Catheter-Based Renal Denervation (RDN)
Symplicity HTN Trials

Presentation Slide Deck

Staged Clinical Evaluation

Symplicity HTN-1

First-in-Man ✓

Series of Pilot studies ✓

Symplicity HTN-2 ✓
EU/AU Randomized Clinical Trial

USA

Symplicity HTN-3
US Randomized Clinical Trial
(upcoming)

EU/AU

Other Areas of Research:
Insulin Resistance, HF/Cardiorenal,
Sleep Apnea, More

Symplicity HTN-1


THE LANCET

Volume 373 · Number 9671 · Pages 1223-1310 · April 11-17, 2009 www.thelancet.com

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Bogusław Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

Lancet. 2009;373:1275-1281


Hypertension

Celebrating 30 Years: 1979 to 2009

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension

Durability of Blood Pressure Reduction Out to 24 Months

Symplicity HTN-1 Investigators*

Hypertension. 2011;57:911-917.

Initial Cohort – Reported in the *Lancet*, 2009:

-First-in-man, non-randomized

-Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)

- 12-month data

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Expanded Cohort – This Report (Symplicity HTN-1):

-Expanded cohort of patients (n=153)

-24-month follow-up

Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Medtronic

Baseline Patient Characteristics (n=153)

Demographics	Age (years)	57 ± 11
	Gender (% female)	39%
	Race (% non-Caucasian)	5%
Co-morbidities	Diabetes Mellitus II (%)	31%
	CAD (%)	22%
	Hyperlipidemia (%)	68%
	eGFR (mL/min/1.73m^2)	83 ± 20
Blood Pressure	**Baseline BP (mmHg)**	**176/98 ± 17/15**
	Number of anti-HTN meds (mean)	**5.1 ± 1.4**
	Diuretic (%)	95%
	Aldosterone blocker(%)	22%
	ACE/ARB (%)	91%
	Direct Renin Inhibitor	14%
	Beta-blocker (%)	82%
	Calcium channel blocker (%)	75%
	Centrally acting sympatholytic (%)	33%
	Vasodilator (%)	19%
	Alpha-1 blocker	19%

Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Procedure Detail & Safety (n=153)

- 38 minute median procedure time
  - Average of 4 ablations per artery
- Intravenous narcotics & sedatives used to manage pain during delivery of RF energy
- No catheter or generator malfunctions
- No major complications
- Minor complications 4/153:
  - 1 renal artery dissection during catheter delivery (prior to RF energy), no sequelae
  - 3 access site complications, treated without further sequelae

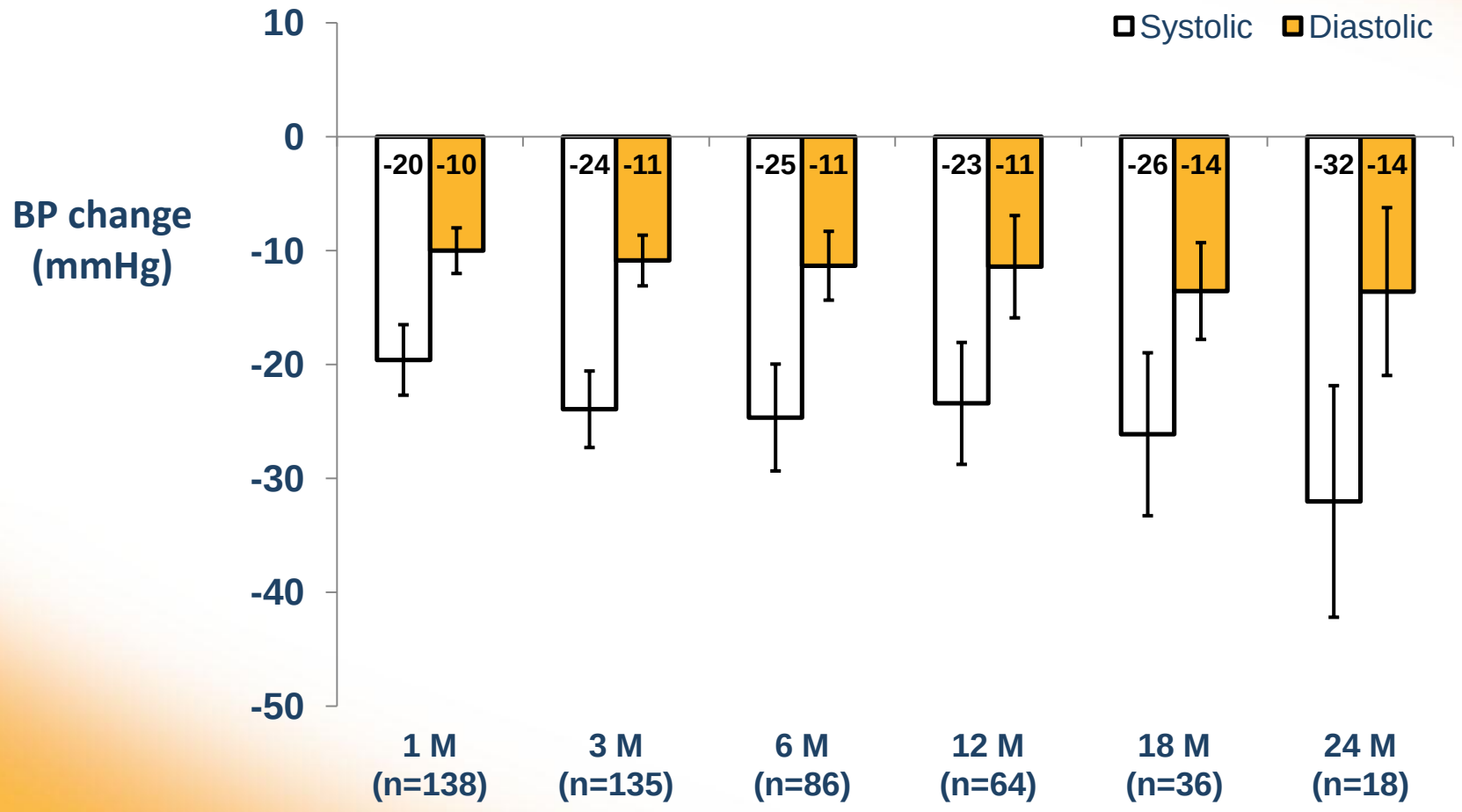
Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Chronic Safety

- 81 patients with 6-month renal CTA, MRA, or Duplex
  - No vascular abnormalities at any site of RF delivery
  - One progression of a pre-existing stenosis unrelated to RF treatment (stented without further sequelae)
- Two deaths within the follow-up period; both unrelated to the device or therapy
- No orthostatic or electrolyte disturbances
- No change in renal function at one year (Δ eGFR)
  - 12 Months: -2.9 mL/min/1.73m^2 (n.s.) (n=64)

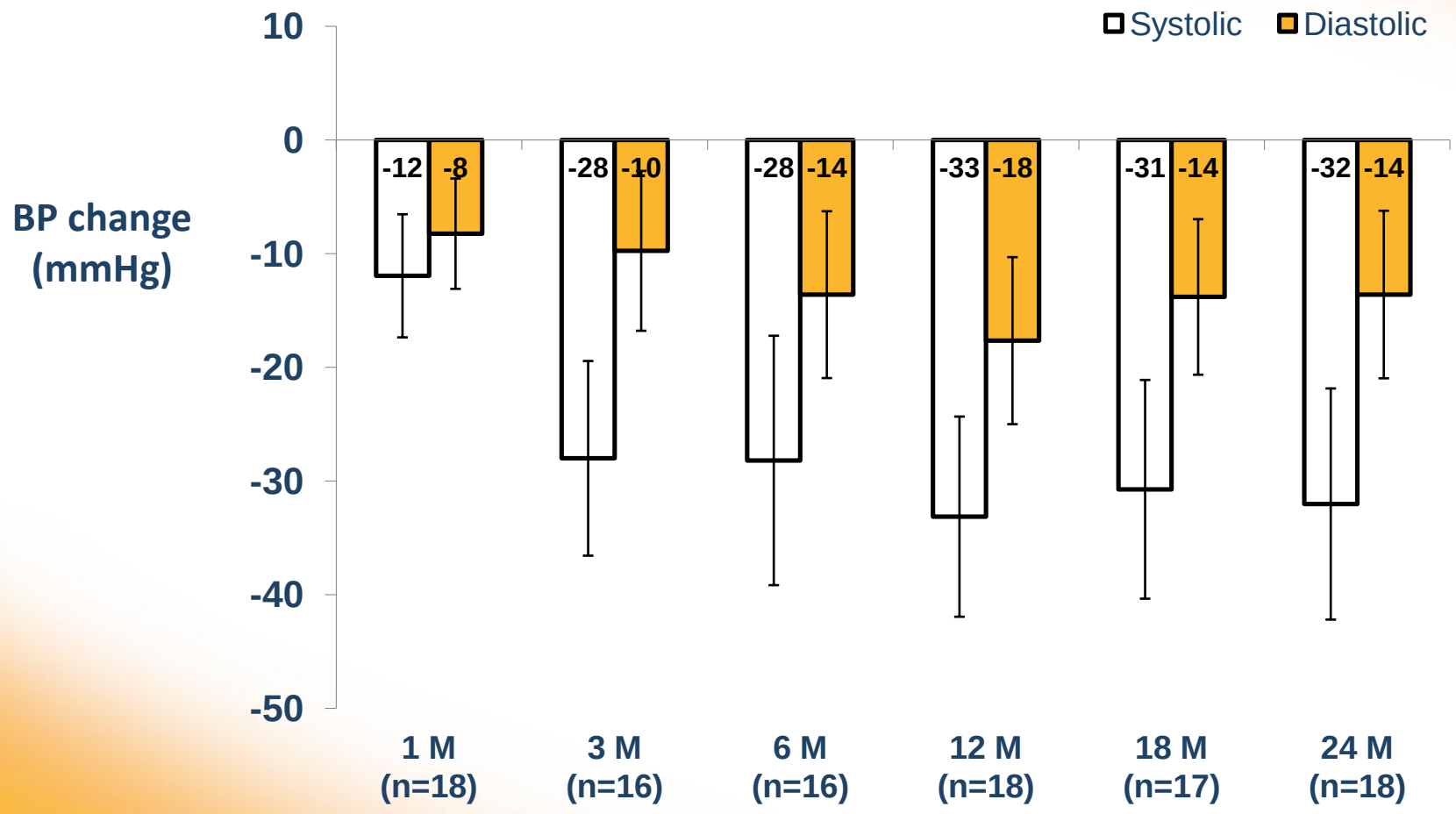
Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Significant, Sustained BP Reduction



Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Results for 18 Patients with 2-year Follow-up



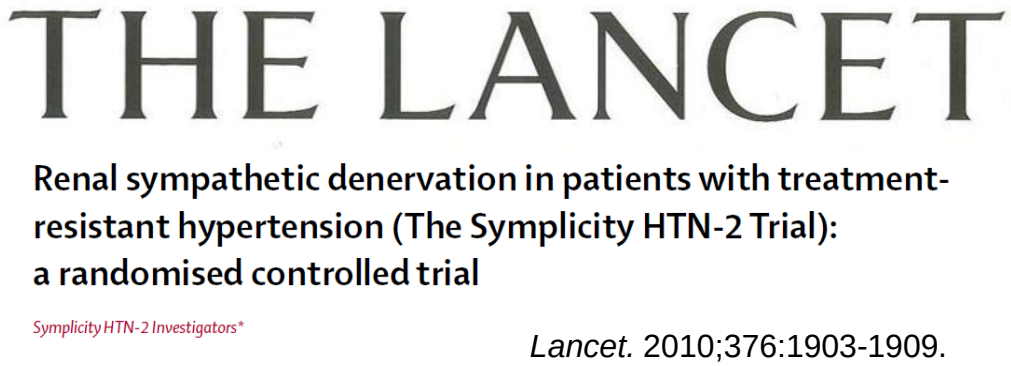
Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Medtronic

Office Systolic BP Distribution at Baseline, 12 Months, and 24 Months

Symplicity HTN-1 Investigators. Hypertension. 2011;57:911-917.

Symplicity HTN-2


THE LANCET

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Symplicity HTN-2 Investigators*

Lancet. 2010;376:1903-1909.

- **Purpose:** To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial
- **Patients:** 106 patients randomized 1:1 to treatment with renal denervation vs. control
- **Clinical Sites:** 24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence)

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Symplicity HTN-2 Trial

Inclusion Criteria:

- Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)
- Stable drug regimen of 3+ more anti-HTN medications
- Age 18-85 years

Exclusion Criteria:

- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- eGFR < 45 mL/min/1.73m^2 (MDRD formula)
- Type 1 diabetes mellitus
- Contraindication to MRI
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Symplicity HTN-2 Study Centers

Europe & Australia/NZ

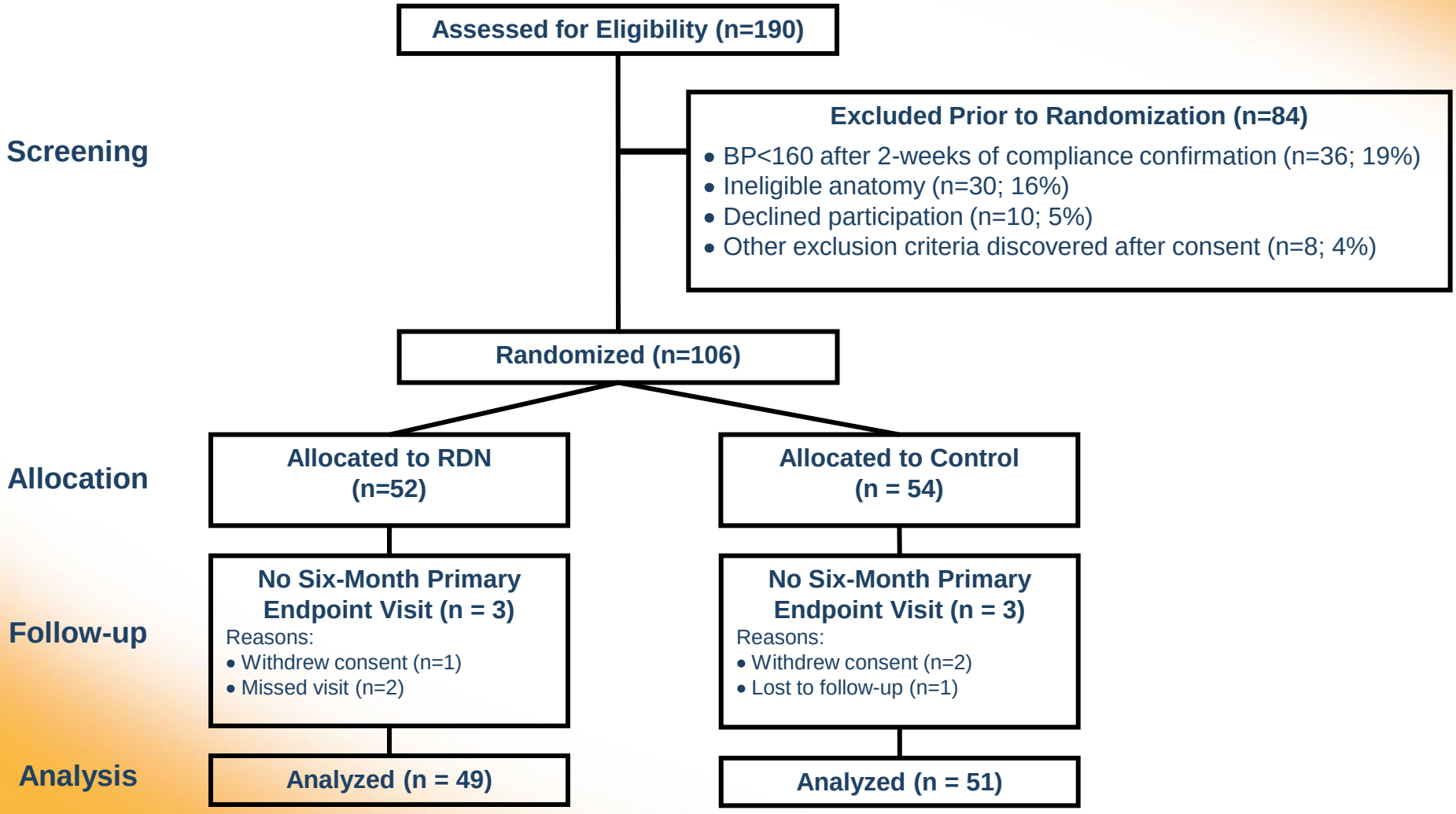
PI: Prof. Murray Esler

Universitätsklinikum des Saarlandes, Homburg, Germany
CardioVascular Center Frankfurt, Frankfurt, Germany
Universitätsklinikum Düsseldorf, Düsseldorf, Germany
Universität Erlangen-Nürnberg, Erlangen, Germany
William Harvey Research Institute, Queen Mary University of London and Barts, London, UK
Pauls Stradins Clinical University Hospital, Riga, Latvia
Assistance Publique des Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France
John Hunter Hospital, Newcastle, Australia
Cliniques Universitaires Saint-Luc, Brussels, Belgium
Universitaetsklinikum Schleswig-Holstein, Lübeck, Germany
Universität zu Köln, Köln, Germany
The Alfred Hospital, Melbourne, Australia
Universität Leipzig – Herzzentrum, Leipzig, Germany
Allgemeines Krankenhaus der Stadt Wien, Vienna, Austria
Samodzielna Pracownia Hemodynamiczna, Warsaw, Poland
Hospital 12 de Octubre, Madrid, Spain
St. Vincent's Hospital, Melbourne, Australia
Universitätsklinikum Essen, Essen, Germany
Kent and Canterbury Hospital, Canterbury, UK
University Hospital Zurich, Zurich, Switzerland
University of Glasgow, Glasgow, UK
Auckland City Hospital, Auckland, New Zealand
Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany
The John Paul II Hospital, Krakow, Poland

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Medtronic

Patient Disposition



Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Baseline Characteristics

	RDN (n=52)	Control (n=54)	p-value
Baseline Systolic BP (mmHg)	178 ± 18	178 ± 16	0.97
Baseline Diastolic BP (mmHg)	97 ± 16	98 ± 17	0.80
Age	58 ± 12	58 ± 12	0.97
Gender (% female)	35%	50%	0.12
Race (% Caucasian)	98%	96%	>0.99
BMI (kg/m^2)	31 ± 5	31 ± 5	0.77
Type 2 diabetes	40%	28%	0.22
Coronary Artery Disease	19%	7%	0.09
Hypercholesterolemia	52%	52%	>0.99
eGFR (MDRD, $ml/min/1.73m^2$)	77 ± 19	86 ± 20	0.013
eGFR 45-60 (% patients)	21%	11%	0.19
Serum Creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.2	0.003
Urine Alb/Creat Ratio (mg/g)†	128 ± 363	109 ± 254	0.64
Cystatin C (mg/L)††	0.9 ± 0.2	0.8 ± 0.2	0.16
Heart rate (bpm)	75 ± 15	71 ± 15	0.23

† n=42 for RDN and n=43 for Control, Wilcoxon rank-sum test for two independent samples used for between-group comparisons of UACR
†† n=39 for RDN and n=42 for Control

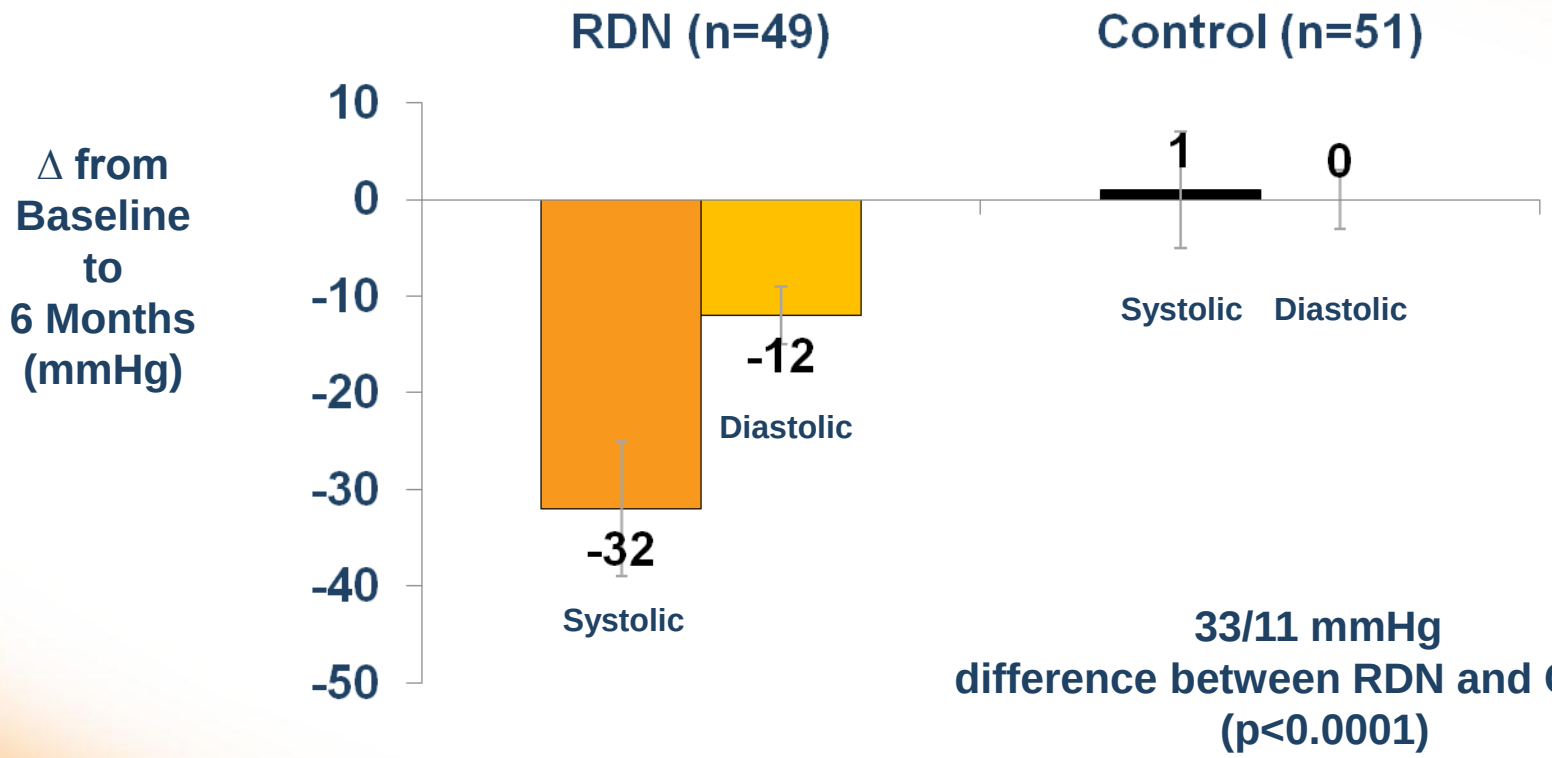
Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Baseline Medications

	RDN (n=52)	Control (n=54)	p-value
Number Anti-HTN medications	5.2 ± 1.5	5.3 ± 1.8	0.75
% patients on HTN meds >5 years	71%	78%	0.51
% percent patients on ≥5 medications	67%	57%	0.32
% patients on drug class:			
ACEi/ARB	96%	94%	>0.99
Direct renin inhibitor	15%	19%	0.80
Beta-adrenergic blocker	83%	69%	0.12
Calcium channel blocker	79%	83%	0.62
Diuretic	89%	91%	0.76
Aldosterone antagonist	17%	17%	>0.99
Vasodilator	15%	17%	>0.99
Alpha-1 adrenergic blocker	33%	19%	0.12
Centrally acting sympatholytic	52%	52%	>0.99

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Primary Endpoint: 6-Month Office BP



- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Medication Changes

Despite protocol guidance to maintain medications, some medication changes were required:

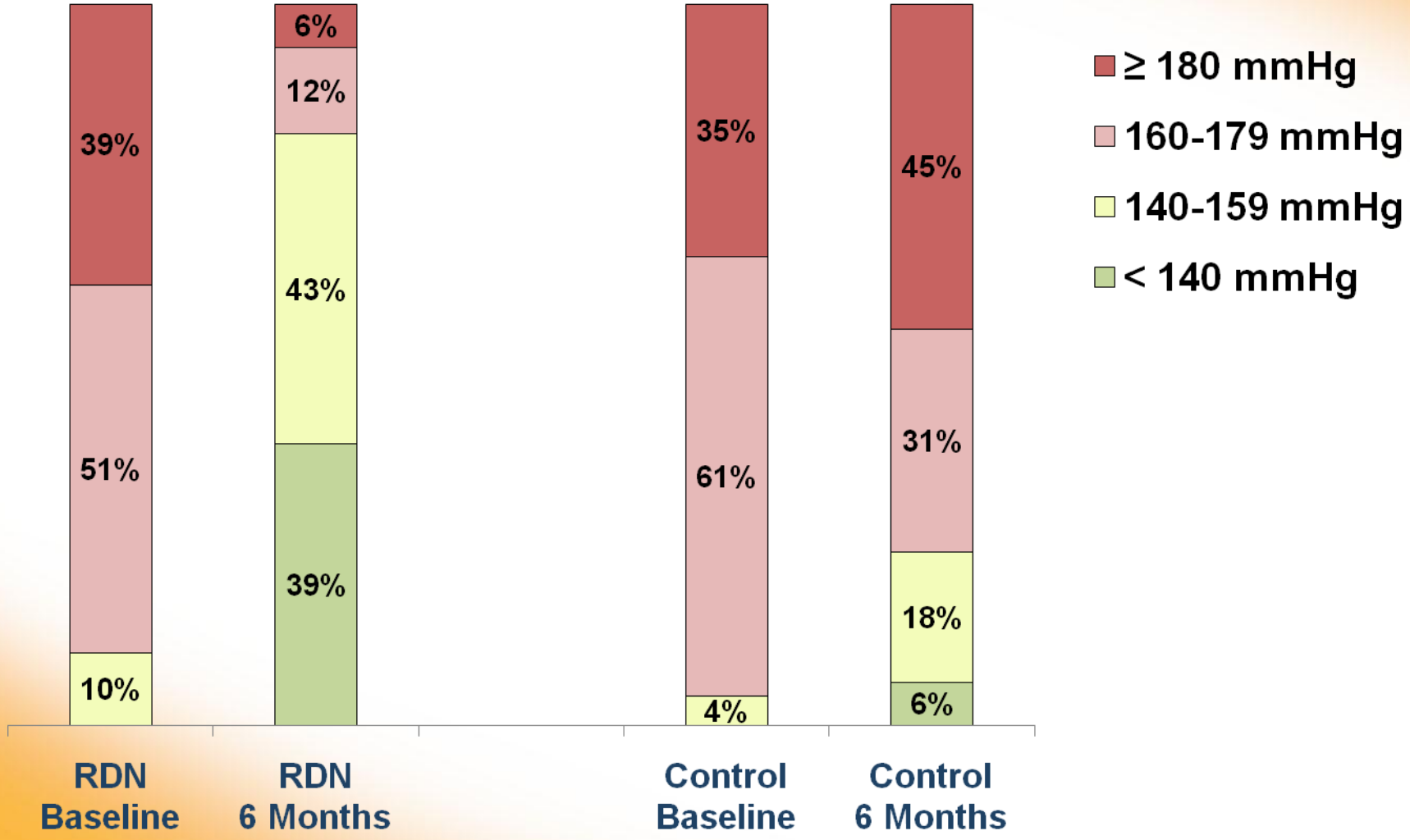
	RDN (n=49)	Control (n=51)	P-value
# Med Dose Decrease (%)	10 (20%)	3 (6%)	**0.04**
# Med Dose Increase (%)	4 (8%)	6 (12%)	0.74

Censoring BP after medication increases:

- Renal Denervation → Reduction of 31/12 ± 22/11 mmHg ($p<0.0001$ for SBP & DBP)
- Control → Change of 0/-1 ± 20/10 mmHg ($p=0.90$ & $p=0.61$ for SBP & DBP, respectively)

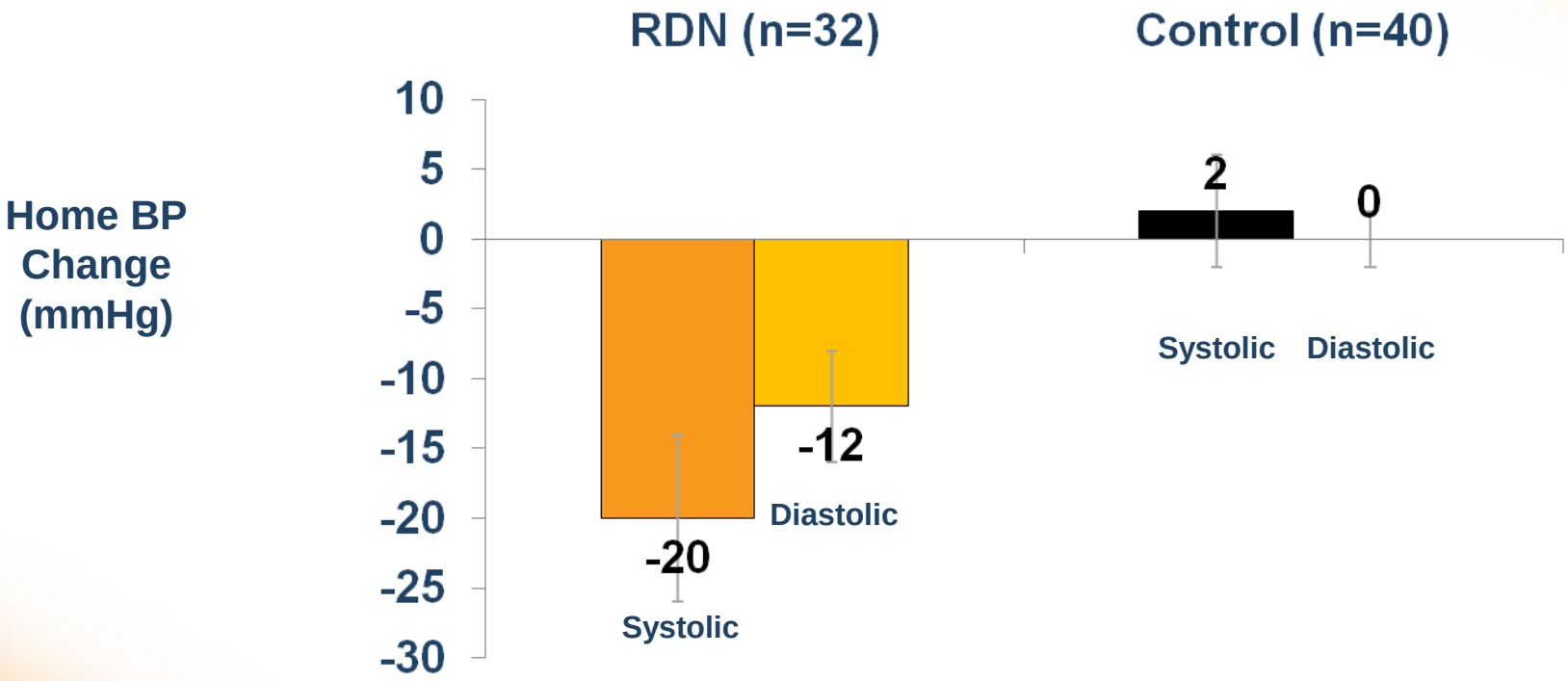
Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Office Systolic BP Distribution



Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Home & 24 Hour Ambulatory BP

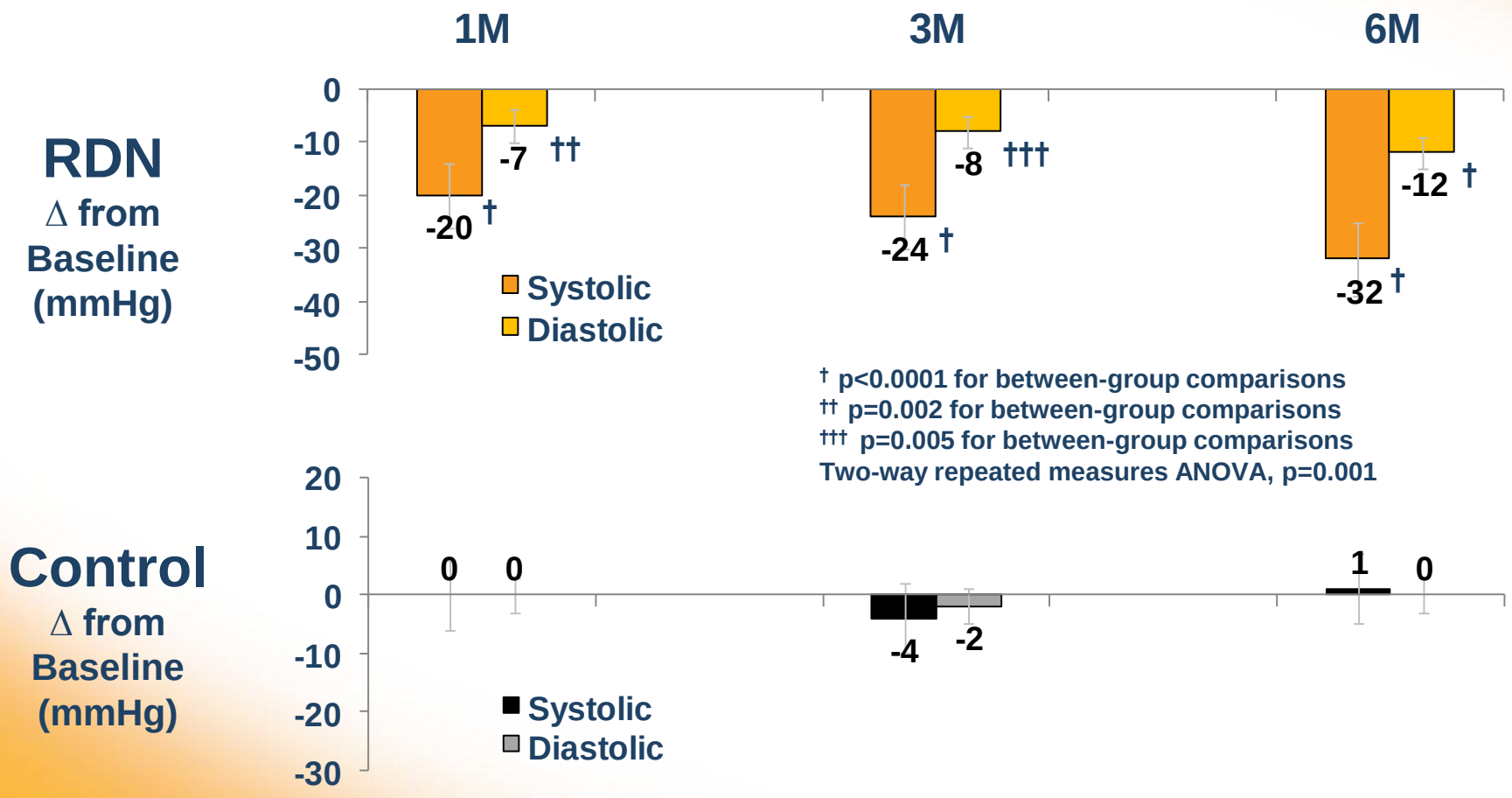


24-h ABPM:

- Analysis on technically sufficient (>70% of readings) paired baseline and 6-month
- RDN (n=20): -11/-7 mmHg (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)
- Control (n=25): -3/ -1 mmHg (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Time Course of Office BP Change



Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Procedural Safety

- No serious device or procedure related adverse events (n=52)
- Minor adverse events
  - 1 femoral artery pseudoaneurysm treated with manual compression
  - 1 post-procedural drop in BP resulting in a reduction in medication
  - 1 urinary tract infection
  - 1 prolonged hospitalization for evaluation of paraesthesias
  - 1 back pain treated with pain medications & resolved after one month
- 6-month renal imaging (n=43)
  - No vascular abnormality at any RF treatment site
  - 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy warranted)

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Renal Function

Δ Renal Function (baseline - 6M)	RDN Mean ± SD (n)	Control Mean ± SD (n)	Difference (95% CI)	p-value
eGFR (MDRD) (mL/min/1.73m^2)	0 ± 11 (49)	1 ± 12 (51)	-1 (-5, 4)	0.76
Serum Creatinine (mg/dL)	0.0 ± 0.2 (49)	0.0 ± 0.1 (51)	0.0 (-0.1, 0.1)	0.66
Cystatin-C (mg/L)	0.1 ± 0.2 (37)	0.0 ± 0.1 (40)	0.0 (-0.0, 0.1)	0.31

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Other Safety

	RDN (n=49)	Control (n=51)
Composite CV Events		
Hypertensive event unrelated to non-adherence to medication	3	2
Other CV events	0	0
Other Serious AEs		
Transient ischemic attack	1	2
Hypertensive event after abruptly stopping clonidine	1	0
Hypotensive episode resulting in reduction of medications	1	0
Coronary stent for angina	1	1
Temporary nausea/edema	1	0

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Lancet Conclusions

- Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, resulted in significant reductions in BP.
- The magnitude of BP reduction can be predicted to affect the development of hypertension-related diseases and mortality
- The technique was applied without major complications.
- This therapeutic innovation, based on the described neural pathophysiology of essential hypertension, affirms the crucial relevance of renal nerves in the maintenance of BP in patients with hypertension.
- Catheter-based renal denervation is beneficial for patients with treatment-resistant essential hypertension.

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.