First-in-Man Study of a Pacemaker-Mediated Programmable Hypertension Control Therapy

Authors:
Petr Neuzil, Béla Merkely, Andrejs Erglis, Germanas Marinskis, Joris R. de Groot, Herwig Schmidinger, Manuel Rodriguez Venegas, Michiel Voskuil, Thomas Sturmberger, Jan Petru, Niels Jongejan, Josef Aichinger, Ginta Kamzola, Audrius Aidietis, Laszlo Gellér, Tomas Mraz, Istvan Osztheimer, Karl-Heinz Kuck for the BackBeat Study Investigators*

Na Homolce Hospital, Prague, Czech Republic
Semmelweis University Budapest, Heart and Vascular Center, Budapest, Hungary
Pauls Stradins Clinical University Hospital, Latvian Centre of Cardiology, Riga, Latvia
Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania
Department of Cardiology, Academic Medical Center, Amsterdam The Netherlands
AKH - Universitätsklinik für Innere Medizin II, Abteilung für Kardiologie, Vienna, Austria
Hospital Dr. Sótero del Río, Santiago Chile
University Medical Center Utrecht, Department of Cardiology, Utrecht The Netherlands
Krankenhaus der Elisabethinen Linz GmbH, Interne 2 – Kardiologie, Linz Austria
Asklepios Klinik St. Georg, Lohmühlenstr. Hamburg Germany

Hypertension

Remains a major global health problem

- >25% of adults in the world
- #1 attributable risk for death worldwide according WHO

Many patients (> 40% in US) remain with blood pressures above guideline recommendations despite multi-drug regimens

- Variable drug effectiveness
- Noncompliance

Hypertension increases risk of morbidity and mortality

- Every 20 mmHg increase doubles risk of mortality

Non-pharmacological therapies are being investigated

- Renal Denervation
- Arterial-venous shunts
- Neurostimulation-based therapies

26.4%

~972 M of the world adult population has **HYPERTENSION**

~70%

of pacemaker patients ~ 700K a year have **HYPERTENSION**

(2)

The Concept:
Programmable Hypertension Control (PHC) Therapy

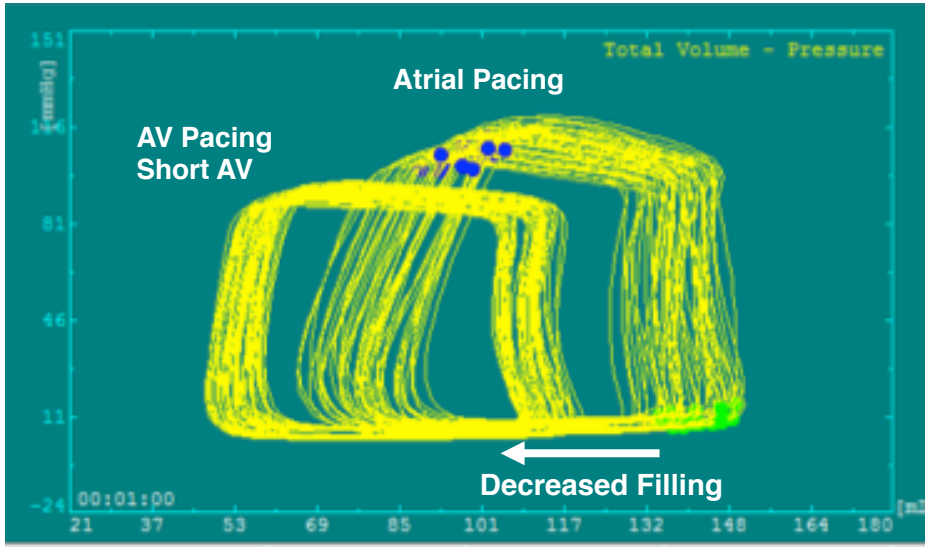
PHC therapy is an algorithm embedded in a standard dual chamber pacemaker with regular transvenous leads and implant procedure.

The algorithm delivers a sequence of **alternating shorter and longer** AV intervals pacing

The algorithm **reduces blood pressure by reducing ventricular filling** and **modulating the baroreflex responses**, preventing activation of the autonomic nervous system

The main mechanism of BP reduction is by short AV delay pacing, which reduces LV filling and thus reduces LV pressure generation (Starling Mechanism).

LV Pressure-Volume



Atrial pacing versus AV sequential pacing with short AV interval (40ms).
Acute Porcine Model

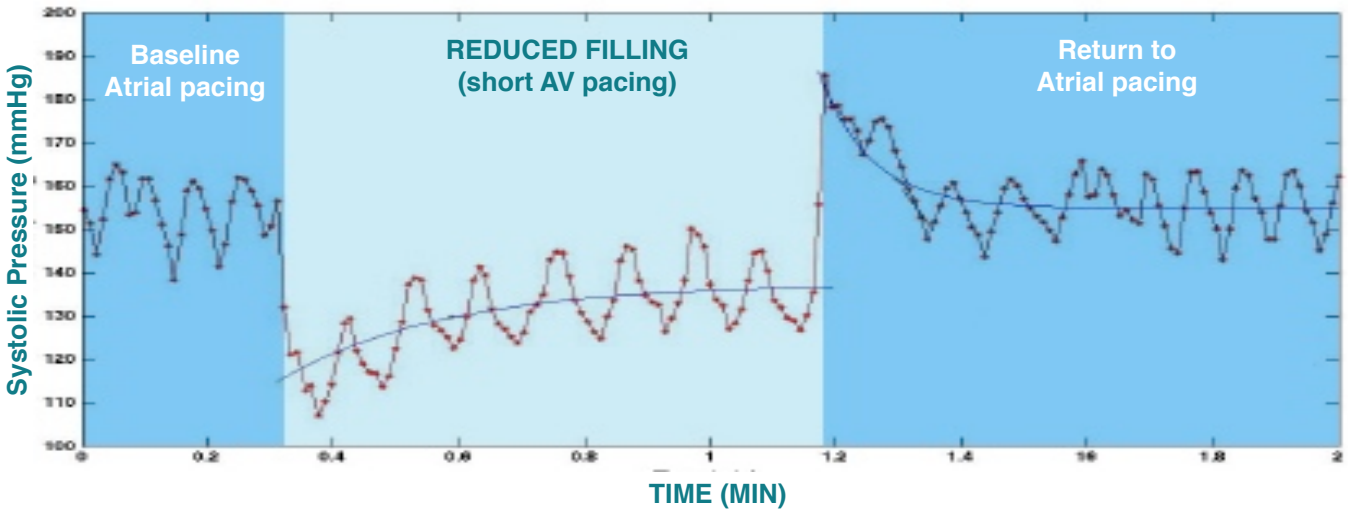
PHC:
Regulating Baroreceptor Response to Reduced BP

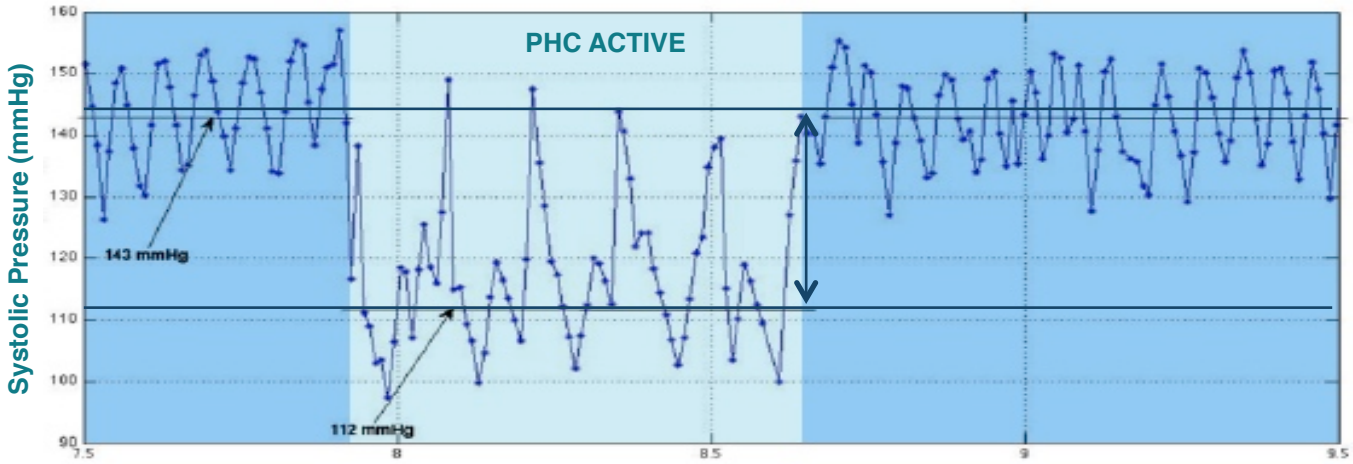
Reduction in ventricular filling immediately reduces blood pressure.

Ordinarily, such a reduction would activate the ANS via baroreceptors, increasing TPR and returning BP towards its original levels.

However, by regularly injecting a few beats with longer AV delays, baroreflex responses can be modulated and nearly abolished.

Data from acute study In patient with hypertension





Alternation Between Short and Long AV Delay

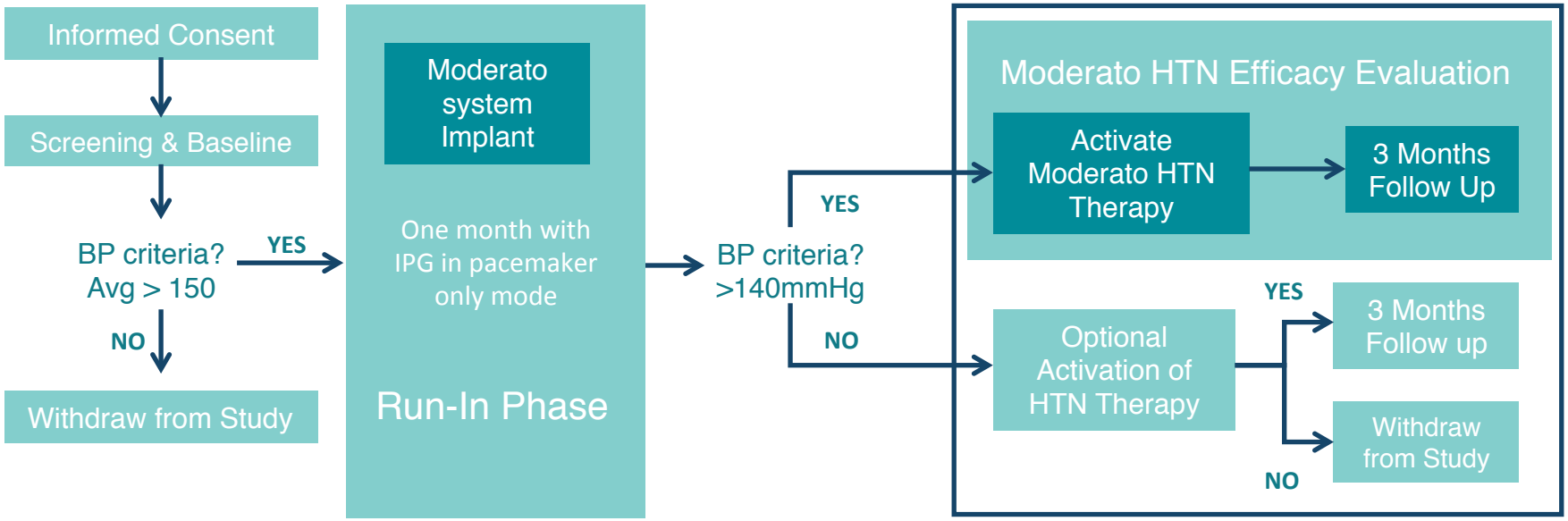
Study Design

Hypothesis

PHC pacing reduces Systolic Blood Pressure (SBP) in patients requiring a dual chamber pacemaker implant or exchange who have persistent hypertension despite ≥ 2 antihypertensive medications.

Measurements:

- Office blood pressure (in triplicate according to standardized procedures)
- 24 Hour ambulatory blood pressure
- Echocardiography
- Medications
- Blood tests (renal function)



Study Endpoints

Co-primary efficacy endpoint

- Change in office SBP measured by sphygmomanometry from the time of pre-activation to 3 months post activation
- Change in 24 hour ambulatory systolic blood pressure from baseline to 3 months post activation

Safety endpoints (measured after 3 months of PHC therapy)

- Effect on cardiac function
  - Changes in ejection fraction
  - Changes in left ventricle volumes
- Changes in the rate of cardiac arrhythmias
- Number and severity of adverse events adjudicated by an independent committee

Inclusion Criteria

Indicated for implantation or replacement of a permanent dual-chamber pacemaker

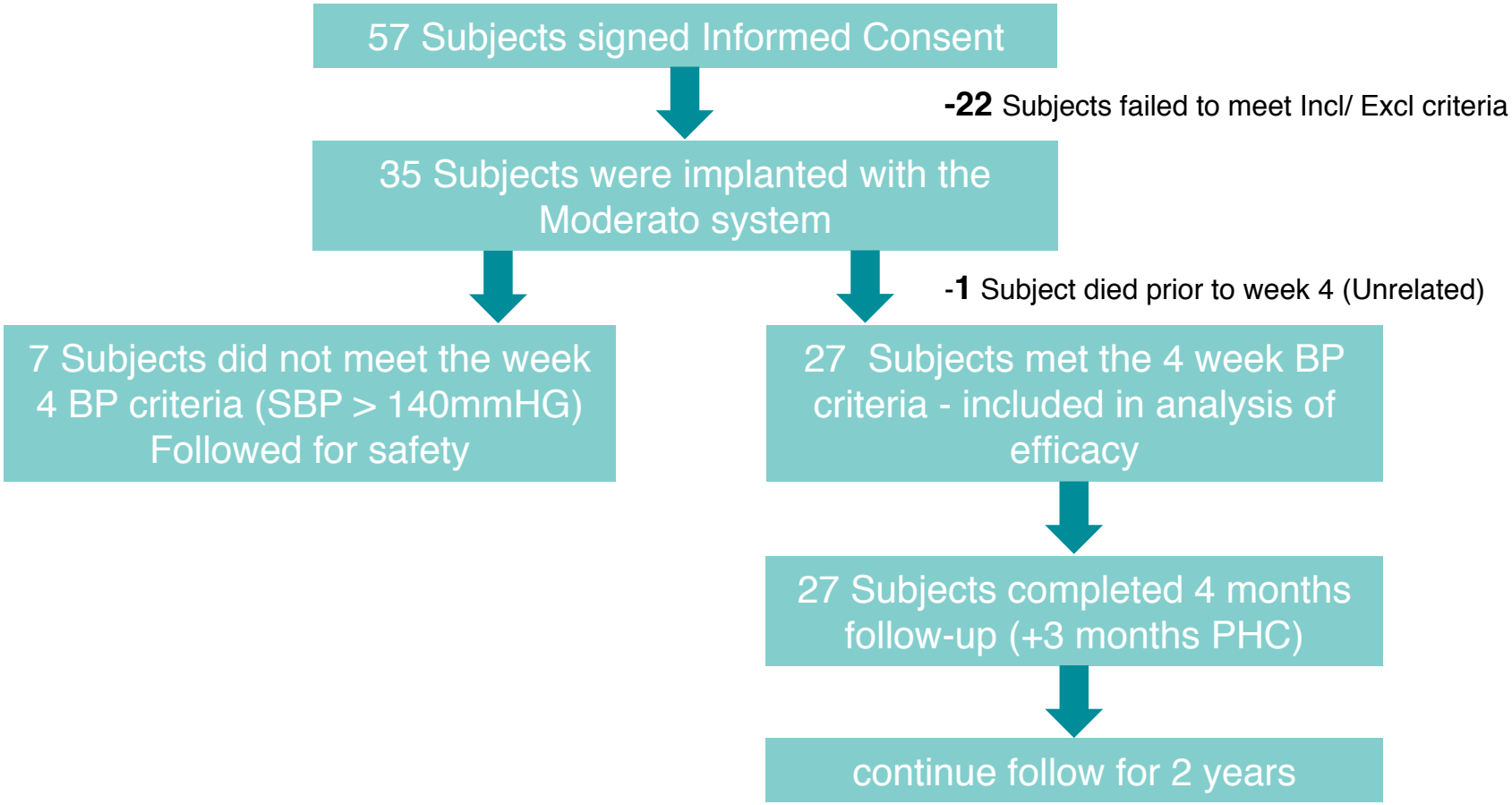
Stable (prior 2 months) regimen of ≥2 maximally tolerated antihypertension medications anticipated to be maintained for 3 months without change

Average office systolic blood pressure ≥ 150 mmHg base on repeated measures over a one-week period prior to enrollment, each measurement > 140 mmHg

Exclusion Criteria

- Subject has known secondary cause of HTN
- Subject has a history in the past year of persistent atrial fibrillation or clinically significant paroxysmal atrial fibrillation.
- Subject has ejection fraction <50%
- Subject has symptoms of heart failure of NYHA Class II or more
- Subject has hypertrophic cardiomyopathy, restrictive cardiomyopathy or interventricular septal thickness ≥15 mm
- Subject is on dialysis
- Subject has estimated Glomerular Filtration Rate (GFR) <30 ml/min/1.73m2
- Subject has prior neurological events (stroke or TIA) or carotid artery disease
- Subject has known autonomic dysfunction
- Subject has a history of clinically significant tachyarrhythmia and is not on a stable medical regimen
- Subject has had previous active device-based treatment for hypertension
- Subject has an existing implant, other than a pacemaker that needs replacing
- Subject is pregnant or has the possibility of becoming pregnant
- Subject with average Systolic BP >190 mmHg
- Subject is currently participating in another clinical study
- Subject cannot or is unwilling to provide informed consent

Patient Flow Through the Study



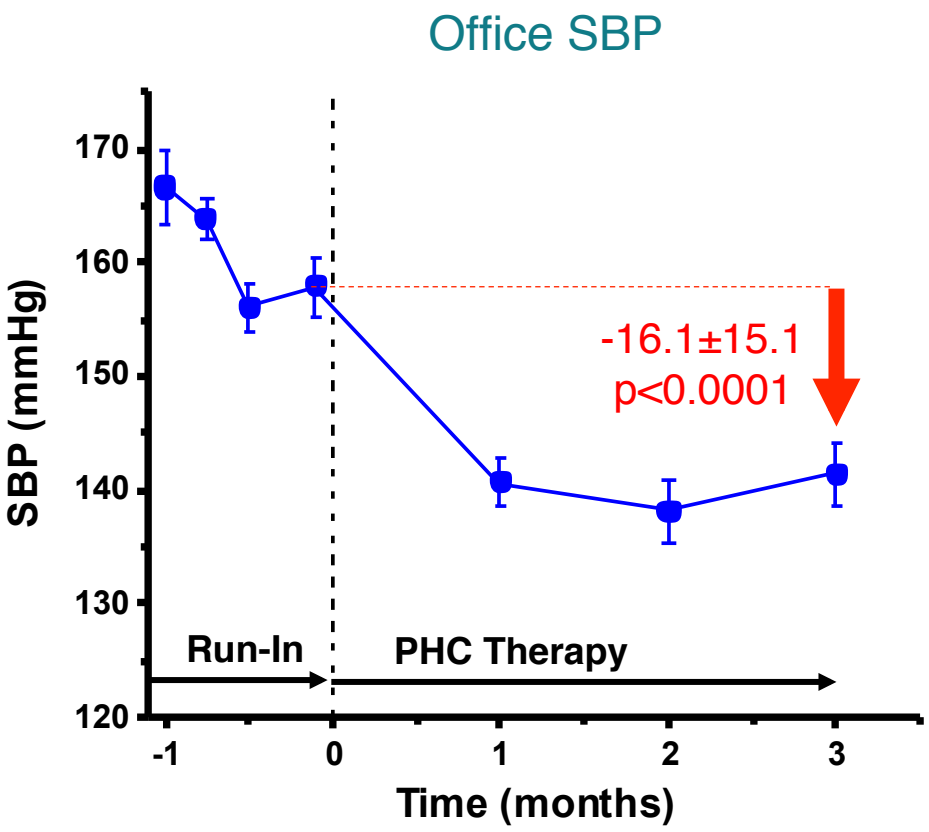
Baseline Demographics

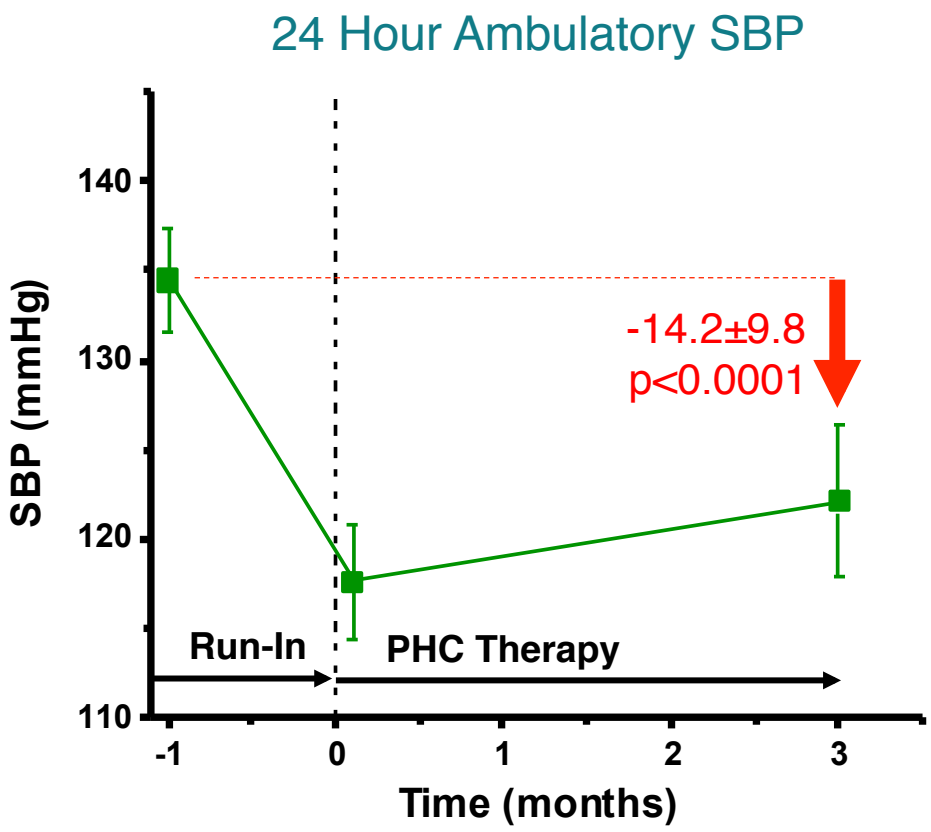
	All Implanted Patients	Patients Continuing to Hypertension Treatment Phase (n=27)	Patients not meeting BP Criteria to Continue (n=7)
Age (yrs)	73 ± 7.2	72 ± 6.8	75.0 ± 6.9
Gender	17 M / 18 F	14 M / 13 F	2 M / 5 F
Physical Exam			
Height (cm)	168.0±10.3	168.3±10.8	166.6±9.8
Weight (kg)	82.3±17.3	84.3±17.8	78.4±13.1
Heart Rate (bpm)	64.1±12.1	62.9±12.7	67.4±9.7
Body Mass Index	29.1±5.5	29.7±5.7	28.2±3.6
LV Ejection Fraction (%)	62.9±5.2	62.7±5.3	65±3.4
Blood Pressure (office)			
Screening			
Systolic BP (mmHg)	165.6±11.6	165.6±11.1	162.1±8.7
Diastolic BP (mmHg)	79.8±9.4	80.4±9.9	76.6±7.4
Pre-activation			
Systolic BP (mmHg)	152.3±15.9	156.4±14.4	136.4±10.9
Diastolic BP (mmHg)	79.9±9.5	81.3±10.0	74.3±2.9

Baseline Demographics

	All Implanted Patients	Patients Continuing to Hypertension Treatment Phase (n=27)	Patients not meeting BP Criteria to Continue (n=7)
HTN Medications			
Average Number	3.2	3.3	3.1
Diuretic	27 (77%)	20 (71%)	7 (100%)
K Sparing Diuretic	4 (11%)	3 (11%)	1 (14%)
b-Blocker	11 (31%)	8 (29%)	2 (29%)
ACE-I	20 (57%)	16 (57%)	4 (57%)
ARB	12 (34%)	10 (36%)	2 (29%)
Ca++ Channel Blocker	21 (60%)	18 (64%)	3 (43%)
α-adrenergic antagonist	9 (26%)	6 (21%)	2 (29%)
Ang-II antagonist	1 (3%)	0 (0%)	1 (14%)
Past Medical History			
Diabetes	10 (29%)	8 (29%)	2 (29%)
History of AF	2 (6%)	2 (7%)	0 (0%)
Cardiovascular Disease	1 (3%)	1 (4%)	0 (0%)
PVD	3 (9%)	2 (7%)	1 (14%)
Renal Dysfunction	2 (6%)	1 (4%)	1 (14%)
Pacemaker Indication			
Sick Sinus Syndrome	13 (37%)	10 (37%)	3 (43%)
Brady-/Tachy-Syndrome	7 (20%)	3 (11%)	3 (43%)
II^0 AV Block	12 (34%)	8 (30%)	4 (57%)
III^0 AV Block	4 (11%)	4 (15%)	0 (0%)
Other	7 (20%)	6 (22%)	1 (14%)

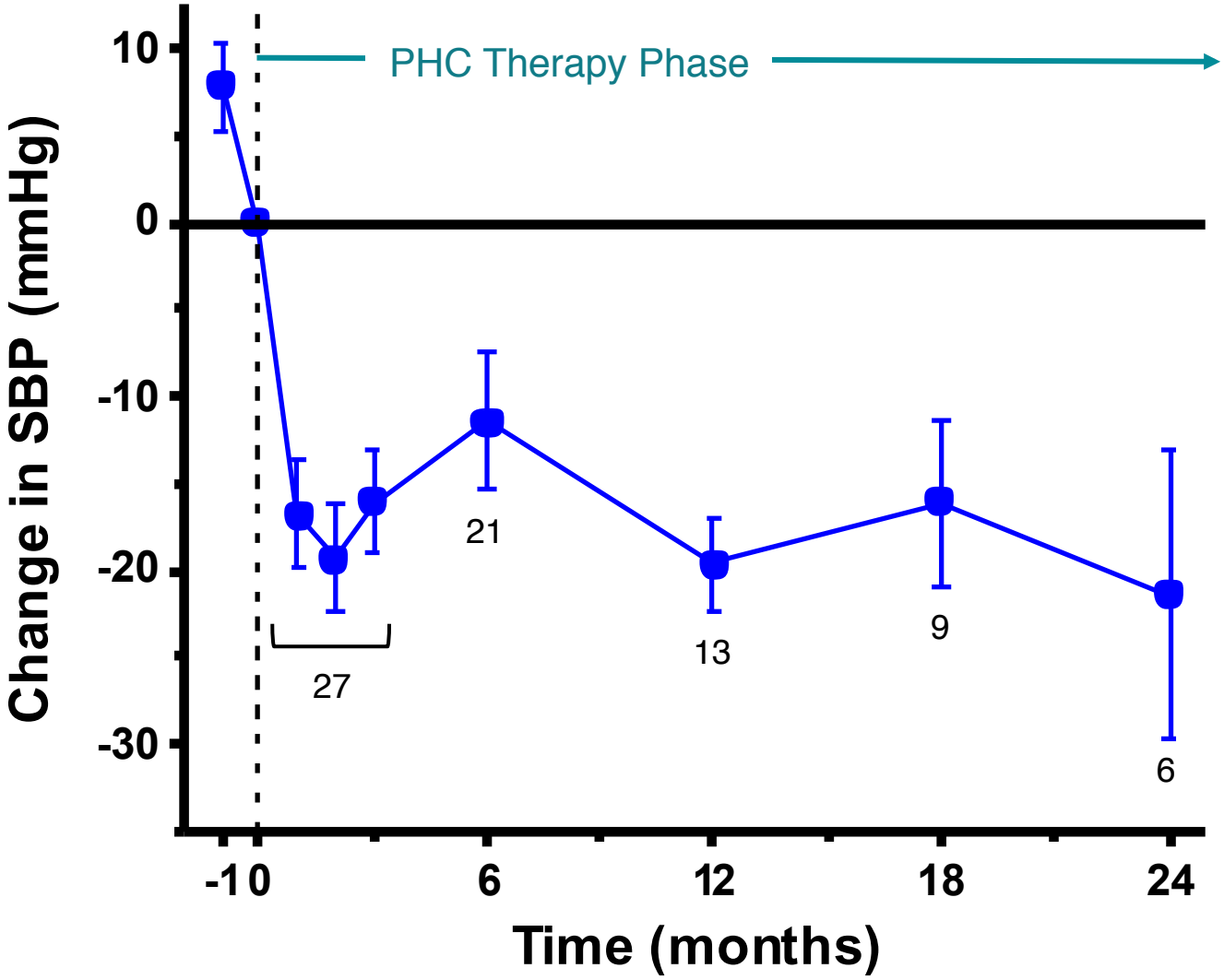
Co-Primary Endpoints





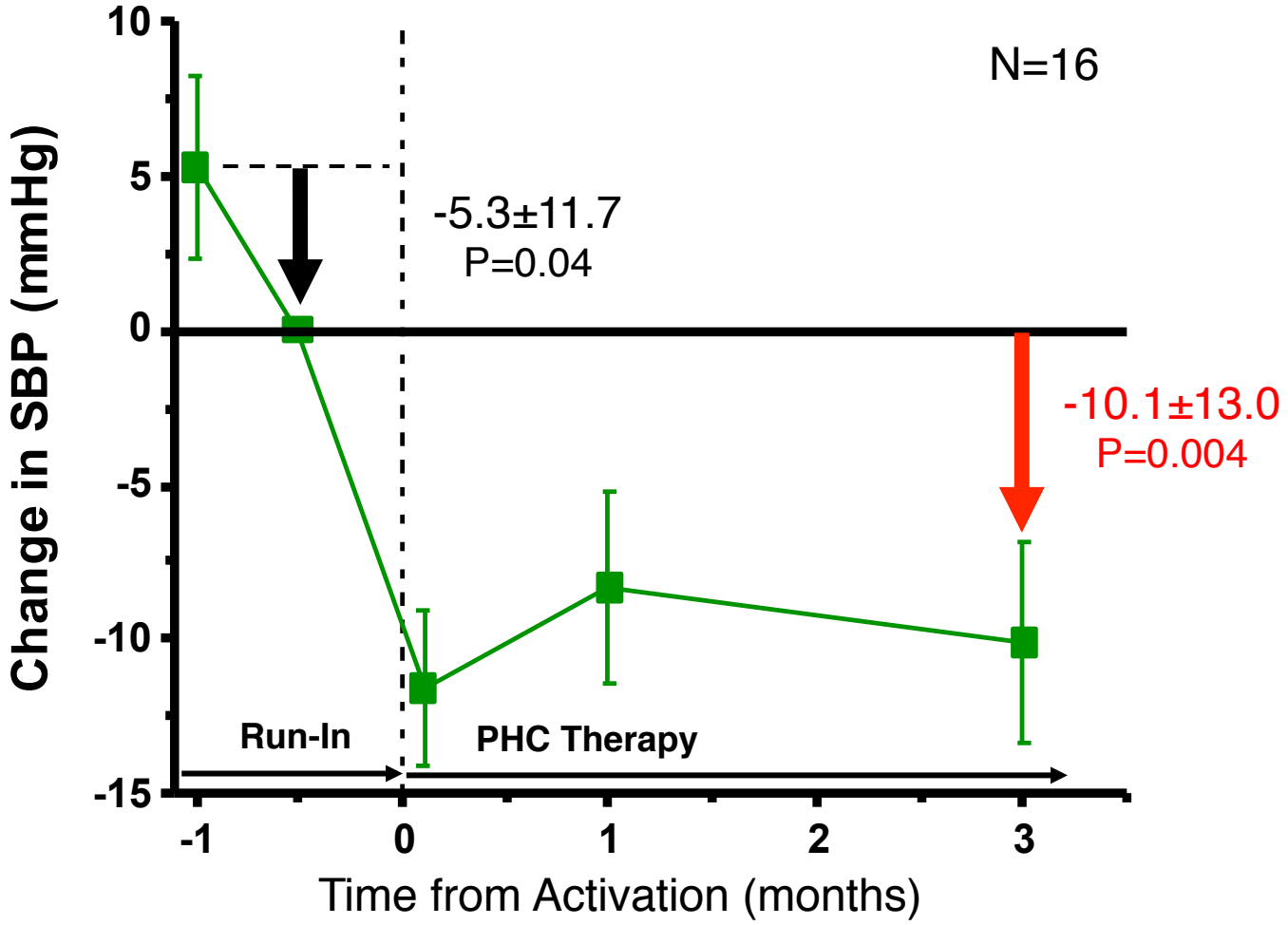
Office Systolic Blood Pressure

Ongoing Longer Term Follow Up in Subset of Patients



P<0.01
for all time points

Changes in 24Hours Ambulatory Systolic Blood Pressure from Pre-activation



Safety

One patient died during the Run-In phase (unrelated)

11 SAEs in 5 patients (adjudicated by an independent committee)

- 8 events adjudicated as being **unrelated** to the PHC therapy
- 3 events adjudicated as being **possibly related** to the PHC therapy

  ambulatory MI with development of heart failure, prolonged atrial fibrillation requiring DC cardioversion, cardiac asthma

No significant change in global cardiac function or ejection function

Significant reduction in ventricular volumes

No significant change in rate of ventricular or superventricular arrhythmias

No significant change in kidney function

Summary and Conclusions

In hypertensive patients requiring a pacemaker, PHC therapy reduces office blood pressure by an average of 23.8 mmHg and 24Hr ambulatory pressure by an average of 14.2 mmHg

Study design having a run-in period allows estimation of the impact of study participation (Hawthorne/Placebo effects) on blood pressure

- Office and ambulatory blood pressures decreased by 7.8 and 5.3 mmHg, respectively, during the run-in period
- After PHC activation, office and ambulatory blood pressure decreased further by additional16.1 and 10.1 mmHg, respectively

This is a pilot study providing proof of concept of a novel approach to treating hypertension

Study limitations: nonrandomized, open label, small number of patients, short duration of follow-up

First Patients Already Enrolled in a Randomized Double-Blind Study

Summary and Conclusions

The therapy is currently investigated for patients requiring a pacemaker:

- Implant required irrespective of the therapy
- >70% of patients with pacers have HTN
- >50% of these patients have SBP > guideline recommendations

If proven safe and effective, this therapy could be applicable to a broader population of patients with medically refractory hypertension

Contributing Sites

- Na Homolce Hospital, Prague, Czech Republic
- Semmelweis University Budapest, Heart and Vascular Center, Budapest, Hungary
- Pauls Stradins Clinical University Hospital, Latvian Centre of Cardiology, Riga, Latvia
- Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania
- Department of Cardiology, Academic Medical Center, AZ Amsterdam The Netherlands
- AKH - Universitätsklinik für Innere Medizin II, Abteilung für Kardiologie, Vienna, Austria
- Hospital Dr. Sótero del Río, Santiago Chile
- University Medical Center Utrecht, Department of Cardiology, Utrecht The Netherlands
- Krankenhaus der Elisabethinen Linz GmbH, Interne 2 - Kardiologie, Angiologie & Interne Intensivmedizin, Linz Austria
- Asklepios Klinik St. Georg, Lohmühlenstr. Hamburg Germany