MUNI MED

FAKULTNÍ NEMOCNICE BRNO

ČESKÁ ASOCIACE **INTERVENČNÍ KARDIOLOGIE**

SYMPLICITY HTN-3 FINAL FOLLOW UP

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Sympatická inervace a HTN

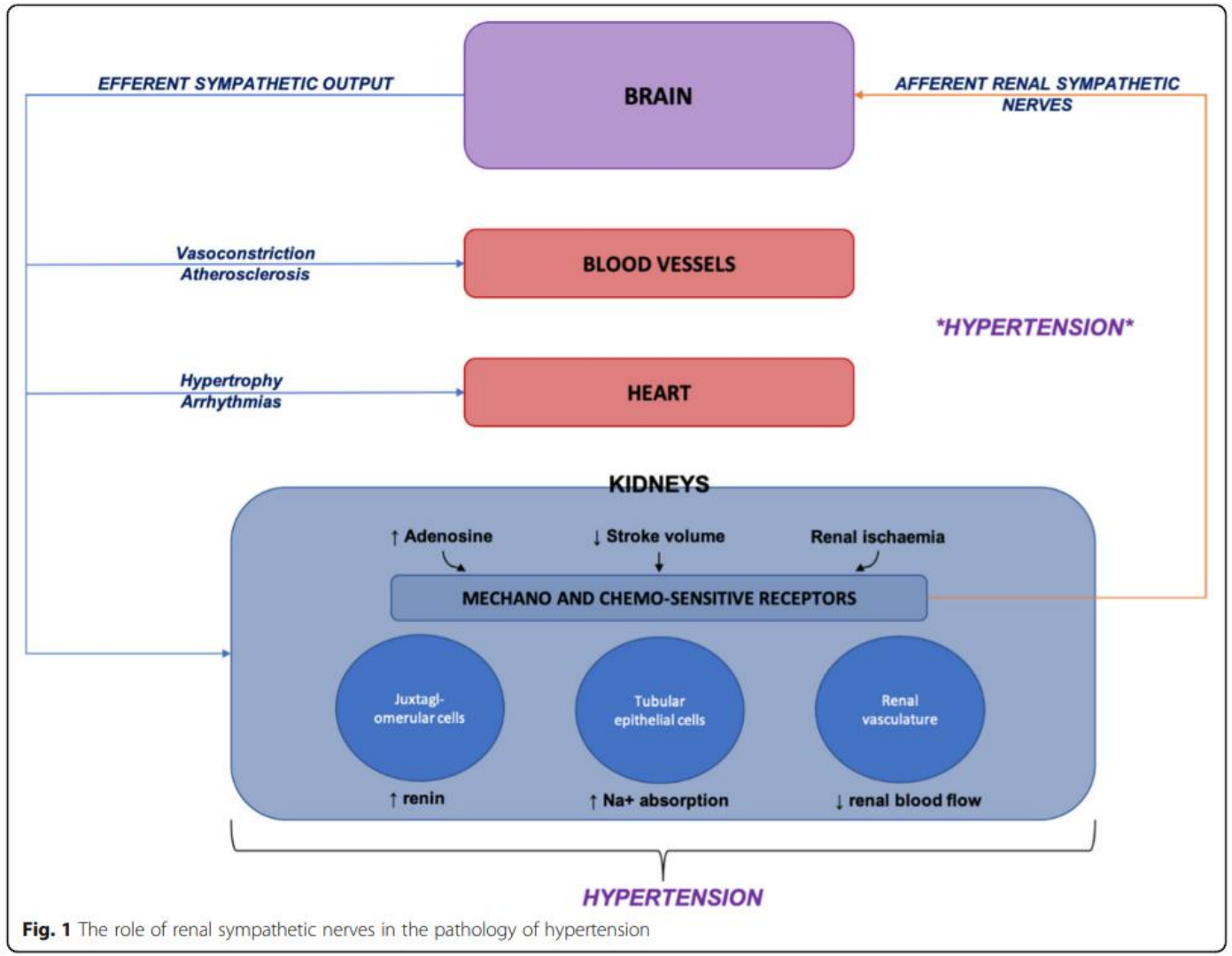
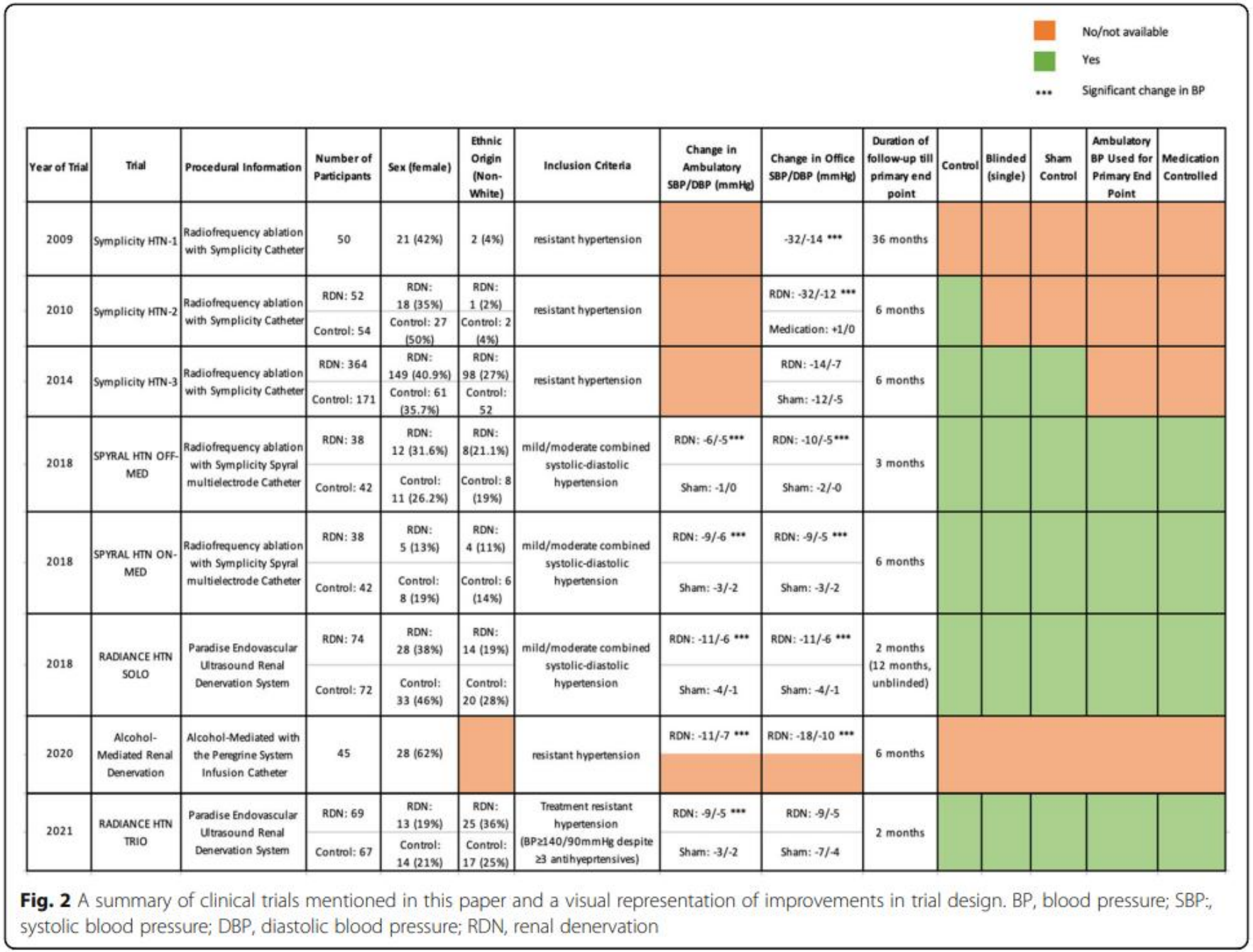


Fig. 1 The role of renal sympathetic nerves in the pathology of hypertension

Shah and Wang Clinical Hypertension (2022



Year of Trial	Trial	Procedural Information	Number of Participants	Sex (female)	Ethnic Origin (Non-White)	Inclusion Criteria	Change in Ambulatory SBP/DBP (mmHg)	Change in Office SBP/DBP (mmHg)	Duration of follow-up till primary end point	Control	Blinded (single)	Sham Control	Ambulatory BP Used for Primary End Point	Medication Controlled
2009	Symplicity HTN-1	Radiofrequency ablation with Symplicity Catheter	50	21 (42%)	2 (4%)	resistant hypertension		-32/-14 ***	36 months					
2010	Symplicity HTN-2	Radiofrequency ablation with Symplicity Catheter	RDN: 52 Control: 54	RDN: 18 (35%) Control: 27 (50%)	RDN: 1 (2%) Control: 2 (4%)	resistant hypertension		RDN: -32/-12 *** Medication: +1/0	6 months					
2014	Symplicity HTN-3	Radiofrequency ablation with Symplicity Catheter	RDN: 364 Control: 171	RDN: 149 (40.9%) Control: 61 (35.7%)	RDN: 98 (27%) Control: 52	resistant hypertension		RDN: -14/-7 Sham: -12/-5	6 months					
2018	SPYRAL HTN OFF-MED	Radiofrequency ablation with Symplicity Spyral multielectrode Catheter	RDN: 38 Control: 42	RDN: 12 (31.6%) Control: 11 (26.2%)	RDN: 8(21.1%) Control: 8 (19%)	mild/moderate combined systolic-diastolic hypertension	RDN: -6/-5*** Sham: -1/0	RDN: -10/-5*** Sham: -2/-0	3 months					
2018	SPYRAL HTN ON-MED	Radiofrequency ablation with Symplicity Spyral multielectrode Catheter	RDN: 38 Control: 42	RDN: 5 (13%) Control: 8 (19%)	RDN: 4 (11%) Control: 6 (14%)	mild/moderate combined systolic-diastolic hypertension	RDN: -9/-6 *** Sham: -3/-2	RDN: -9/-5 *** Sham: -3/-2	6 months					
2018	RADIANCE HTN SOLO	Paradise Endovascular Ultrasound Renal Denervation System	RDN: 74 Control: 72	RDN: 28 (38%) Control: 33 (46%)	RDN: 14 (19%) Control: 20 (28%)	mild/moderate combined systolic-diastolic hypertension	RDN: -11/-6 *** Sham: -4/-1	RDN: -11/-6 *** Sham: -4/-1	2 months (12 months, unblinded)					
2020	Alcohol-Mediated Renal Denervation	Alcohol-Mediated with the Peregrine System Infusion Catheter	45	28 (62%)		resistant hypertension	RDN: -11/-7 ***	RDN: -18/-10 ***	6 months					
2021	RADIANCE HTN TRIO	Paradise Endovascular Ultrasound Renal Denervation System	RDN: 69 Control: 67	RDN: 13 (19%) Control: 14 (21%)	RDN: 25 (36%) Control: 17 (25%)	Treatment resistant hypertension (BP≥140/90mmHg despite ≥3 antihyeprtensives)	RDN: -9/-5 *** Sham: -3/-2	RDN: -9/-5 Sham: -7/-4	2 months					

Fig. 2 A summary of clinical trials mentioned in this paper and a visual representation of improvements in trial design. BP, blood pressure; SBP:, systolic blood pressure; DBP, diastolic blood pressure; RDN, renal denervation

Shah and Wang Clinical Hypertension (2022

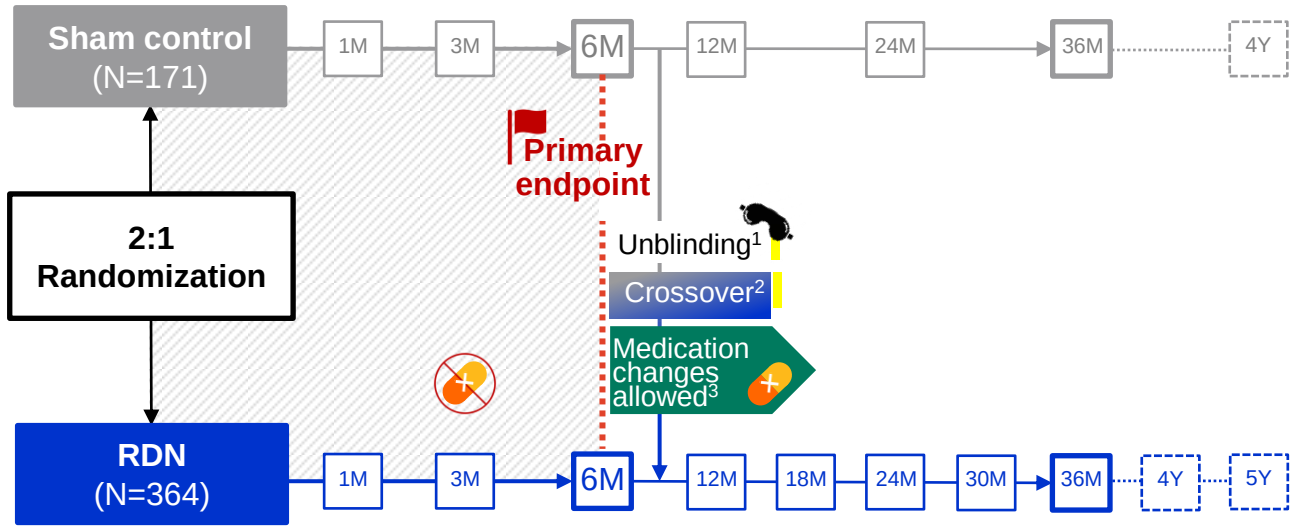
HTN-3 Trial Design

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*

CRF TCT

Clinicaltrials.gov: NCT01418261
Bhatt DL, et al. *N Engl J Med*. 2014;370:1393-1401.

HTN-3 *vs* SPYRAL HTN – ON MED

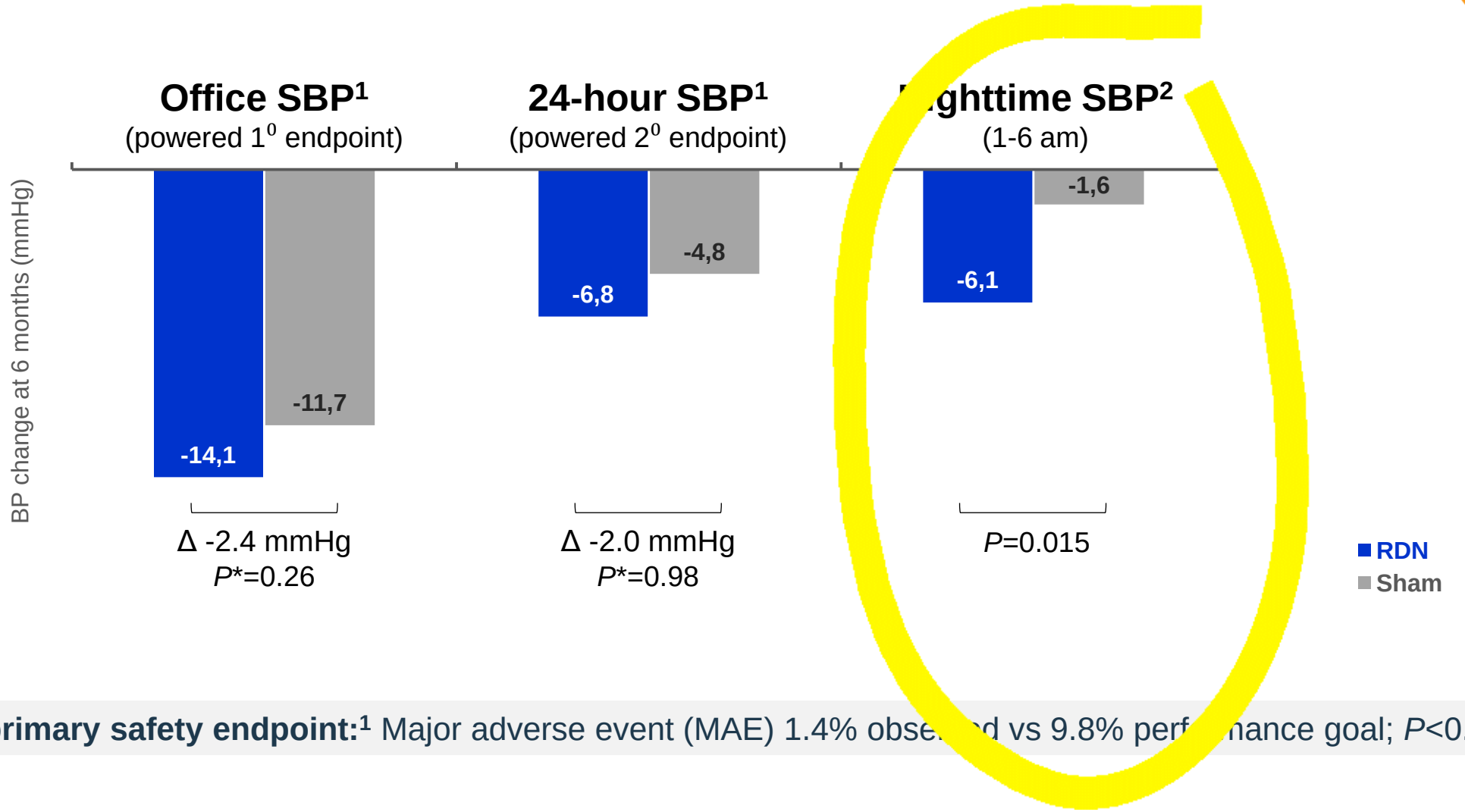
Study Comparison

	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

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

Endpoints at 6 Months

Symplicity® HTN - 3 Clinical Study



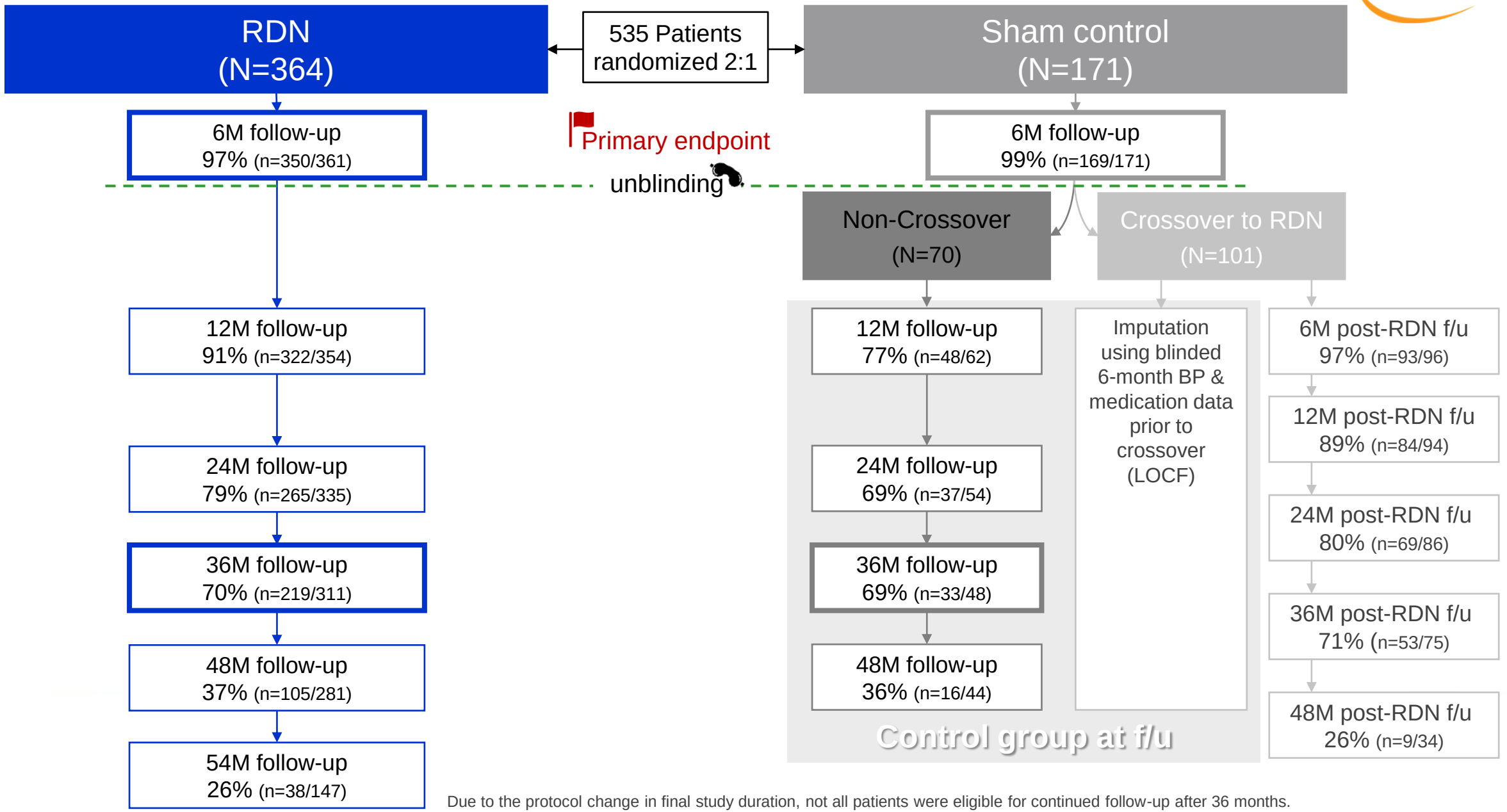
Met primary safety endpoint:[1] Major adverse event (MAE) 1.4% obse d vs 9.8% perf nance goal; *P*<0.001

**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.

Patient Disposition

Symplicity® HTN - 3 Clinical Study



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

Safety Outcomes

Symplicity® HTN - 3 Clinical Study

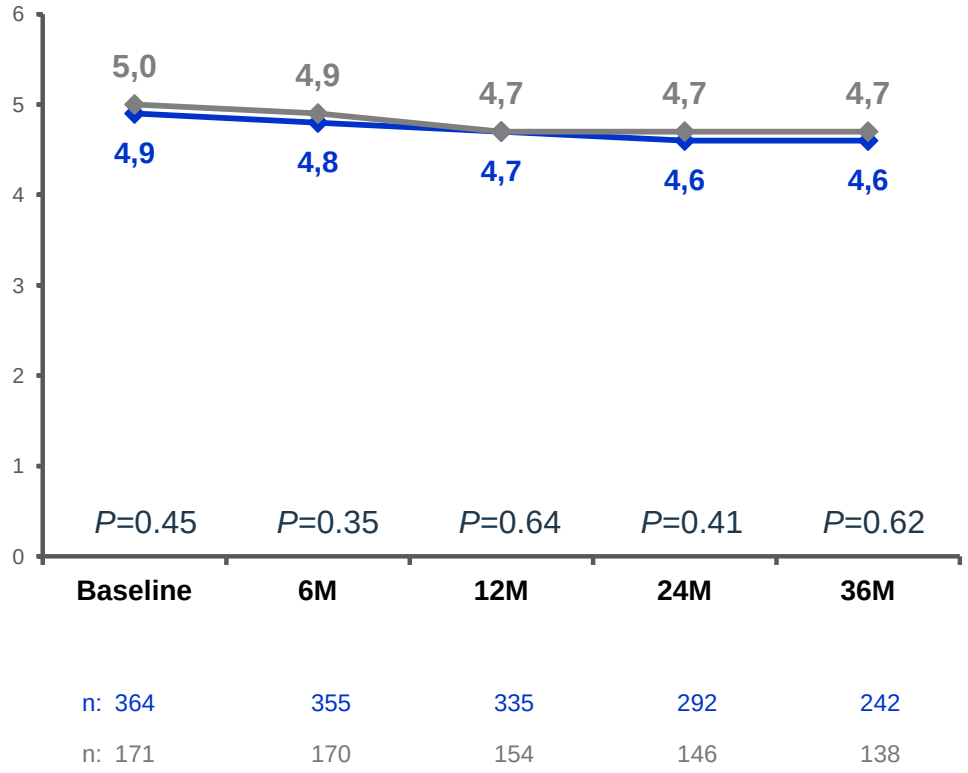
% (n)	RDN	Crossover*	Non-Crossover
To 36 Months	**(n=290)**	**(n=68)**	**(n=46)**
Composite Safety Endpoint to 36 months**	12.4%	12.4%	14.5%
Death	4.1% (12)	5.9% (4)	10.9% (5)
New-onset end-stage renal disease	3.4% (10)	0	0
Sig. embolic event resulting in end-organ damage	0.3% (1)	0	0
Vascular complication	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

Symplicity® HTN - 3 Clinical Study

Number of medication classes[1]

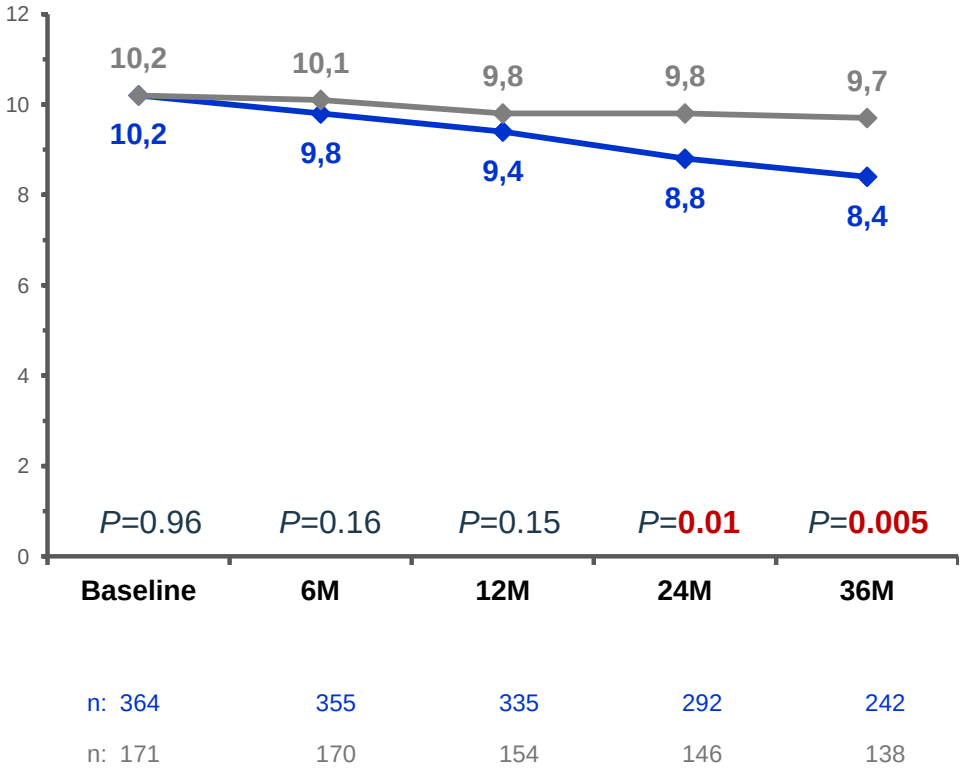


	Baseline	6M	12M	24M	36M
n: RDN	364	355	335	292	242
n: Control	171	170	154	146	138

RDN
Control

Medication burden[1,2]

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



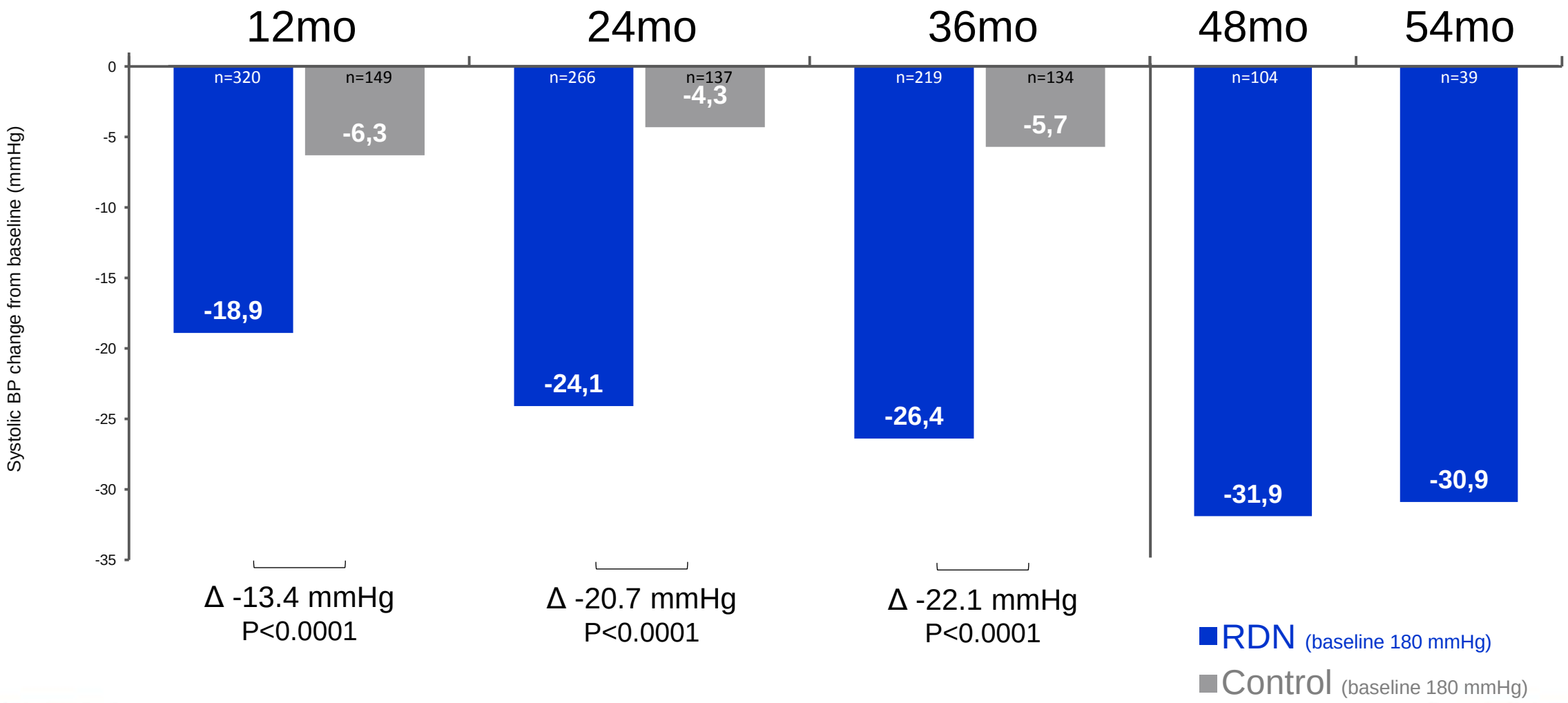
	Baseline	6M	12M	24M	36M
n: RDN	364	355	335	292	242
n: Control	171	170	154	146	138

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

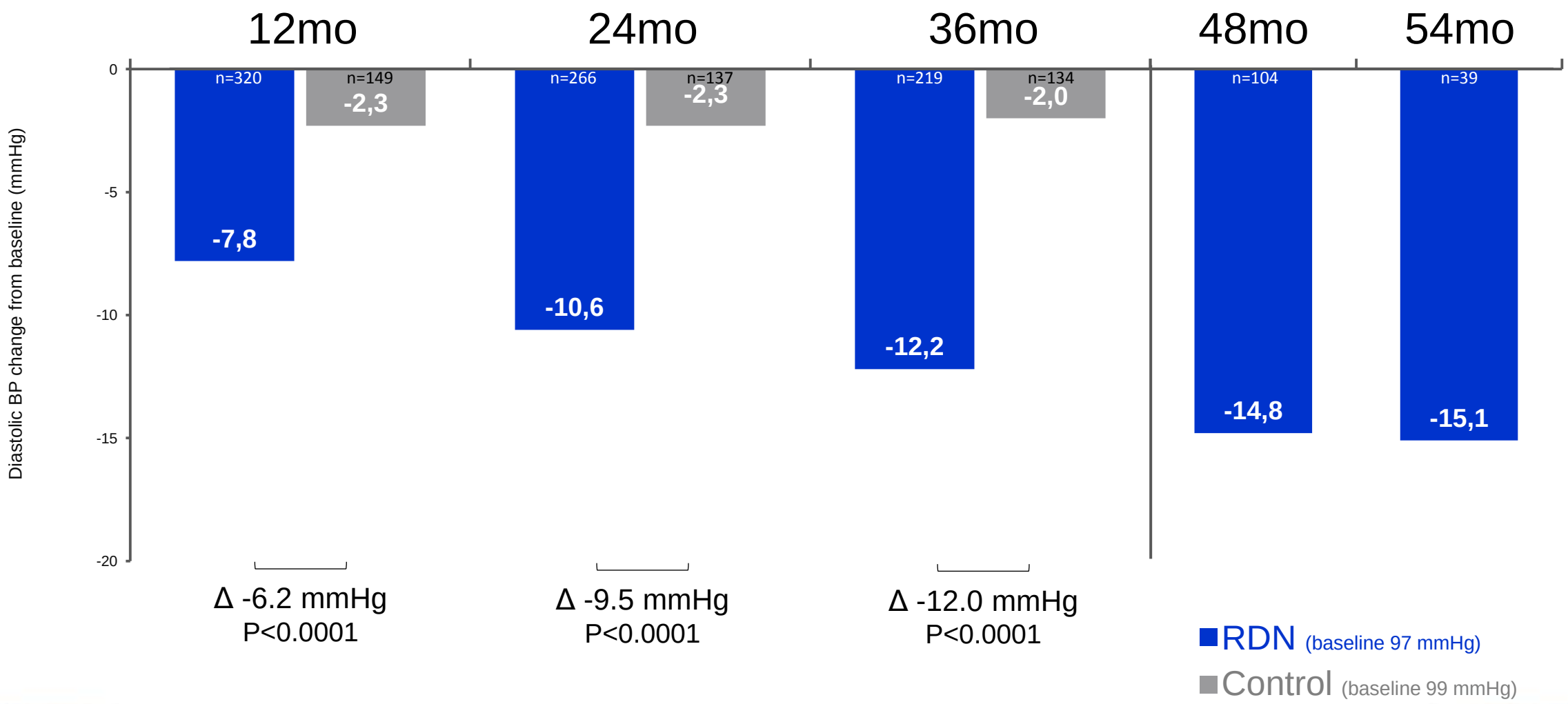
Symplicity® HTN - 3 Clinical Study



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

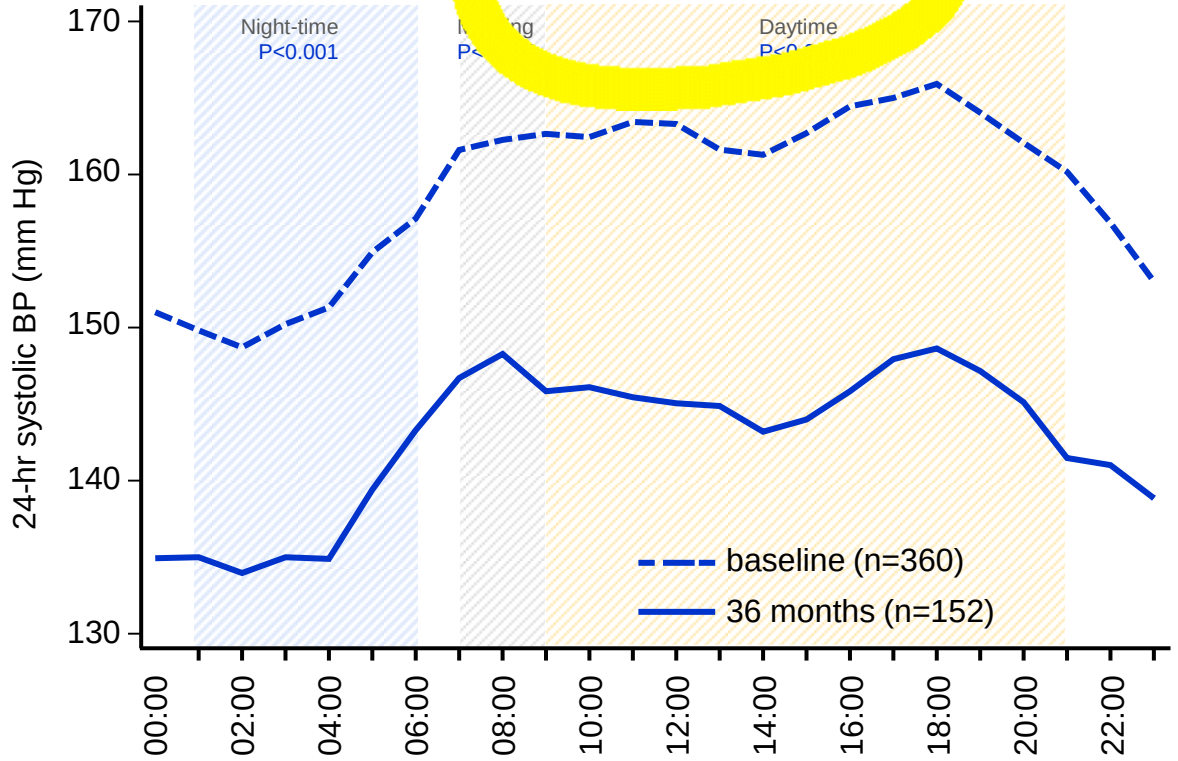
Treatment differences and p-values are ANCOVA adjusted for baseline BP.
Control blood pressure measures include LOCF for crossover patients from 6 months (blinded).
Data beyond 36 months are not reported for the control arm because sample size was too small for imputation.

24-Hour Systolic BP

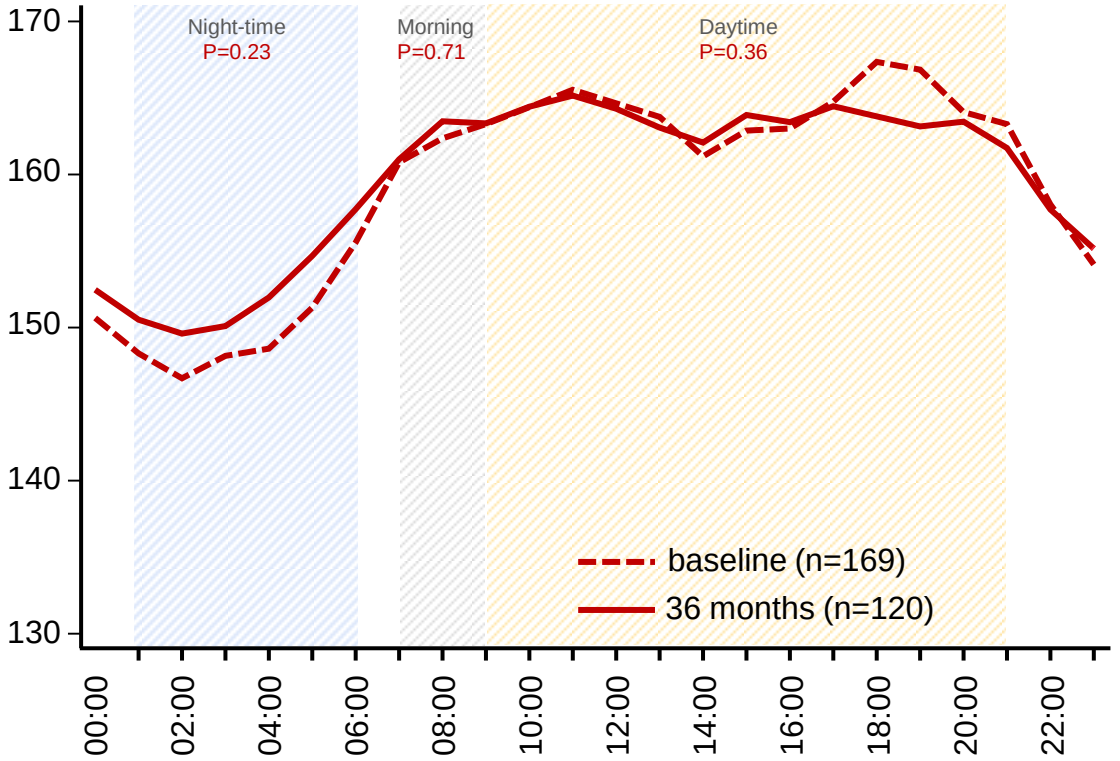
Baseline vs 36 Months

Symplicity® HTN - 3 Clinical Study

RDN



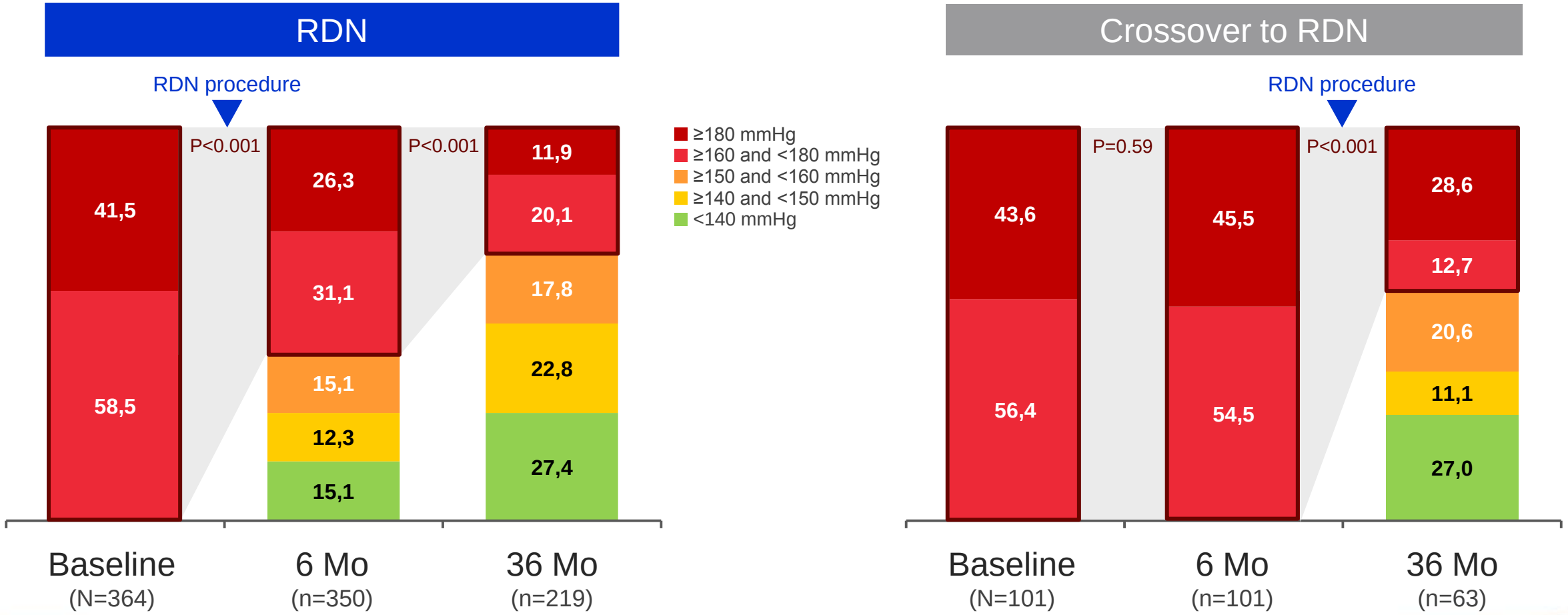
Control



Office Systolic BP Distribution

(% Patients)

Symplicity® HTN - 3 Clinical Study



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 at 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 clinically 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.

Potenciální kandidáti RDN

- Pacienti s resistentní hypertenzí
- Pacienti netolerující medikaci
- Pacienti preferující RDN po konsensuálním rozhodnutí
- Non-adherentní pacienti
- Pacienti s vyšším KV rizikem
- **Podmínkou je potvrzení hypertenze pomocí AMTK a vyloučení sekundární příčiny.**

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Děkuji za pozornost