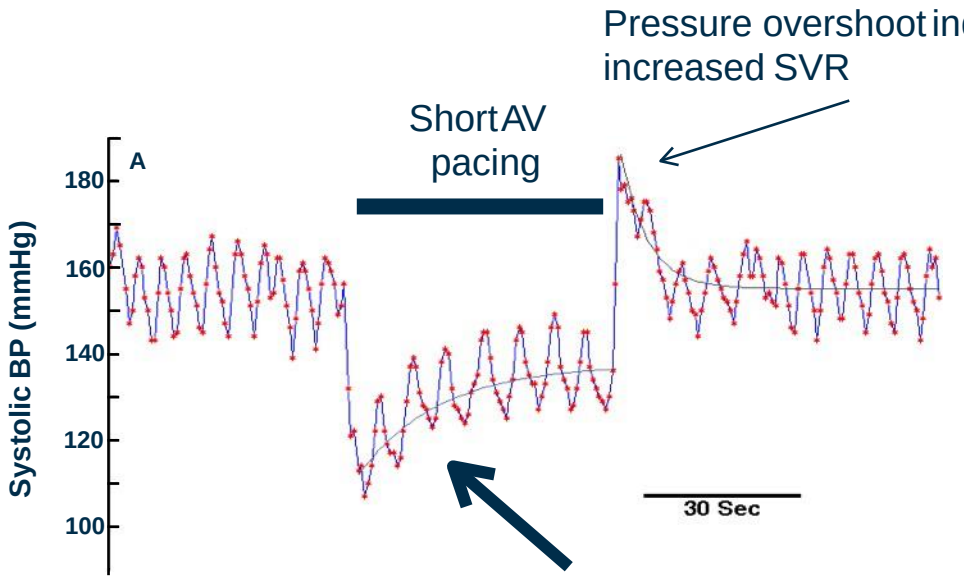
BackBeat CNT Initial Target Population

- **Hypertension patients indicated for pacemaker**
  - >1M pacemaker implants globally per year
  - >70% of pacemaker patients have hypertension
    - ~ 60% uncontrolled despite treatment
  - Older, co-morbid population at increased risk of major events
  - High rate of Isolated Systolic Hypertension (ISH)

BackBeat CNT Mechanism of Action

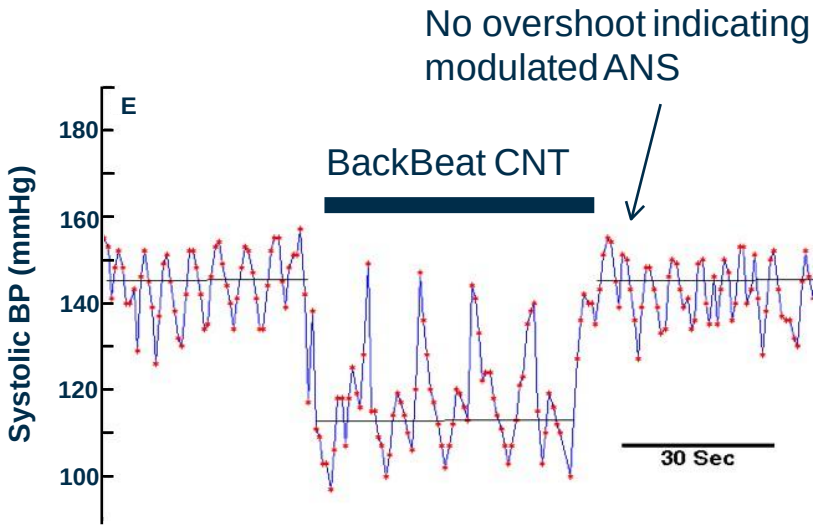
Bioelectronic Control of Ventricular Filling Immediately Reduces Blood Pressure (BP)

Utilizing Programmed Variable Pressure Patterns, **BackBeat CNT Modulates ANS Response**



BP reduction activates sympathetic ANS response via natural pressure sensors (baroreceptors), driving physiologic changes that **push BP back to original levels**

BackBeat CNT Activation



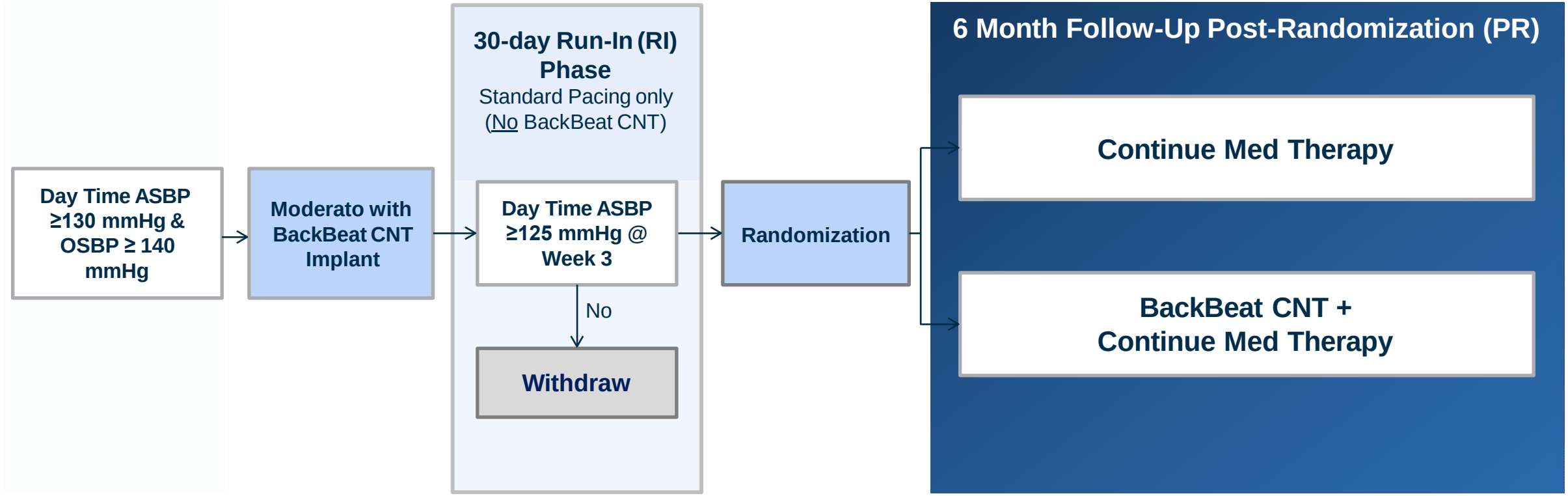
BackBeat CNT- induced neuromodulation enables immediate & sustained reduction in BP

MODERATO II Study

- **Prospective, multi-center, randomized, double-blind study of BackBeat CNT vs. Medical Therapy (Control)**
  - 9 sites in EU
  - Pilot study to inform the design and power of the pivotal study

- **Objective**: to assess the efficacy and safety of BackBeat CNT in reducing blood pressure in patients with hypertension despite medical therapy who are also indicated for a pacemaker

MODERATO II: Study Design



100% monitoring by external CRO. Independent Blinded Event Adjudication Committee (CEC) adjudicating all AE and SAEs.
Blinded independent core labs for 24-Hours ASBP, OSBP, Echo and blood tests

Patient Demographics:

	Control (n=21)	BackBeat CNT (n=26)	p-value (Control vs BackBeat CNT)
Age	**74.9 ± 8.5**	**73.2± 9.0**	**0.518**
Gender	15 M / 6 F	15 M / 11F	0.375
Weight (kg)	88.5±16.0	86.1±17.5	0.63
LV EF (%)	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**

Patient Demographics:

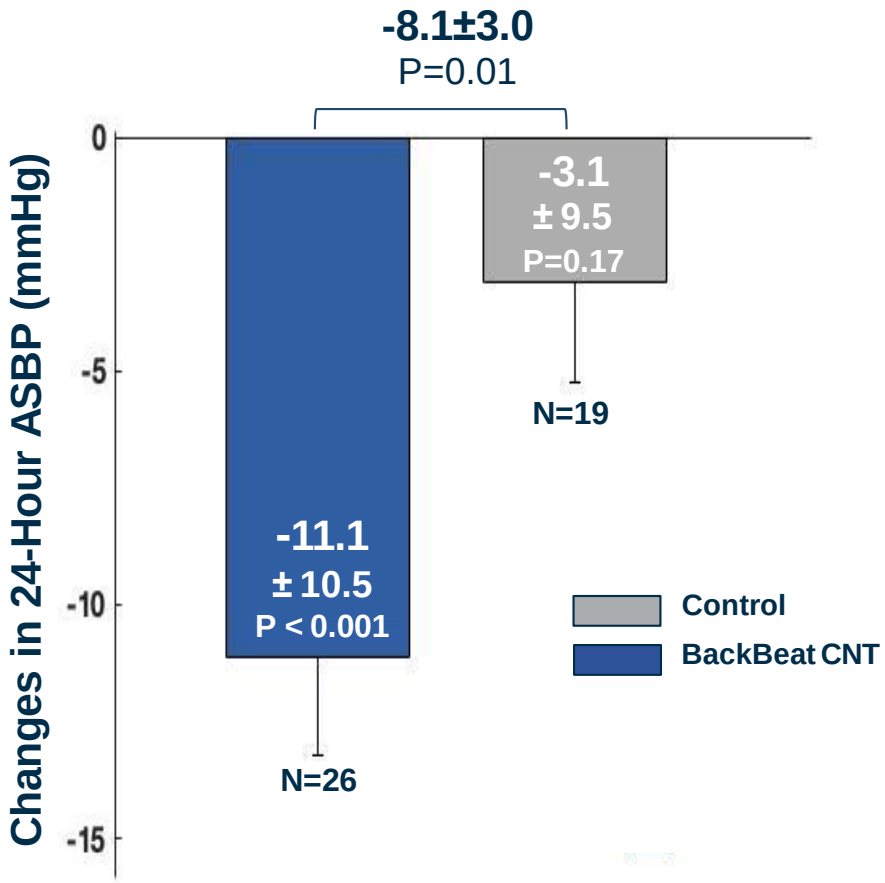
Blood Pressure Prior to Randomization Comparable Between Groups

	Control (n=21)	BackBeat CNT (n=26)	p-value Control vs BackBeat CNT
Isolated Systolic HTN	**71.4%**	**88.5%**	**0.263**
Screening			
24-Hr Ambulatory SBP	**142.8±11.8**	**139.3±10.3**	**0.287**
24-Hr Ambulatory DBP	75.2±9.8	73.8±5.0	0.533
AMB Heart Rate (24H)	64.7±12.5	64.1±8.02	0.857
Screening Office BP			
Office SBP	165.2±15.4	161.4±14.1	0.381
Office DBP	**82.4±13.0**	**82.6±8.49**	**0.955**
Office Heart Rate	63.7±16.6	64.4±8.3	0.860
Week 3 Run-In Phase			
24-Hr Ambulatory SBP	**136.3±12.5**	**136.3±9.2**	**0.995**
AMB DBP (24H)	72.6±6.7	74.0±6.9	0.478
AMB Heart Rate (24H)	68.4±8.5	69.6±9.5	0.670
Week 4 Run-In Phase			
Office SBP	154.4±15.5	153.1±15.8	0.781
Office DBP	81.6±12.4	83.0±10.8	0.693
Office Heart Rate	66.5±10.9	67.1±12.0	0.848

Primary Efficacy Endpoint (ITT)

24-Hour ASBP at 6 Months Post-Randomization vs. Week 3 Run-In

Primary Efficacy Endpoint met: **8.1 +/-3.0, (p=0.01)** Difference in BP Reduction at 6 Months



24-Hour ASBP (mmHg)		
	Week 3 Run-In	6 months Post-Randomization
BackBeat CNT	136.3	125.2
Control	136.3	132.0

Primary Safety Endpoint (ITT)

MACE through 6 Months Post-Randomization

Primary Safety Endpoint Met: **No Difference** in MACE at 6 Months

6 Month MACE*		
	BackBeat CNT	Control
n	26	21
MACE	0 (0.0%)	2 (9.5%)

Control MACE Patients

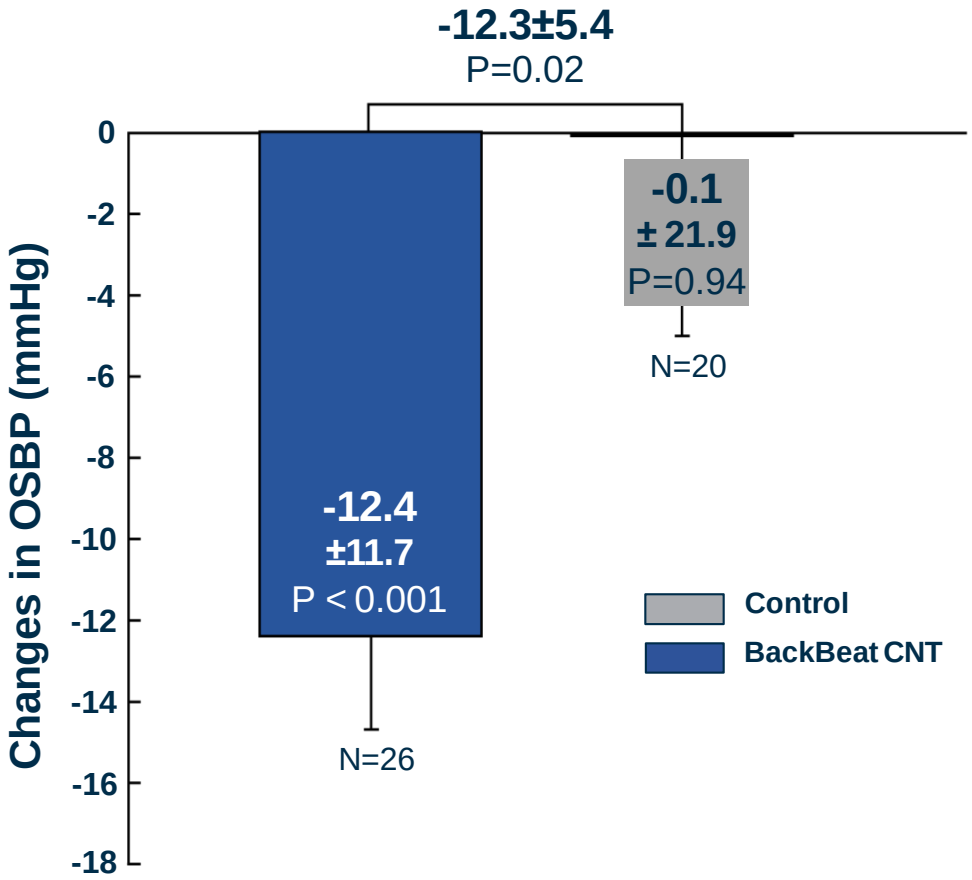
- Pt 1: Death as a result of disseminated adenocarcinoma.
  Angina pectoris leading to right coronary angioplasty and stenting
- Pt 2: Worsening atrial fibrillation requiring cardioversion

MACE: major cardiac adverse events [including death, heart failure, clinically significant arrhythmias (i.e., persistent or increased atrial fibrillation, serious ventricular arrhythmias), myocardial infarction, stroke and renal failure] in treatment versus control groups calculated per patient

Office Systolic Blood Pressure (OSBP)

6 Months Post-Randomization vs. Week 4 Run-In

Significant Difference Between BackBeat CNT and Control in OSBP Reduction:
-12.3 +/-5.4 (p=0.02)



OSBP (mmHg)		
	Week 4 Run-In	6 months Post-Randomization
BackBeat CNT	153.1	140.8
Control	154.4	154.0

BackBeat CNT Responder Analysis

6 Months Post-Randomization vs. Week 3 Run-In

High Overall Response Rate to BackBeat CNT with 54% Experiencing >10 mmHg Reduction in ASBP Despite Lower Starting ASBP and High %ISH

	BackBeat CNT (n=26)	Control (n=19)
% with Increase in ASBP	**15%**	**47%**
% with Reduction in ASBP	85%	53%
% with >5 mmHg Reduction in ASBP	65%	42%
% with >10 mmHg Reduction in ASBP	**54%**	**21%**

MODERATO II Conclusions

- **In patients with arterial hypertension and an indication for a pacemaker, Backbeat CNT demonstrated:**
  - Significant reduction in mean ASBP and OSBP
  - No difference in MACE
  - No differences in diastolic blood pressure (DBP), heart rate (HR) or echo parameters
  - High responder rate in 88.5% patients with isolated systolic hypertension (65% reduced > 5 mmHg; 54% reduced > 10 mmHg)

- ***Next steps:*** pivotal, double-blind study to test safety and efficacy

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