Long-term Outcomes Following Catheter-Based Renal Denervation in Patients with Uncontrolled Hypertension: Final Follow-up of the SYMPLICITY HTN-3 Trial

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on Behalf of the SYMPLICITY HTN-3 Steering Committee and Investigators

Disclosure Statement of Financial Interest

Dr. Bhatt served as the co-Principal Investigator of SYMPLICITY HTN-3 with funding from Medtronic paid to Brigham and Women's Hospital and discloses the following relationships –

- **Advisory Board**: AngioWave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys;
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- **Data Monitoring Committees**: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial);
- **Honoraria**: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees), Wiley (steering committee);
- **Other**: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither I nor Brigham and Women's Hospital receive any income from this patent.)
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- **Site Co-Investigator**: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solutions;
- **Trustee**: American College of Cardiology;
- **Unfunded Research**: FlowCo, Takeda.

UNLABELED/UNAPPROVED USES DISCLOSURE

In the United States, the use of renal denervation in hypertensive patients is limited to investigational use only.

Background

Symplicity® HTN - 3 Clinical Study

- SYMPLICITY HTN-3 is the first and largest randomized, sham-controlled clinical trial of renal denervation (RDN) for uncontrolled hypertension (HTN)
- At 6 months, the primary safety endpoint was met, however the primary efficacy endpoint was not achieved in the overall trial[1]
  - Predictor analyses for these initial results identified potential confounding factors of medication changes, specific patient subgroups, and procedural factors[2]
- Long term data from HTN-3 assessing progression of the RDN treatment effect, and the impact of sham control, have not been previously presented

[1] Bhatt DL, et al. *N Engl J Med*. 2014;370:1393–1401.
[2] Kandzari DE, et al. *Eur Heart J*. 2015;36(4):219–27.

Endpoints at 6 Months

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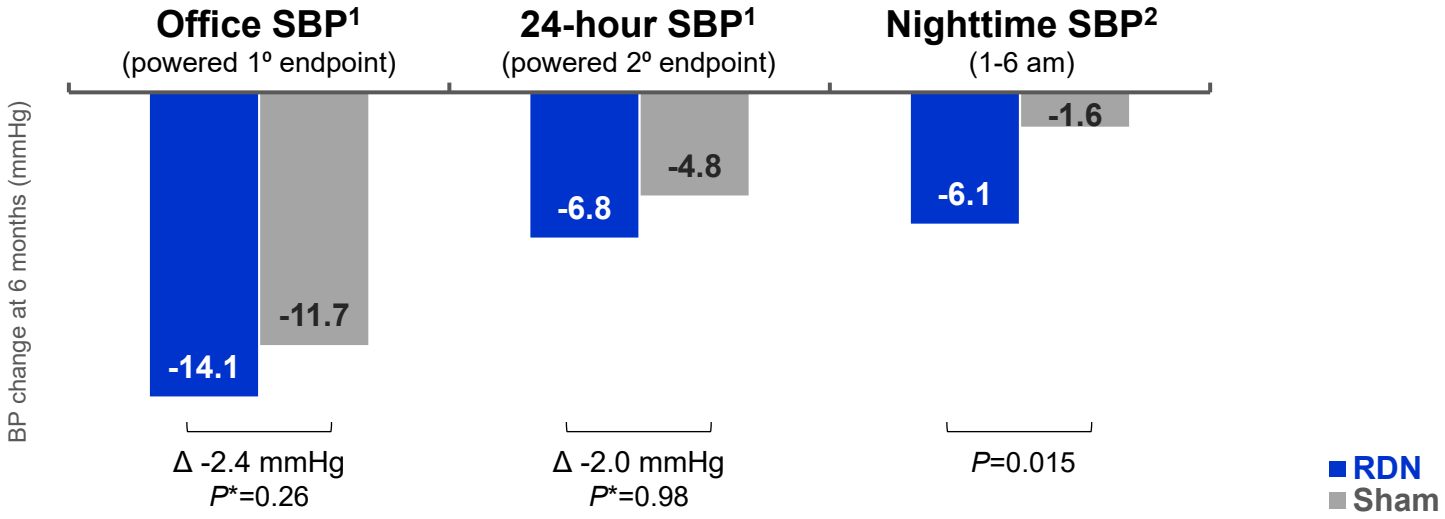


Met primary safety endpoint:[1] Major adverse event (MAE) 1.4% observed vs 9.8% performance goal; *P*<0.001

**P*-value for superiority using a pre-specified superiority margin

[1] Bhatt DL, et al. *N Engl J Med*. 2014;370:1393–1401.
[2] Kario K, et al. *Hypertension*. 2015;66(6):1130-7.

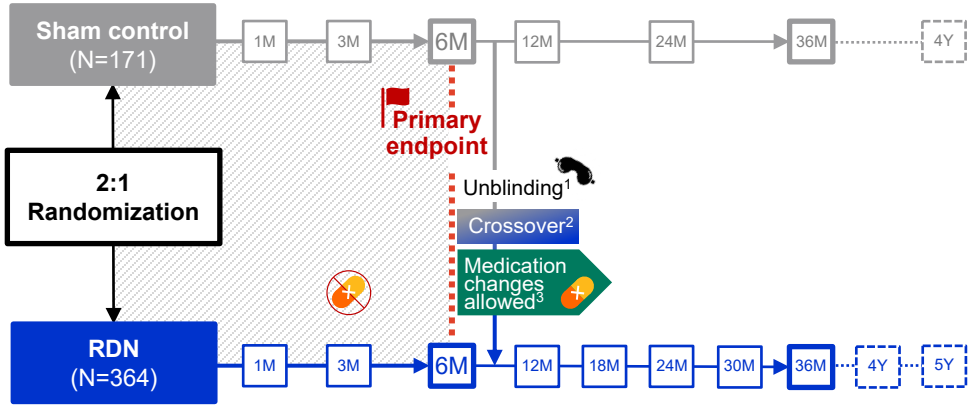
HTN-3 Trial Design

Symplicity® HTN - 3 Clinical Study

- Randomized, sham-controlled, blinded trial at 88 US sites
- Radiofrequency (RF) RDN using 1st gen. Symplicity Flex™ catheter

KEY INCLUSION CRITERIA

- Patients with *resistant* HTN
  - Office SBP ≥160 mm Hg
  - 24hr ABPM ≥135 mm Hg
- On ≥3 anti-HTN medications
  - *Maximum tolerated dose*
  - Including a diuretic
  - *No* drug testing



[1] Patients, BP assessors, and study personnel were all blinded to treatment assignment until 6-month primary endpoint
[2] Sham control patients were allowed to cross over to RDN therapy after 6 months *if they still met inclusion/exclusion criteria*
[3] Until 6-month follow-up, antihypertensive medication changes were not allowed *unless clinically required*

Clinicaltrials.gov: NCT01418261
Bhatt DL, et al. *N Engl J Med*. 2014;370:1393-1401.
In the United States, the use of renal denervation in hypertensive patients is limited to investigational use only.

Methods

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- All clinicians and patients were **un-blinded** after the primary endpoint at 6 months
- Sham control patients were allowed to **cross over** and receive the RDN procedure following the primary endpoint if they continued to meet inclusion/exclusion criteria
  - For control subjects who crossed over to RDN, the last blinded 6-month BP and medication data pre-crossover were imputed out to 3 years by LOCF (last observation carried forward)[1,2]
- Notable protocol changes following the primary endpoint:
  - Additional long-term 24-hr BP measurements were added, but not all patients re-consented
  - Follow-up was reduced from 5 years to 3 years in consultation with the FDA; however, several patients had already completed a FU past 3 years
- Here we present the final long-term outcomes out to *at least* 3 years

[1] Mahfoud F, et al. *Lancet*. 2022;399:1401-10.
[2] Papp KA, et al. *Curr Med Res Opin*. 2008;24(7):2001-8.

Patient Disposition

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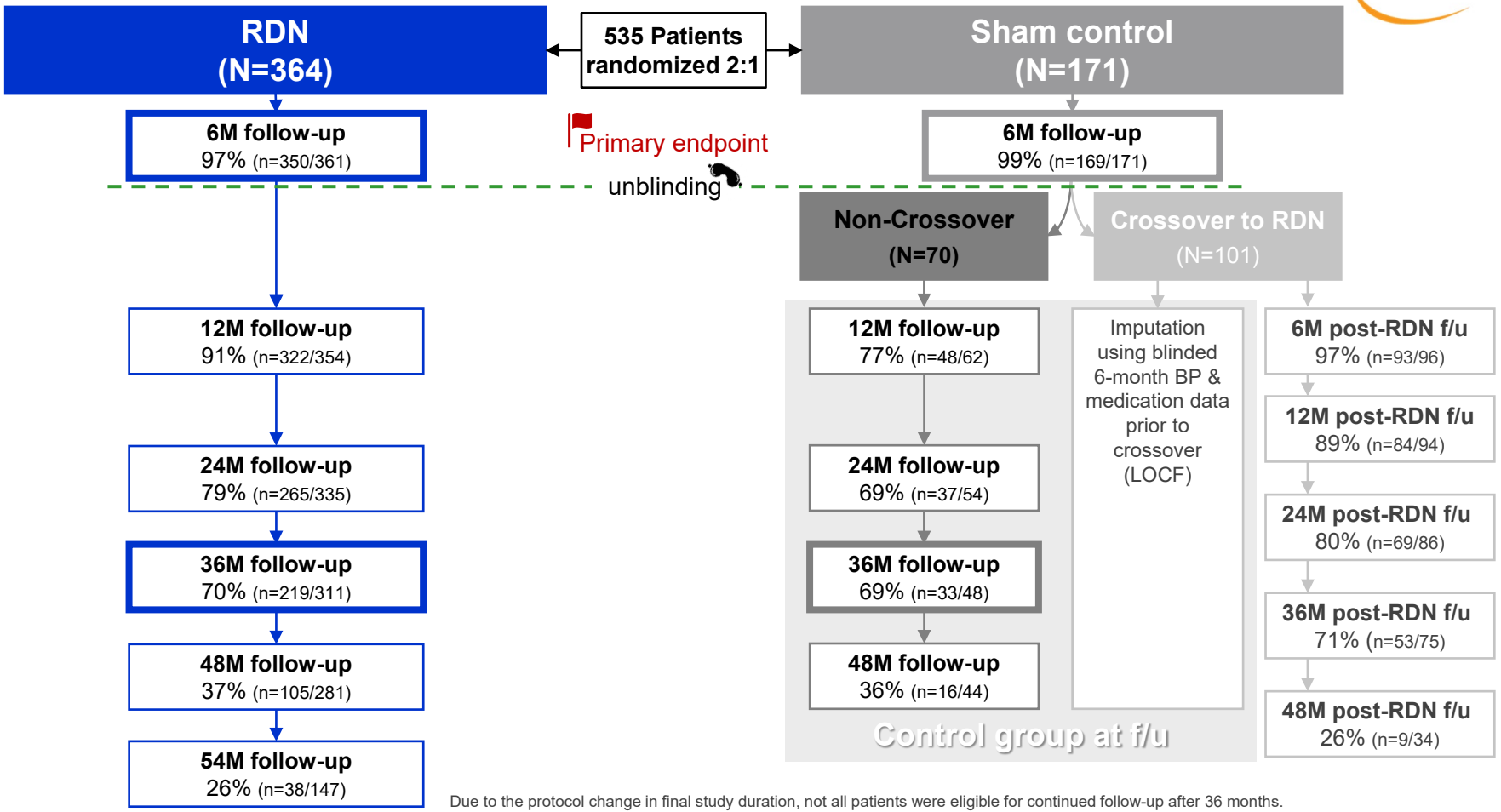

Due to the protocol change in final study duration, not all patients were eligible for continued follow-up after 36 months.

Patient Characteristics

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mean ± SD or %	RDN N=364	Crossover N=101	Non-Crossover N=70	P-value
Blood pressure (BP, mmHg)	*baseline*	*pre-crossover**		
Office systolic BP	**180** ± 16	**184** ± 19*	**146** ± 25*	**<0.0001**
Office diastolic BP	97 ± 17	102 ± 16*	83 ± 13*	**<0.0001**
24-hr ambulatory systolic BP	**159** ± 13	**163** ± 16*	**140** ± 15*	**<0.0001**
24-hr ambulatory diastolic BP	88 ± 14	94 ± 14*	78 ± 11*	**<0.0001**
Baseline demographics				
Age (yrs)	58 ± 10	55 ± 11	58 ± 12	0.08
Male sex	59.1	62.4	67.1	0.19
Black race	24.8	27.7	31.4	0.46
Baseline medical history				
Coronary artery disease	27.7	28.7	22.9	0.47
Diabetes type 2	47.3	37.6	47.1	0.24
Obstructive sleep apnea	25.8	37.6	24.3	0.06
CKD (eGFR <60ml/min/1.73m^2)	9.6	10.9	10.0	0.90
Prior stroke	8.5	11.9	10.0	0.54
History of hypertensive crisis	23.1	20.8	24.3	0.84
Prescribed anti-hypertensive drugs >10 yrs	68.1	72.3	62.9	0.44

CRF TCT

*Measures for the crossover and non-crossover groups are the blinded, 6M f/u values used to determine eligibility for the crossover RDN procedure.
P-values for BP compare crossover with non-crossover only. All other P-values are three-way comparisons.

Safety Outcomes

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% (n)	RDN	Crossover*	Non-Crossover
To 36 Months	**(n=290)**	**(n=68)**	**(n=46)**
Composite Safety Endpoint to 36 months**	12.4%	12.4%	14.5%
Death	4.1% (12)	5.9% (4)	10.9% (5)
New-onset end-stage renal disease	3.4% (10)	0	0
Sig. embolic event resulting in end-organ damage	0.3% (1)	0	0
Vascular complication	0.3% (1)	0	0
Renal artery re-intervention	1.0% (3)	0	0
Hypertensive crisis/emergency	10.7% (31)	11.8% (8)	10.9% (5)
To 48 Months	**(n=217)**	**(n=35)**	**(n=33)**
Composite Safety Endpoint to 48 months**	15.3%	13.5%	14.5%
Death	8.3% (18)	17.1% (6)	15.2% (5)
New-onset end-stage renal disease	5.1% (11)	0	0
Sig. embolic event resulting in end-organ damage	0.5% (1)	0	0
Vascular complication	0.5% (1)	0	0
Renal artery re-intervention	1.4% (3)	0	0
Hypertensive crisis/emergency	16.6% (36)	22.9% (8)	15.2% (5)

* Reported safety events in crossover patients begins at time of crossover.
** Defined as composite of death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, hypertensive crisis, or new renal-artery stenosis >70% within 6 months

Prescribed Anti-Hypertensive Medications

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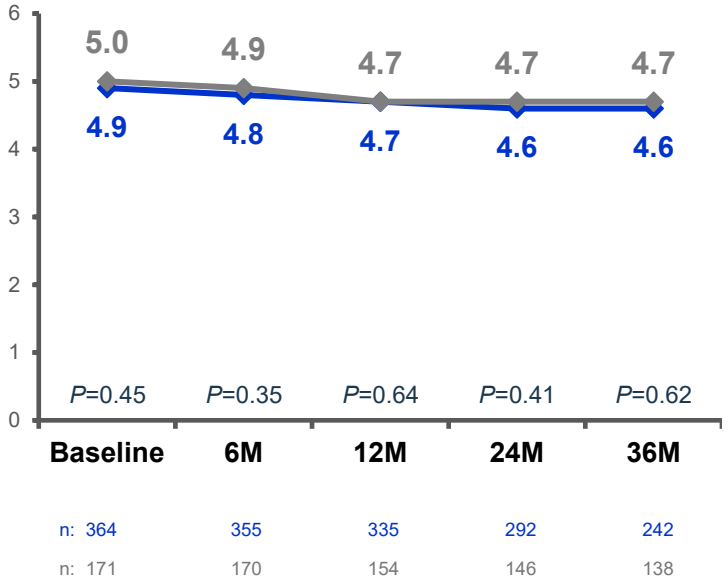
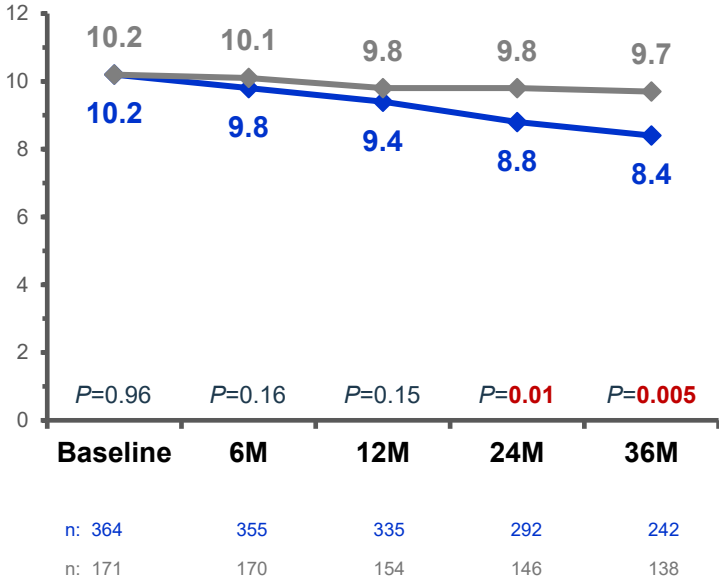
Number of medication classes[1]



Medication burden[1,2]

(based on dose per day of a drug, DDD)



CRF TCT

[1] No drug testing performed to assess medication adherence.
[2] DDD is stated by WHO as the assumed average maintenance dose per day of a drug, based on class and daily dosage per AH medication.
P-value calculated at baseline using t-test and all follow-up comparisons using ANCOVA.
Control group include LOCF medication values for crossover patients from 6 months (blinded).

Change in Office Systolic BP

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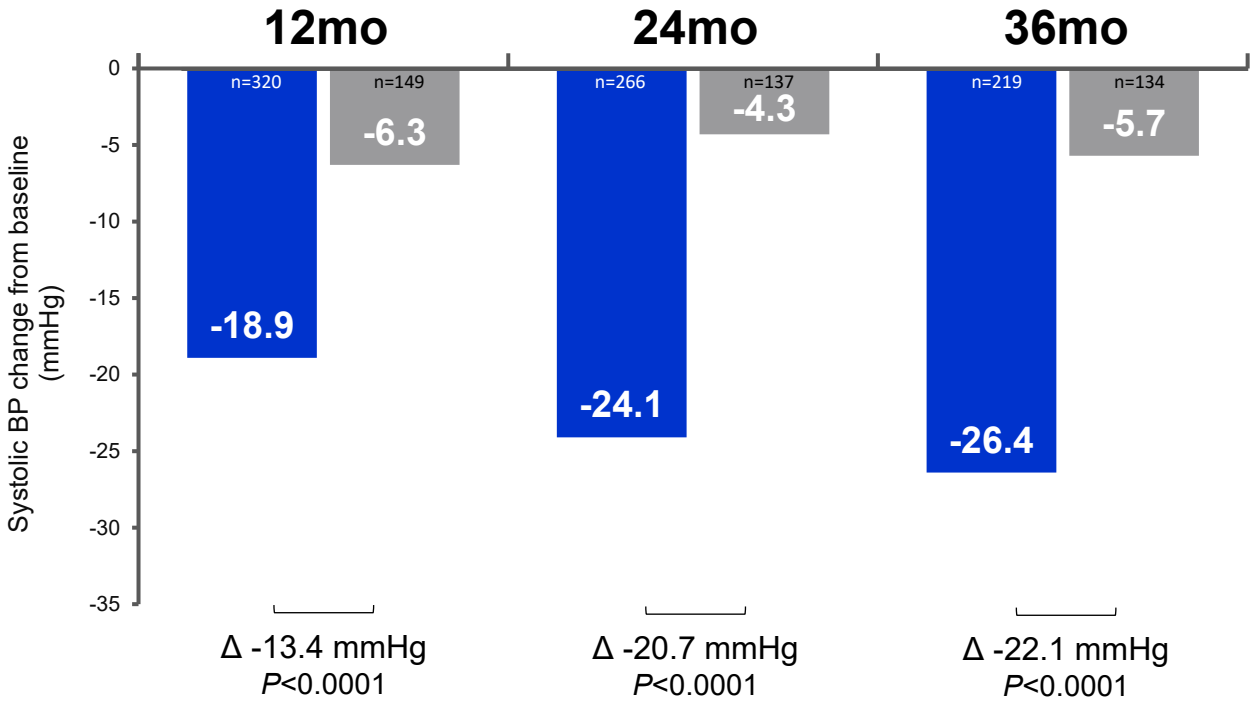


RDN (baseline 180 mmHg)

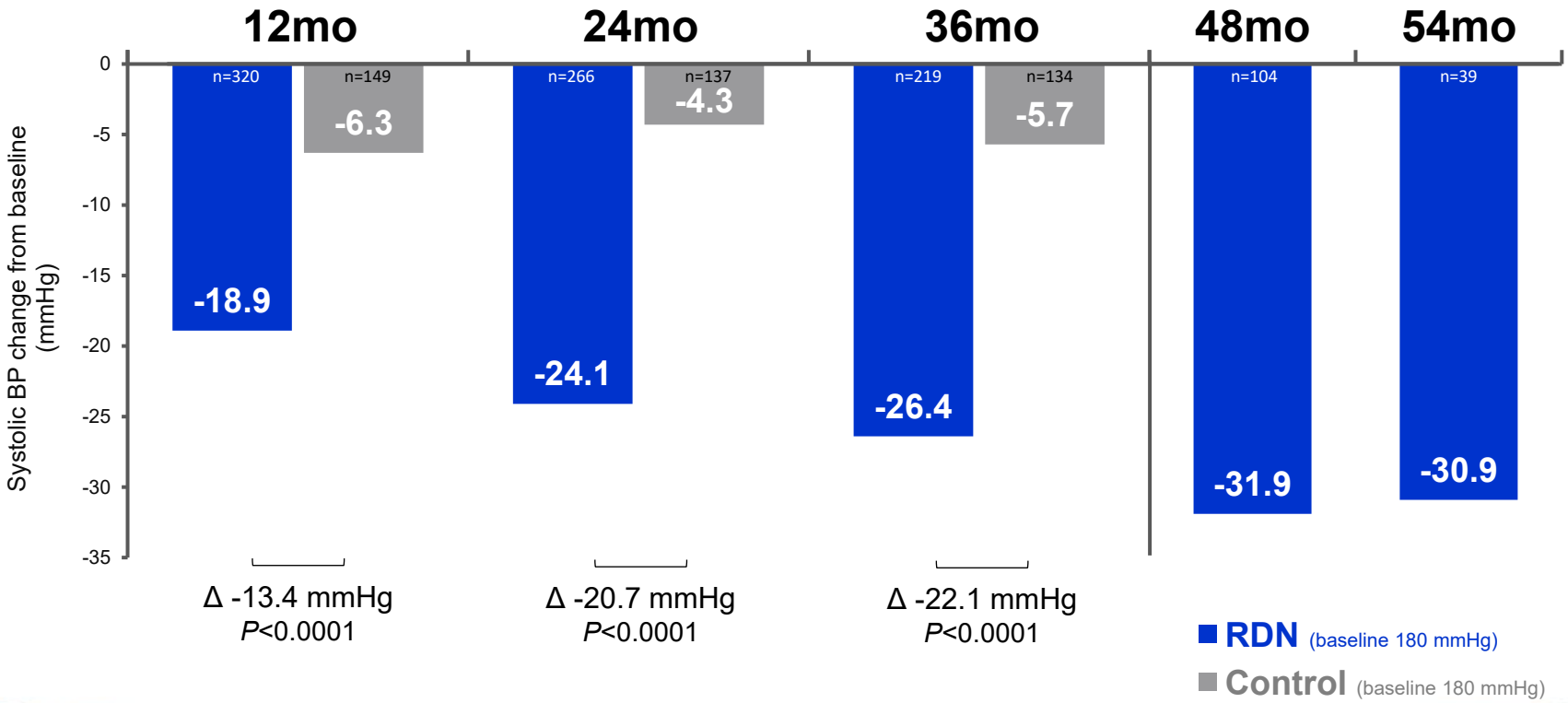
Control (baseline 180 mmHg)

CRF TCT

Treatment differences and p-values are ANCOVA adjusted for baseline BP.
Control blood pressure measures include LOCF for crossover patients from 6 months (blinded).

Change in Office Systolic BP

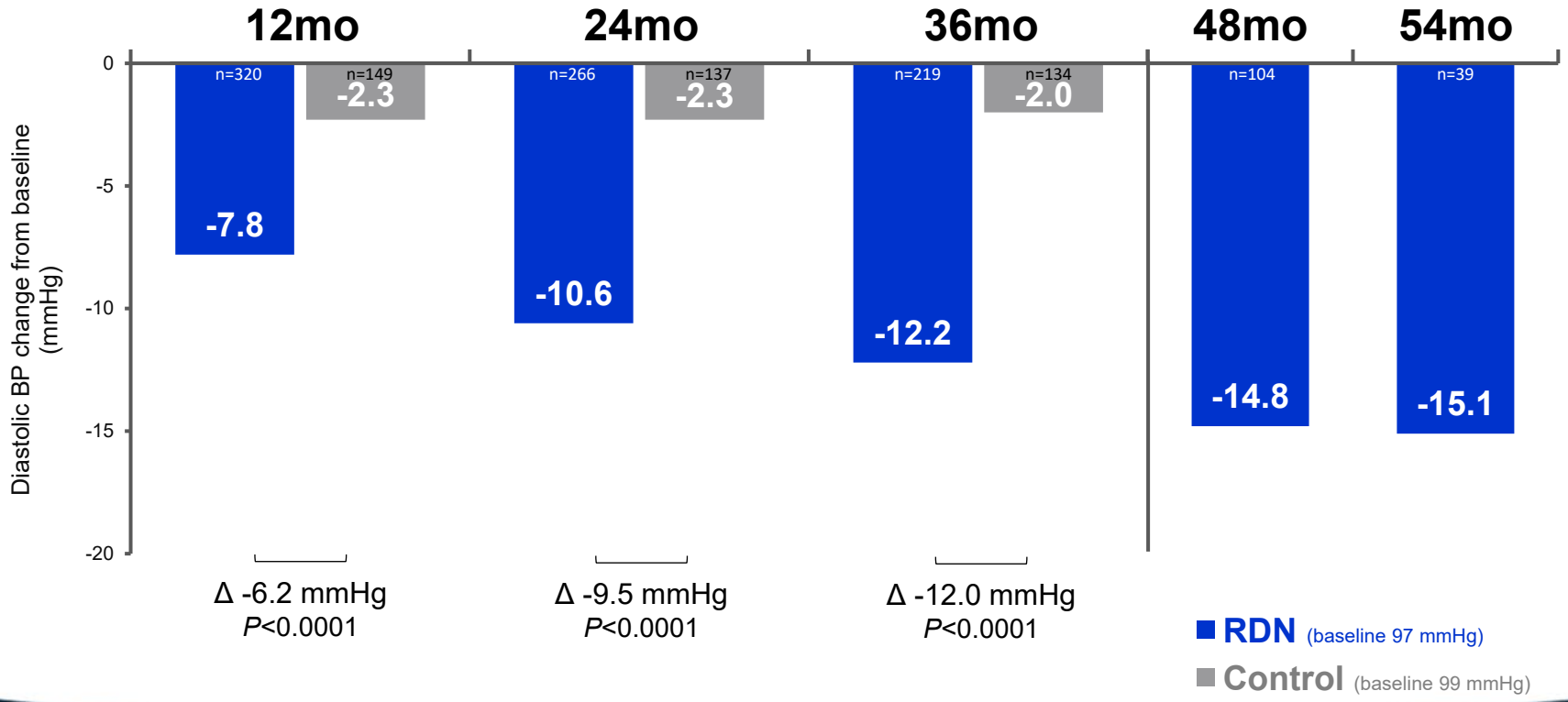
Symplicity® HTN - 3 Clinical Study



Treatment differences and p-values are ANCOVA adjusted for baseline BP.
Control blood pressure measures include LOCF for crossover patients from 6 months (blinded).
Data beyond 36 months are not reported for the control arm because sample size was too small for imputation.

Change in Office Diastolic BP

Symplicity® HTN - 3 Clinical Study

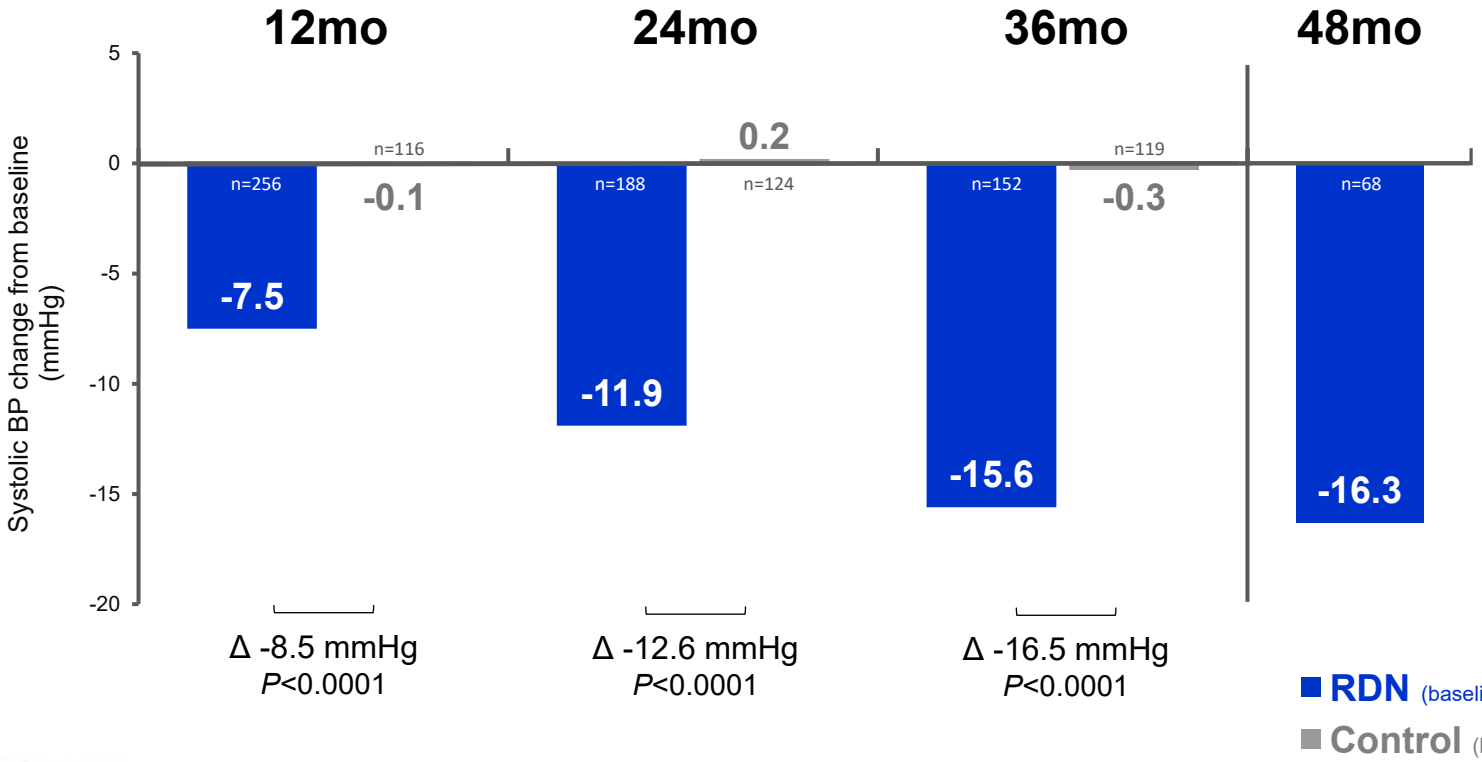


CRF TCT

Treatment differences and p-values are ANCOVA adjusted for baseline BP.
Control blood pressure measures include LOCF for crossover patients from 6 months (blinded).
Data beyond 36 months are not reported for the control arm because sample size was too small for imputation.

Change in 24-Hour Systolic BP

Symplicity® HTN - 3 Clinical Study

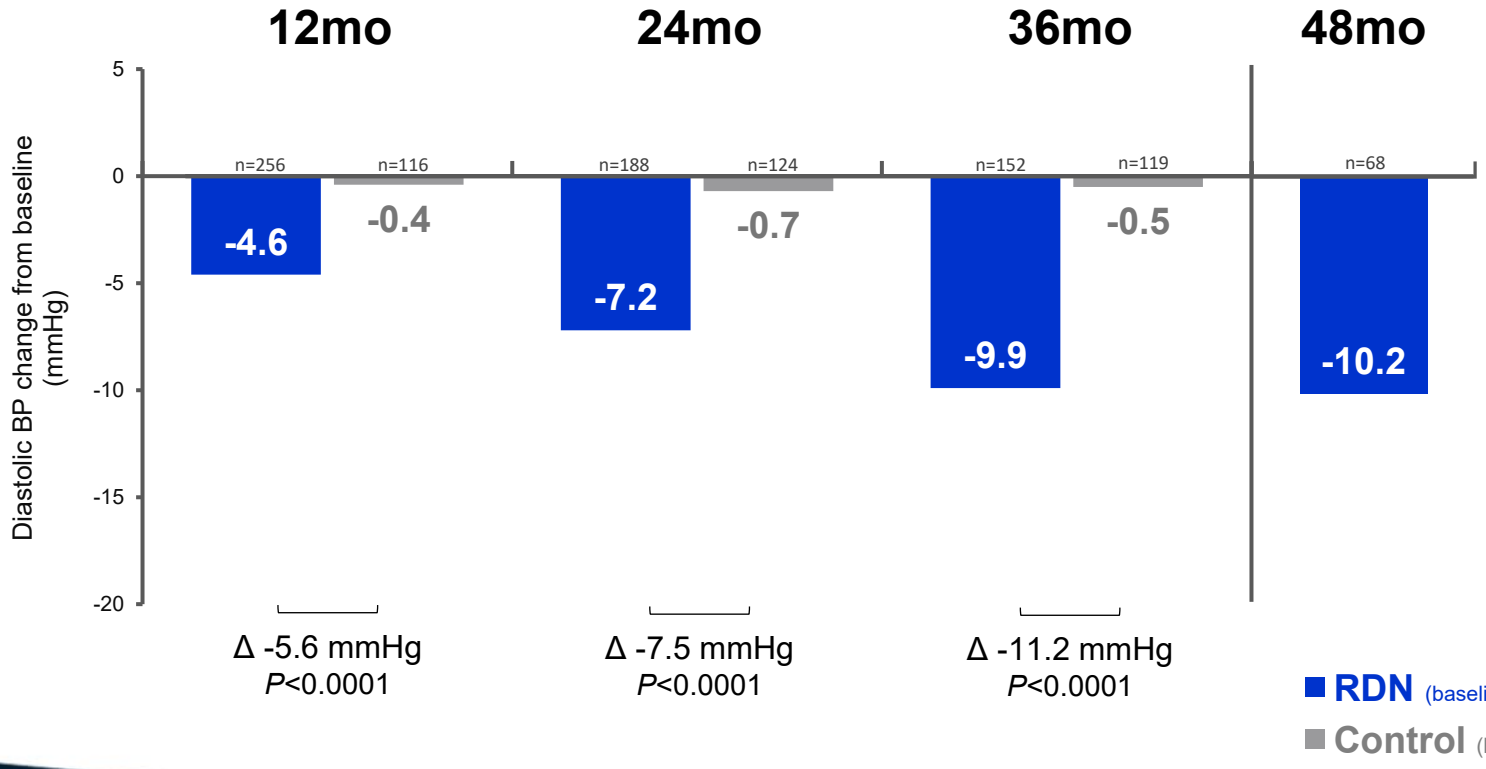


CRF TCT

Treatment differences and p-values are ANCOVA adjusted for baseline BP.
Control blood pressure measures include LOCF for crossover patients from 6 months (blinded).
Data beyond 36 months are not reported for the control arm because sample size was too small for imputation.

Change in 24-hour Diastolic BP

Symplicity® HTN - 3 Clinical Study



CRF TCT

Treatment differences and p-values are ANCOVA adjusted for baseline BP.
Control blood pressure measures include LOCF for crossover patients from 6 months (blinded).
Data beyond 36 months are not reported for the control arm because sample size was too small for imputation.

24-Hour Systolic BP

Baseline vs 36 Months

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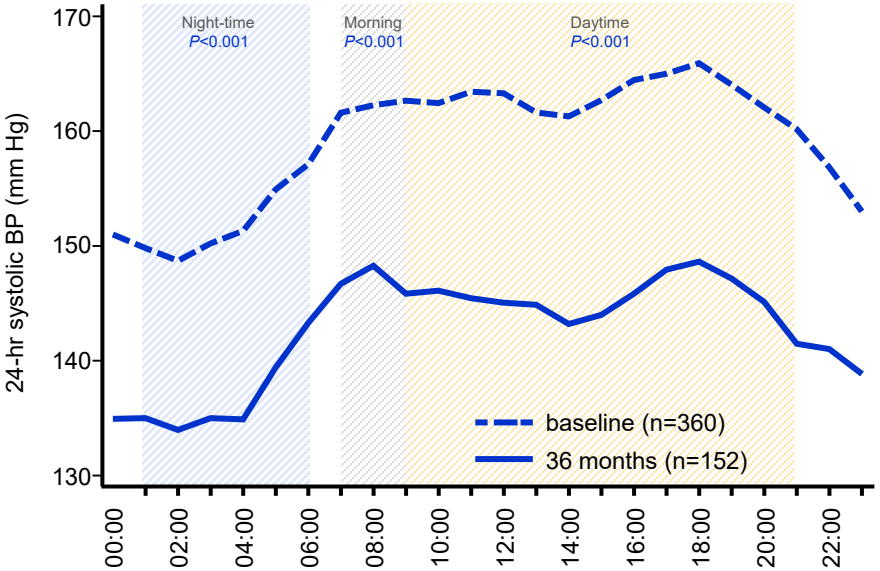
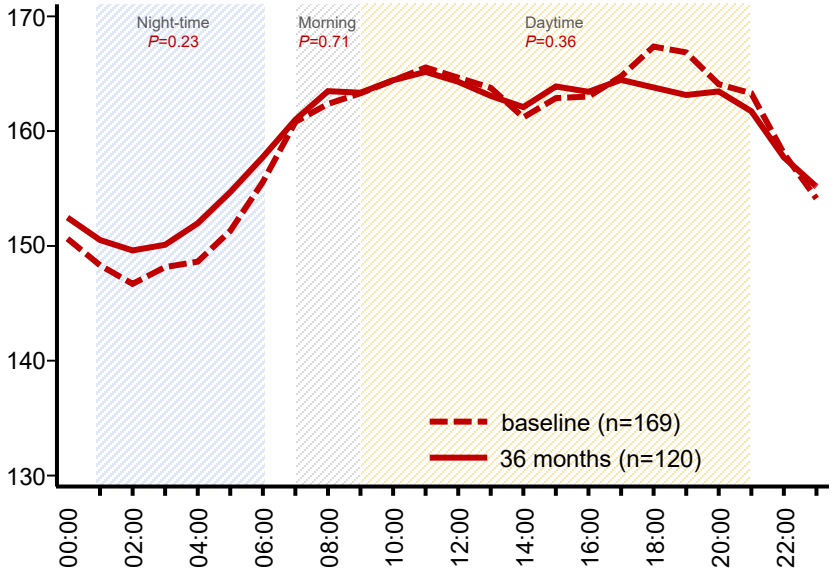
RDN



Control



Office Systolic BP Distribution

(% Patients)

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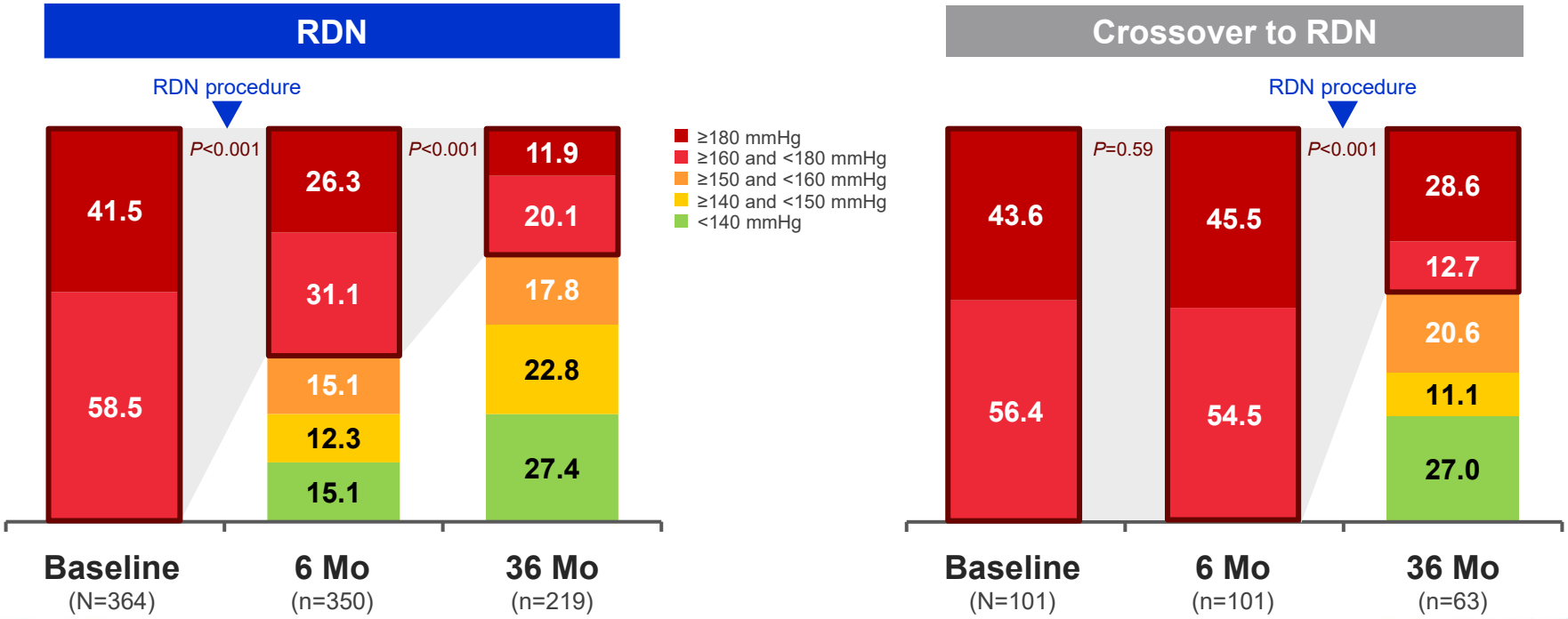


CRF TCT

Limitations

Symplicity® HTN - 3 Clinical Study

- Patients were unblinded after 6 months; however, crossover patients' BPs after 6 months were imputed utilizing blinded 6-month BP values
- Due to crossover, the number of control patients at long term follow up was smaller, but sensitivity analyses in which all missing data were imputed showed consistent results
- Drug testing (urine/serum) to assess patient adherence to antihypertensive medications was not performed; however, patients were on maximum tolerated doses of medications

Conclusion

Symplicity® HTN - 3 Clinical Study

The final follow-up from the SYMPLICITY HTN-3 trial, the largest and longest RCT of RDN to date, demonstrates:

- RDN was safe through long-term follow-up, with no late-emerging complications
- Despite potential confounding factors, significant reductions were seen after RDN *vs* control in office and 24-h BP out to 3 years, independent of medications

These findings support that durable blood pressure reductions with radiofrequency renal artery denervation in the presence of lifestyle modification and maximal medical therapy are safely achievable

Simultaneous Publication

Symplicity® HTN - 3 Clinical Study

Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 Trial

Deepak L Bhatt, Muthiah Vaduganathan, David E Kandzari, Martin B Leon, Krishna Rocha-Singh, Raymond R Townsend, Barry T Katzen, Suzanne Oparil, Sandeep Brar, Vanessa DeBruin, Martin Fahy, George L Bakris for the SYMPLICITY HTN-3 Steering Committee and Investigators*

Bhatt DL, et al. *Lancet*. Published online September 18, 2022.

Long-term Outcomes Following Catheter-Based Renal Denervation in Patients with Uncontrolled Hypertension: Final Follow-up of the SYMPLICITY HTN-3 Trial

Deepak L. Bhatt, MD, MPH, MSCAI
on Behalf of the SYMPLICITY HTN-3 Steering Committee and Investigators

HTN-3 *vs* SPYRAL HTN – ON MED

Study Comparison

Symplicity® HTN - 3 Clinical Study

	HTN-3	SPYRAL HTN – ON MED[1]
RDN technology	Radio-frequency ablation	Radio-frequency ablation
Catheter	1st generation, Symplicity (Flex)™  1 electrode	2nd generation, Symplicity Spyral™  4 electrodes
Treatment location	Main renal artery only	Main renal artery and branches
Mean number of ablations / pt	11.2 ± 2.8	45.9 ± 13.7

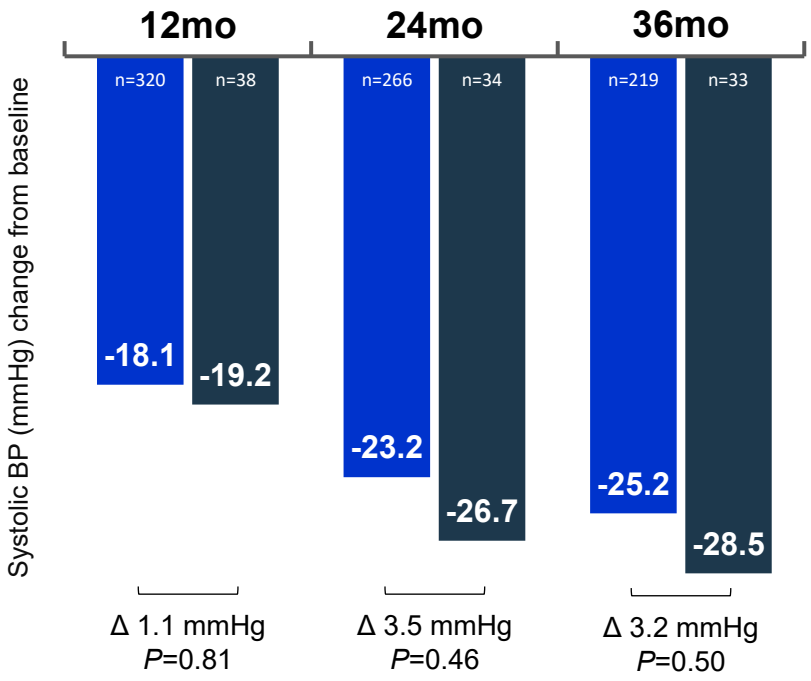
CRF TCT

[1] Mahfoud F, et al. *Lancet*. 2022;399:1401-10.

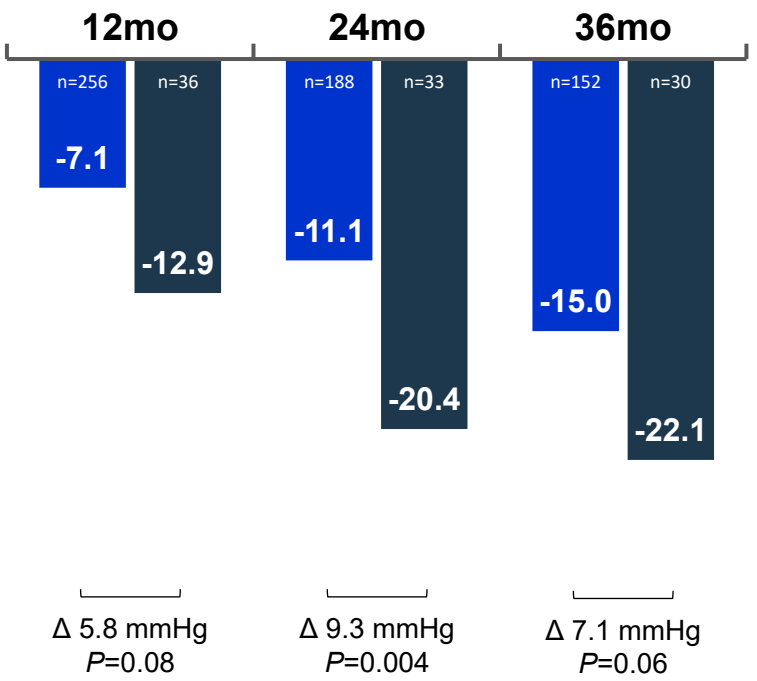
HTN-3 *vs* SPYRAL HTN-ON MED: RDN Patients

Symplicity® HTN - 3 Clinical Study

Office SBP



24hr SBP



SYMPLICITY HTN-3

SPYRAL HTN – ON MED[1]

CRF TCT

Results are ANCOVA adjusted for baseline BP and number of prescribed AH medications at each timepoint.

[1] Mahfoud F, et al. *Lancet*. 2022;399:1401-10.