ROLE OF RENAL DENERVATION
IN HYPERTENSION MANAGEMENT
THE NEXT CHAPTER BEGINS

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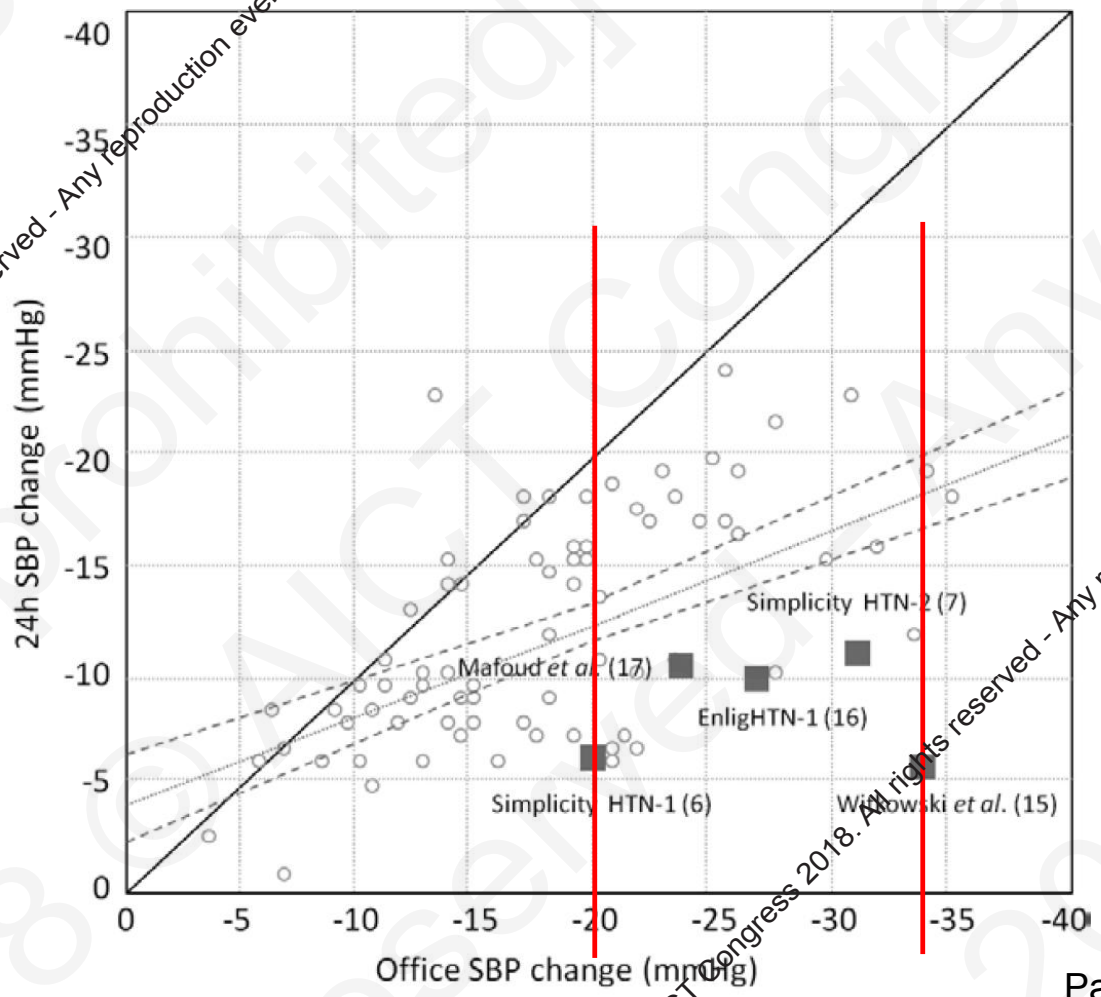
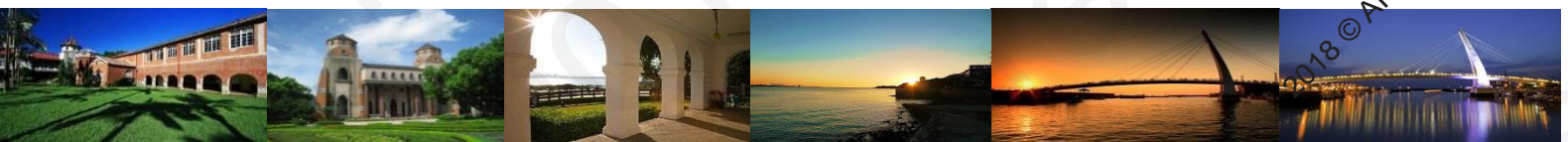
Further, Together

Phase 1 & 2 studies of RDN



Parati et al. *Circulation*. 2013;128:315-317.



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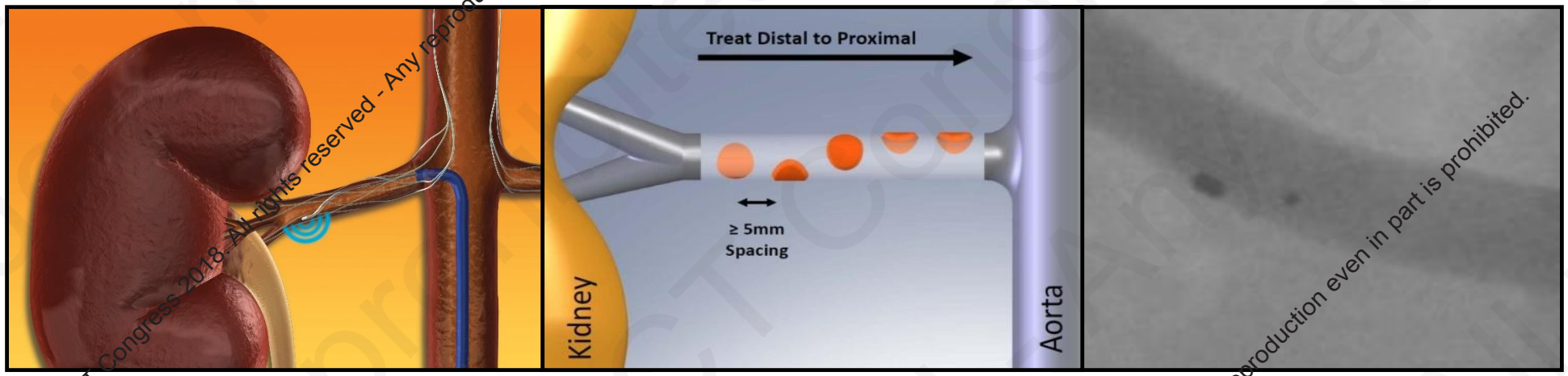
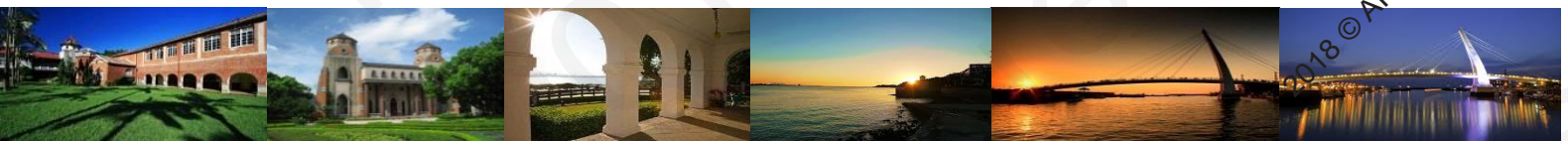
Safety should be concerned while doing an Invasive Procedure



- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF generator
  - Automated
  - Low power
  - Built-in safety algorithms



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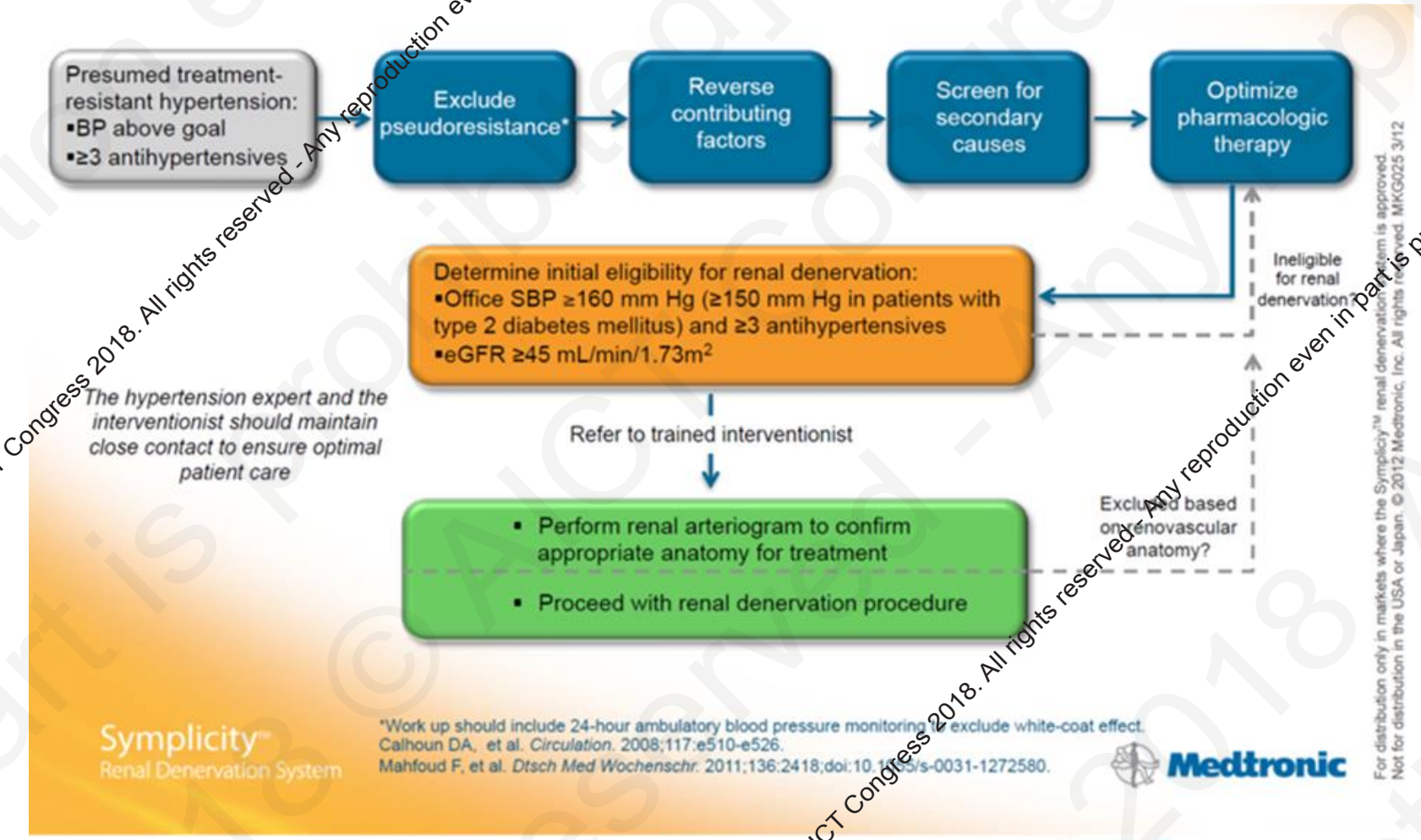
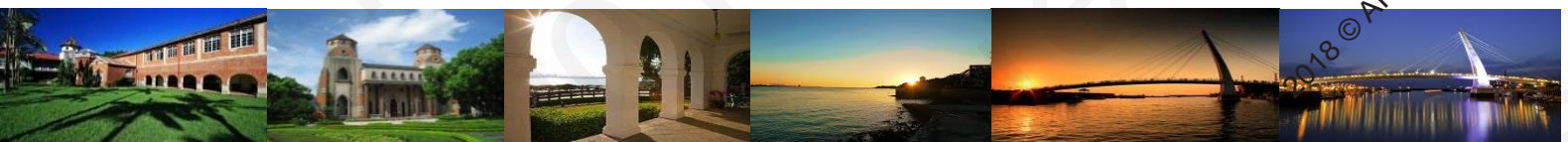
Past: True Resistant HTN





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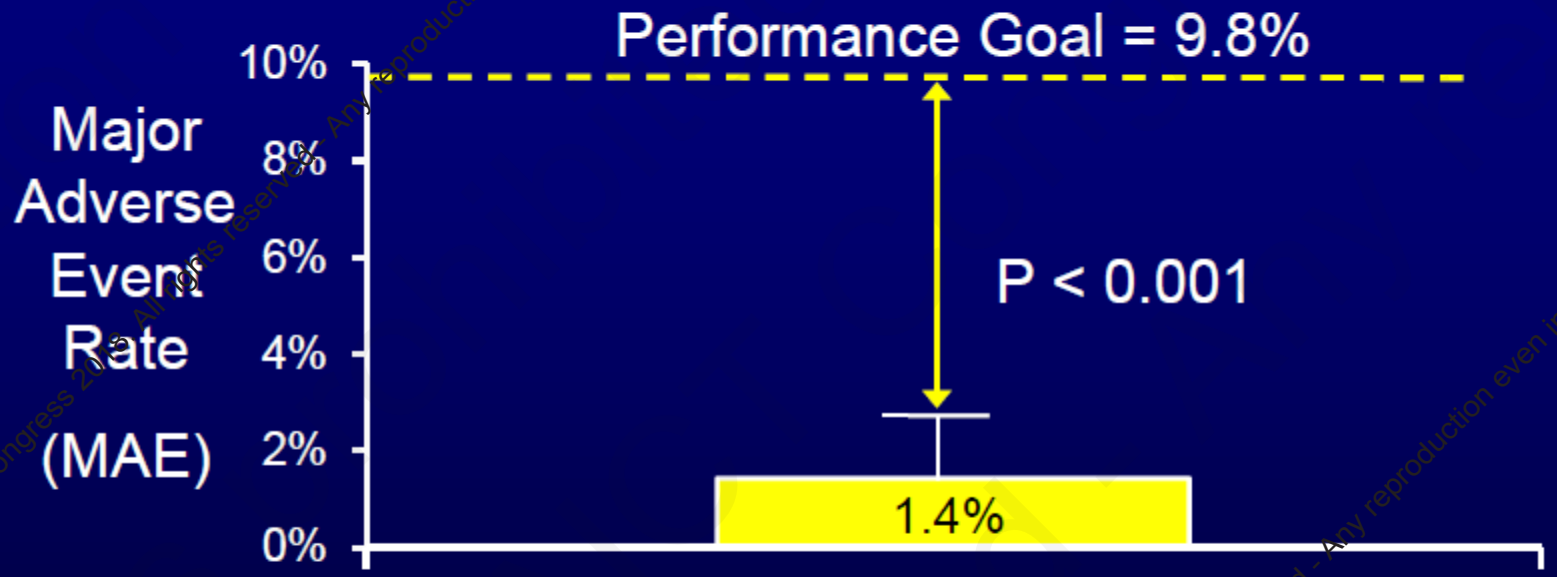
Primary Safety Endpoint

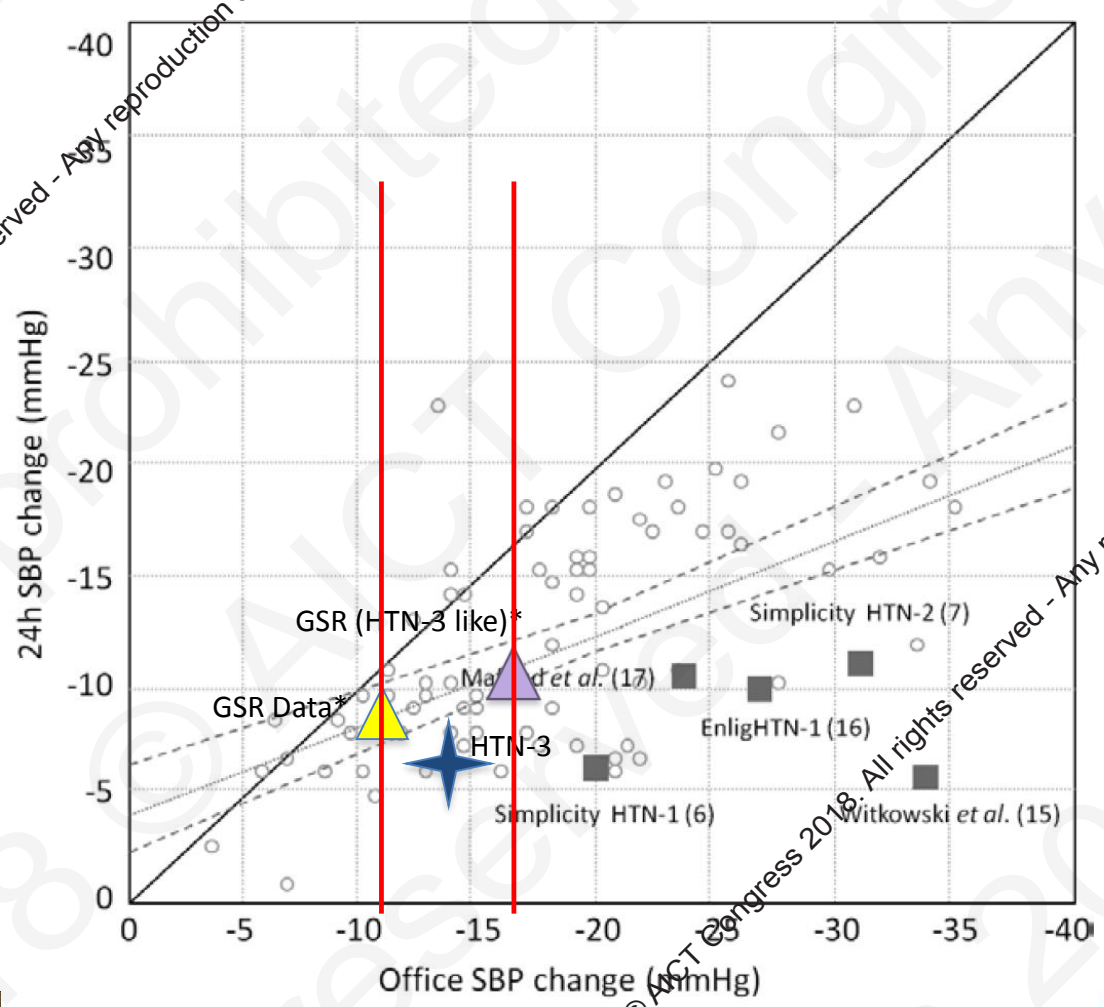
Symplicity HTN - 3 Clinical Study



	Renal Denervation (N=364)	Sham Procedure (N=171)	Difference [95% CI]	P*
MAE	1.4% (5/361)	0.6% (1/171)	0.8% [-0.9%, 2.5%]	0.67

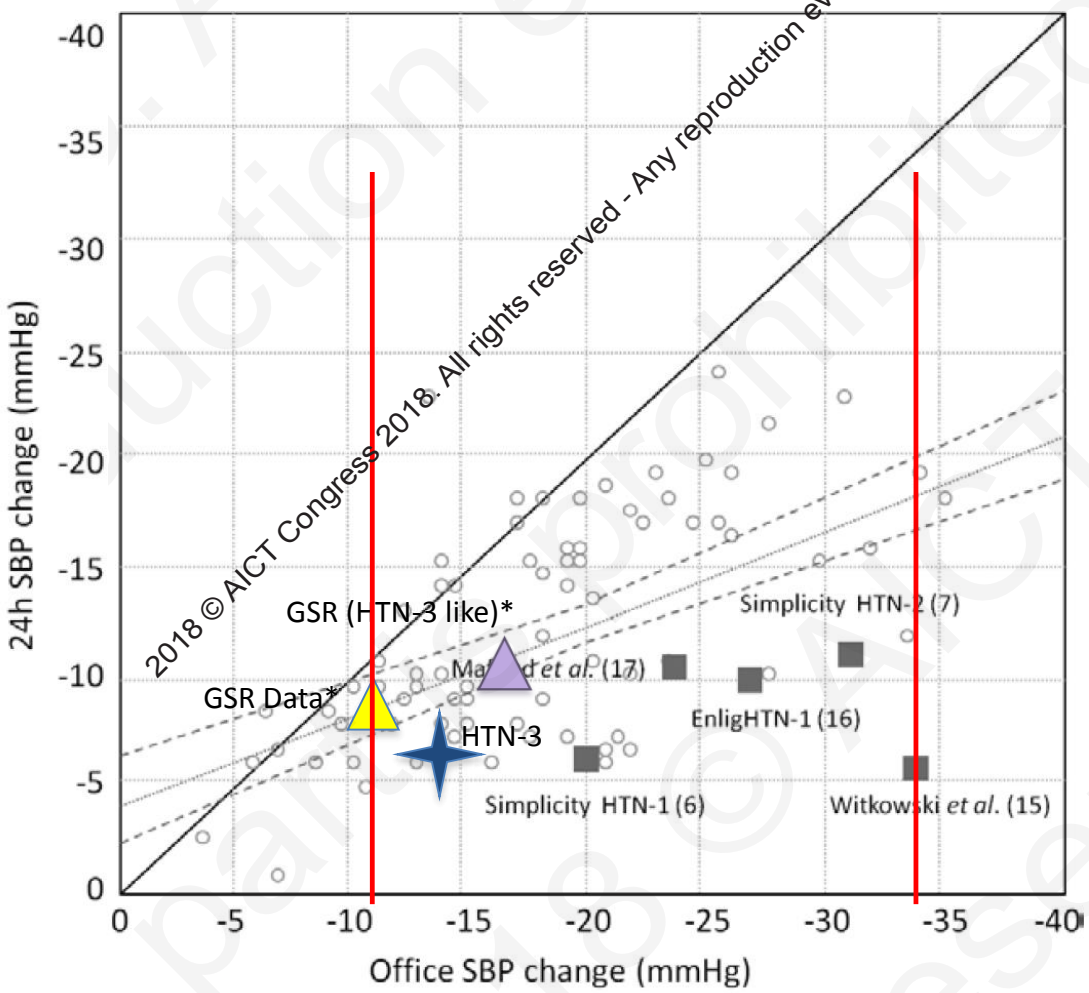
*comparison of MAE to control group

Primary Efficacy Endpoint

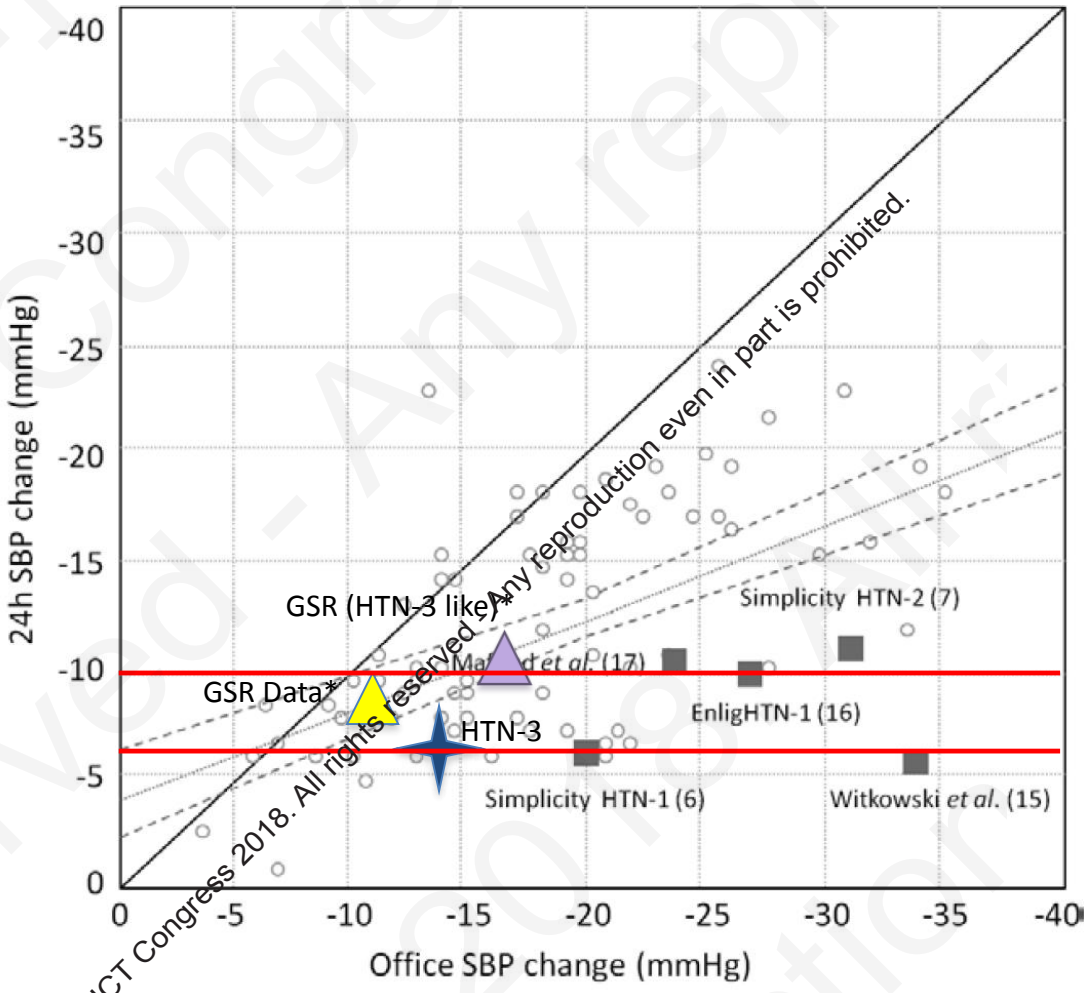


Parati et al. *Circulation*. 2013;128:1315-1317

ΔOBP 11-34 mmHg

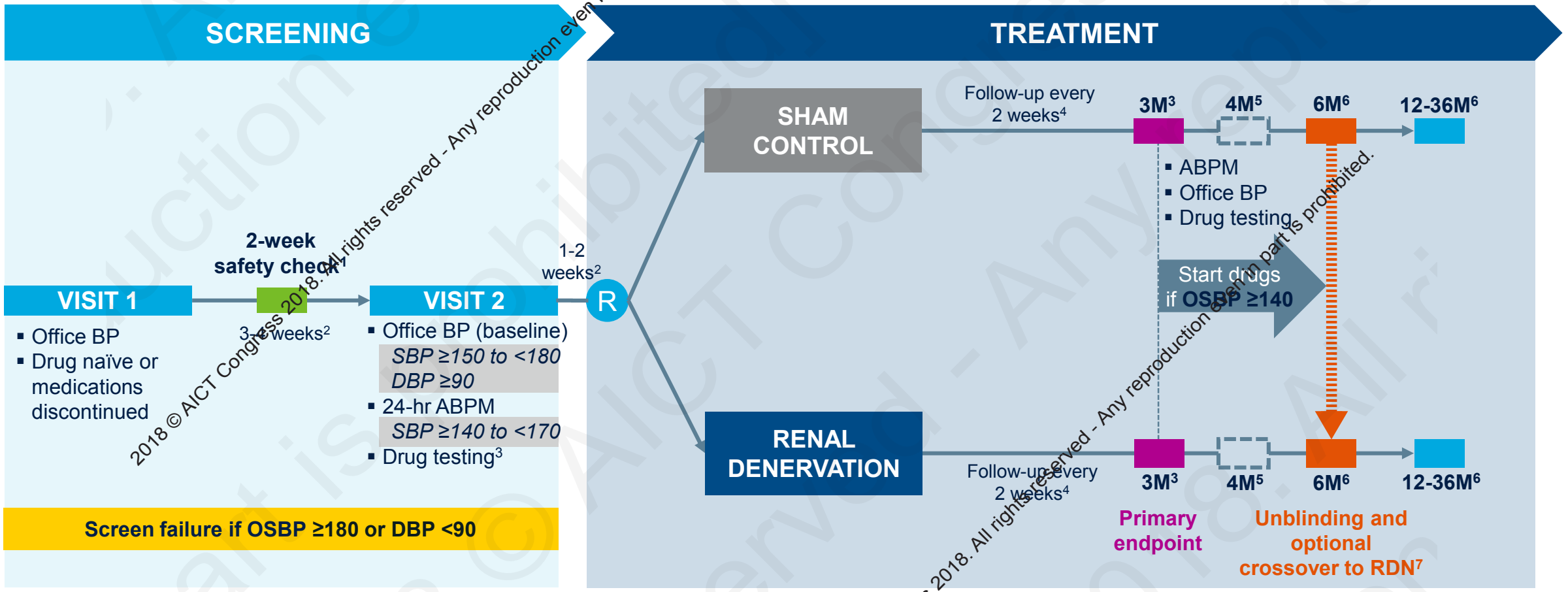


ΔABPM 6-10 mmHg



Parati et al. *Circulation*. 2013;128:1315-1327

SPYRAL HTN-OFF MED
RANDOMIZED, SHAM-CONTROLLED TRIAL



[1]Only for patients discontinuing anti-hypertensive medications. [2]According to scheduling. [3]Drug testing to ensure no medications are present. [4]Optional follow up at weeks 6 and/or 10 if the patient is not controlled. [5]Only for patients with BP ≥140 mmHg at 3M. [6]Drug testing to ensure prescribed medications are present (if on drug). [7]6 and 12 month renal imaging.

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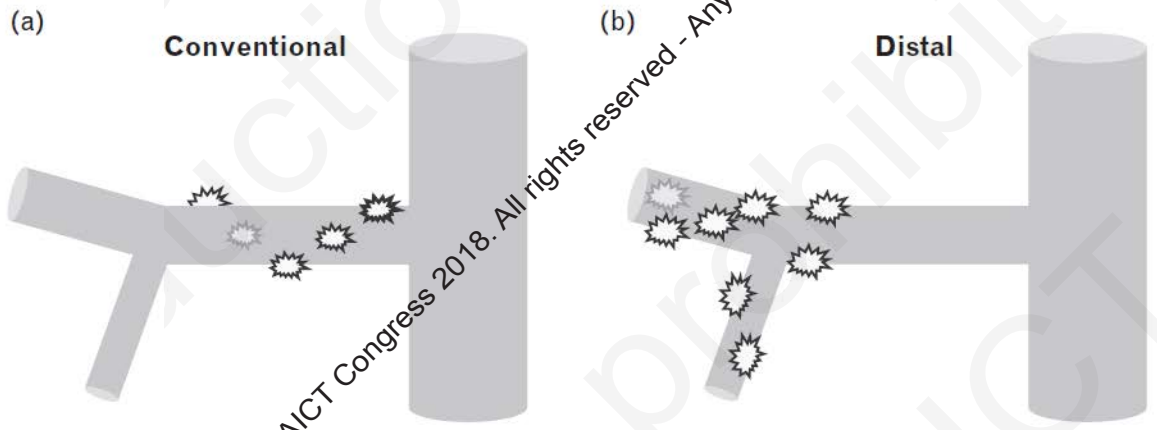
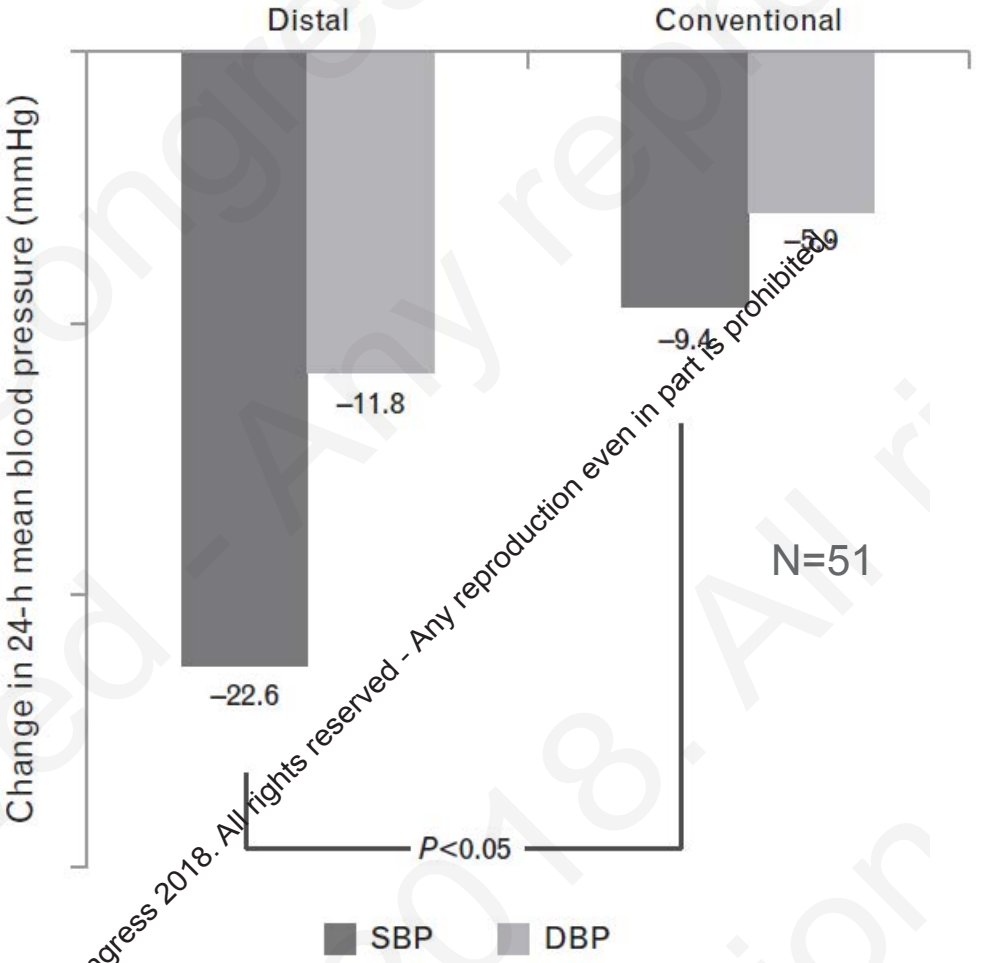
SPYRAL HTN CLINICAL PROGRAM

ADDRESSING CONFOUNDING FACTORS IDENTIFIED FROM SYMPLICITY HTN-3

	Medications	Patients	Procedure
SYMPLICITY HTN-3	Drug changes and variable patient adherence	Heterogenous study population	Procedural experience and variability
SPYRAL HTN	OFF and ON MED **studies with drug testing**	Excluding isolated systolic hypertension patients	**SPYRAL catheter, branch treatment**, case proctoring

RANDOMIZED COMPARISON OF DISTAL VS PROXIMAL RENAL ARTERY ABLATION





Pekarskiy S, et al. *J Hypertens*. 2017 Feb;35(2):369-375.

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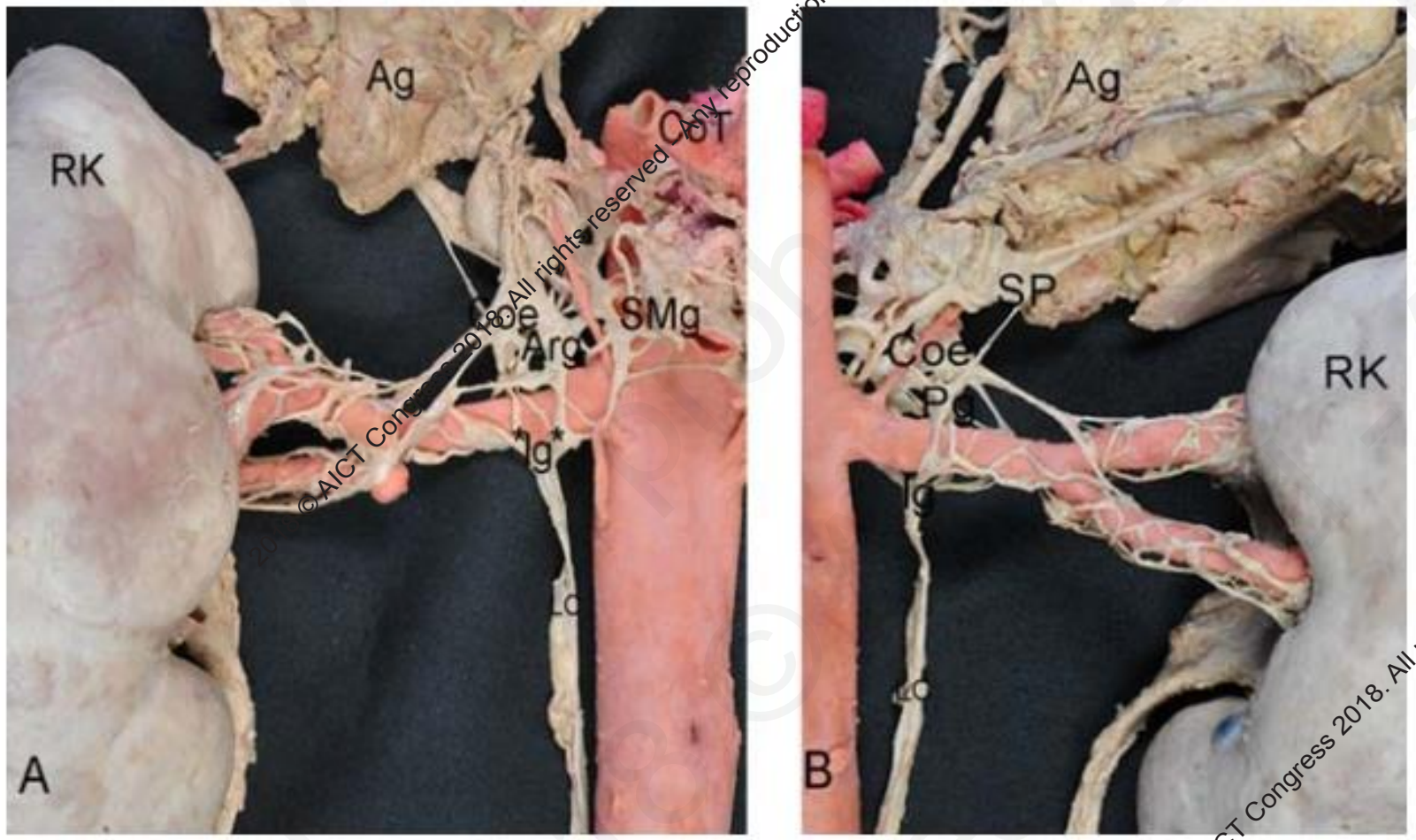
THE PROCEDURE WAS CHANGED TO REFLECT RENAL NERVE ANATOMY

RENAL NERVES HAVE A POSITIONAL BIAS ON RADIAL DISTANCE FROM ARTERIAL LUMEN; DISTAL NERVES ARE CLOSER



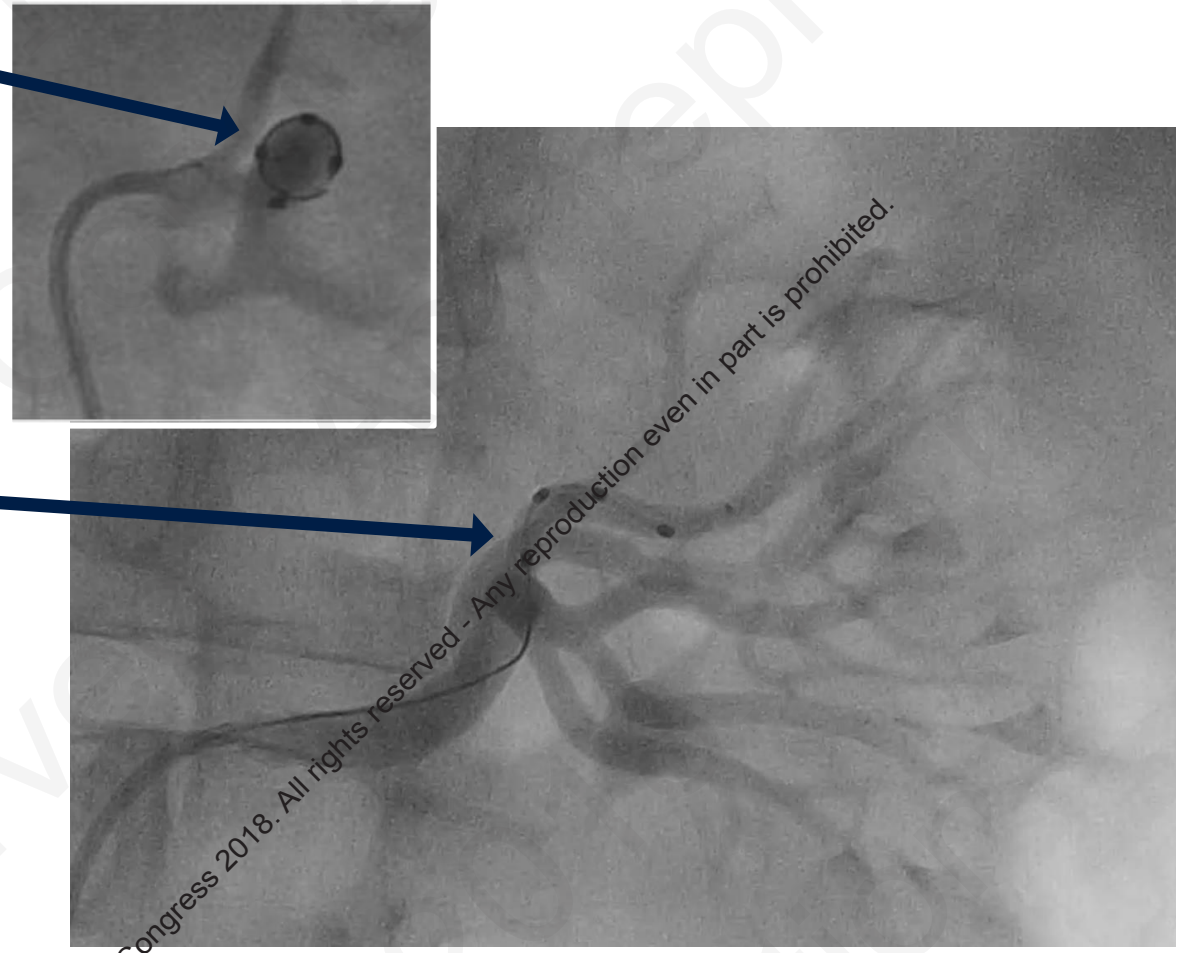
Mompeo et al. Clinical Anatomy. 2016. doi: 10.1002/ca.22720.

- Renal nerves generally originate from the aorta and arborise towards the kidney.
- Nerve fibers do not completely converge on the renal artery until beyond the main bifurcation.
- Accessory arteries, when present, have similar anatomical innervation patterns that mimic the main renal arteries.
- The procedure was changed to ablate as distally as possible where renal nerves congregate closer to the artery.
- Ablations are only done outside of the angiographic shadow of the kidney.

SPYRAL HTN CLINICAL PROGRAM

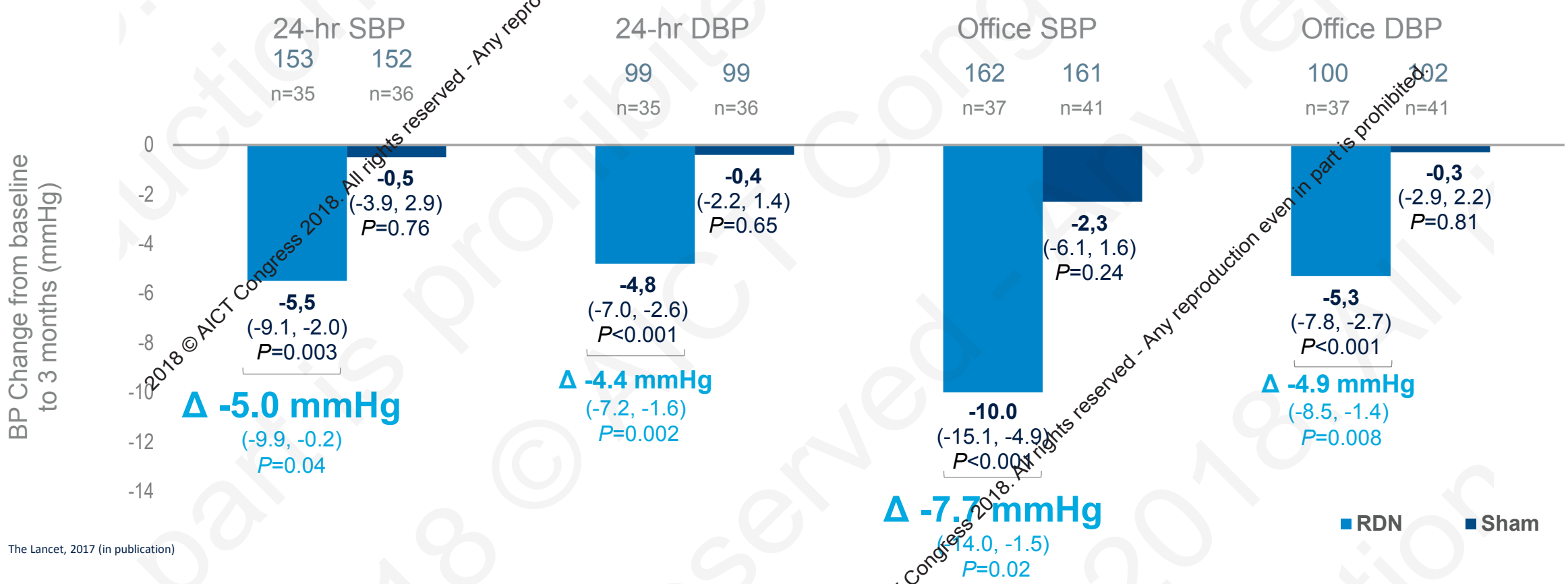
Study Device: Symplicity Spyral™ Catheter

- Multi-electrode catheter with **quadrantic** vessel contact for simultaneous ablation in up to 4 electrodes
- 60-second simultaneous energy delivery
- Vessel diameter range: 3 – 8 mm
- Flexible catheter allows **branch treatment**
- 6F guiding catheter compatible



SPYRAL HTN – OFF MED BLOOD PRESSURE CHANGE FROM BASELINE TO 3 MONTHS

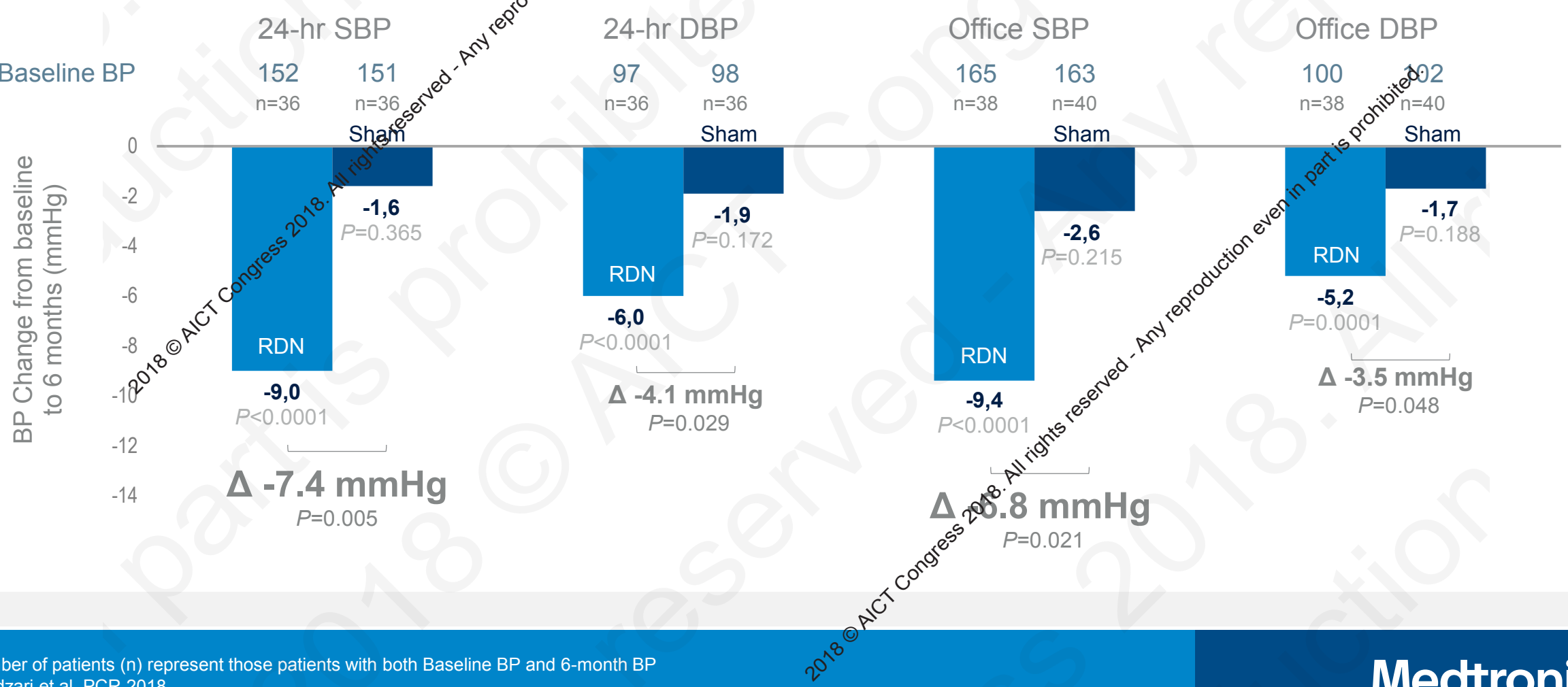
0 medication



The Lancet, 2017 (in publication)

SPYRAL HTN – ON MED BLOOD PRESSURE CHANGE FROM BASELINE TO 6 MONTHS

1-3 medications



Number of patients (n) represent those patients with both Baseline BP and 6-month BP
Kandzari et al, PCR 2018

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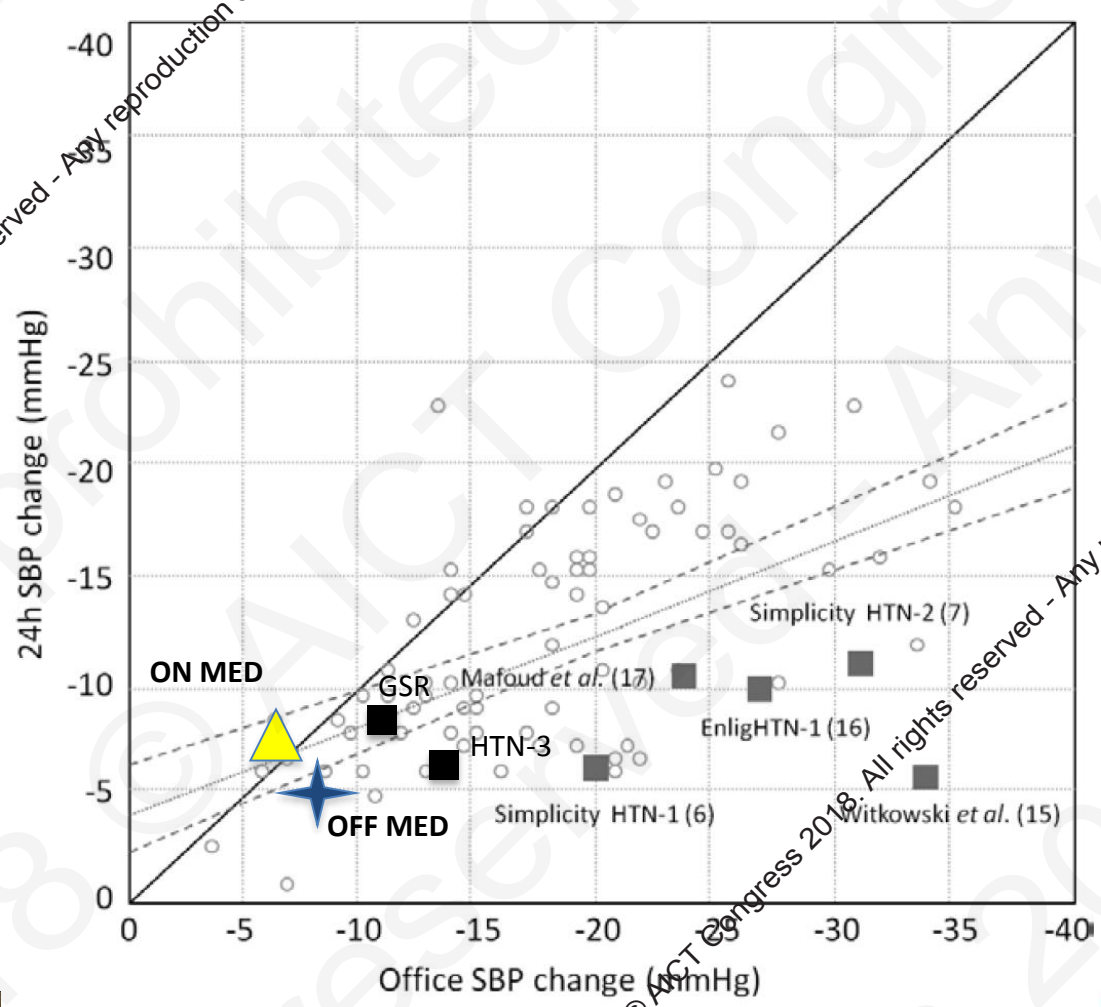
True Effect



Parati et al. *Circulation*. 2013;128:1315-1327

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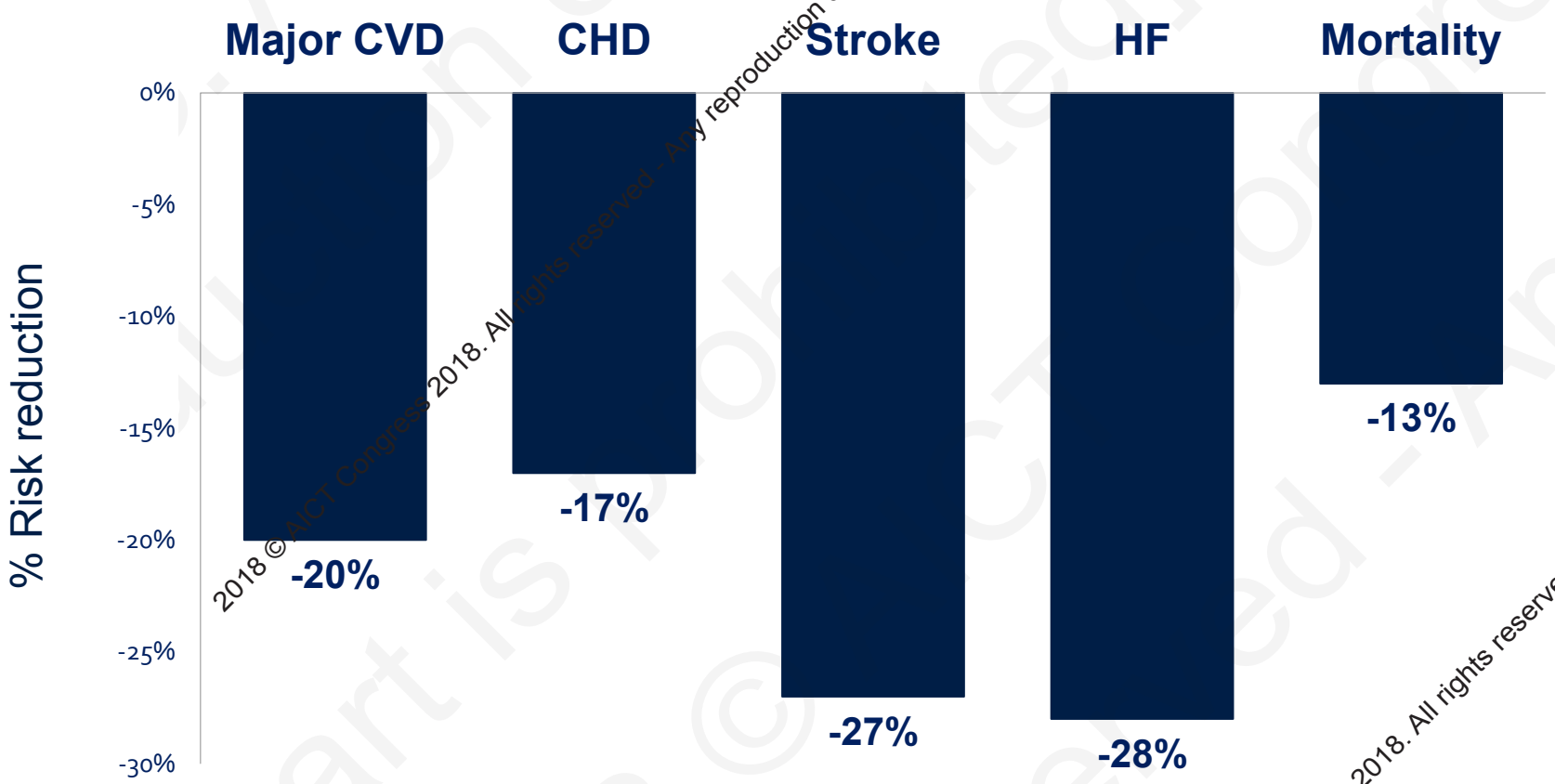
RISK REDUCTION FOR A 10 mmHG FALL IN OFFICE SBP



Irrespective of baseline BP or pre-existing conditions

n = 613,815

Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; 387: 957-67

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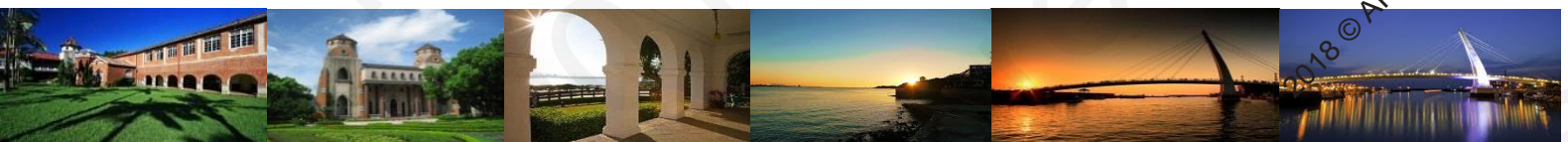
RDN is a **safe** 2nd-line antihypertensive therapy

Routine use not **YET** recommended

OBP
>150/90
+
ABPM
SBP >135
or
DBP >85
+
Rx MRA
+/- efficacy

- **Resistant**
  - ✓ ≥3 classes on max dose
  - ✓ ≥4 classes on ≥50% max dose
- **Nonadherent**
  - ✓ Patient's preference after unbiased discussion
  - ✓ Inscrutable cause, e.g. inconvenience, forgetfulness, and work style.
- **Intolerant**
  - ✓ Pregnancy concern or multiple drugs intolerance
- **Organ-damaged**
  - ✓ End-organ damage, e.g. CVA, ASCVD, CKD, and aortic dissection; with suitable anatomy
- **2°-caused**
  - ✓ BP uncontrolled despite thorough treatment
  - ✓ Irreversible, e.g. CoA and parenchymal CKD



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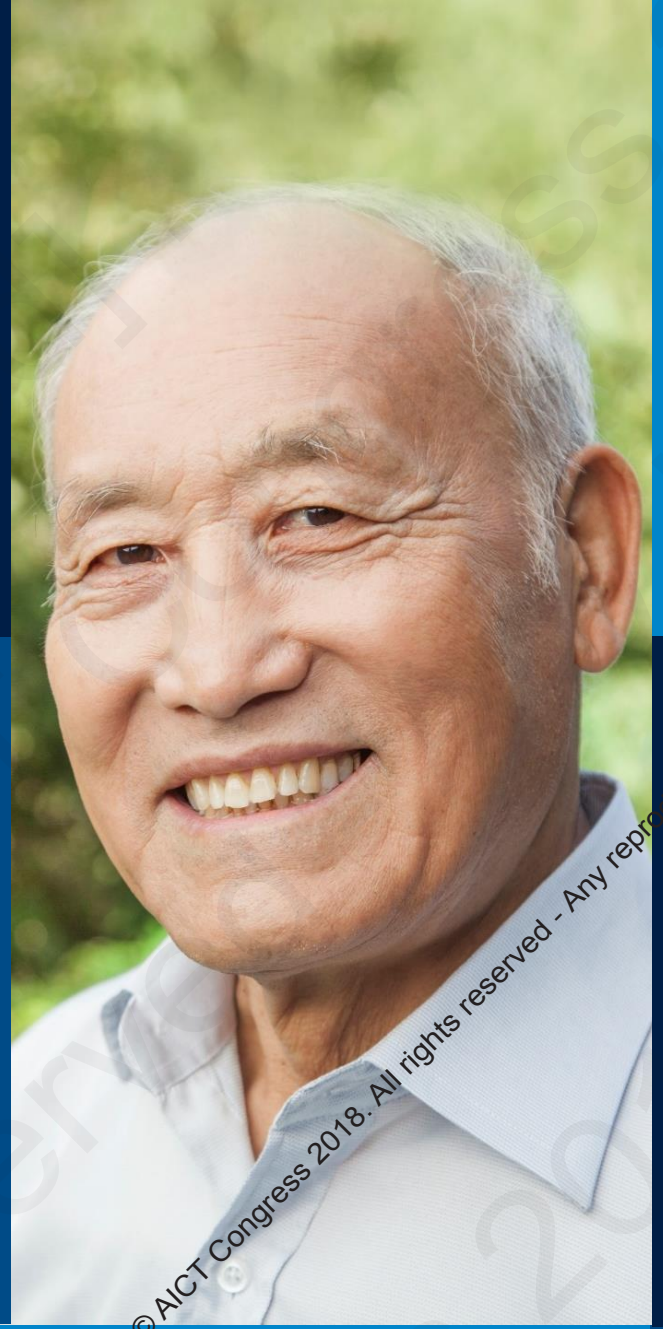
PATIENT ADHERENCE IS WORSE THAN YOU MIGHT THINK

Studies have shown doctors overestimate adherence. "Physicians generally tend to overestimate patient's adherence. Studies have demonstrated that clinicians' estimates of non-adherence are very poor, with a positive predictive value of only approximately 30%[1]. In fact,

detecting non-adherence in clinical practice is almost impossible."

- Jung O et.al., Journal of Hypertension. 2013, 31: 766-774



8.2%

of adults would give up two years of their lives to avoid adding one daily pill[2]

Nearly

50%

of patients become non-adherent to antihypertensive therapy within one year of initiating therapy[3]

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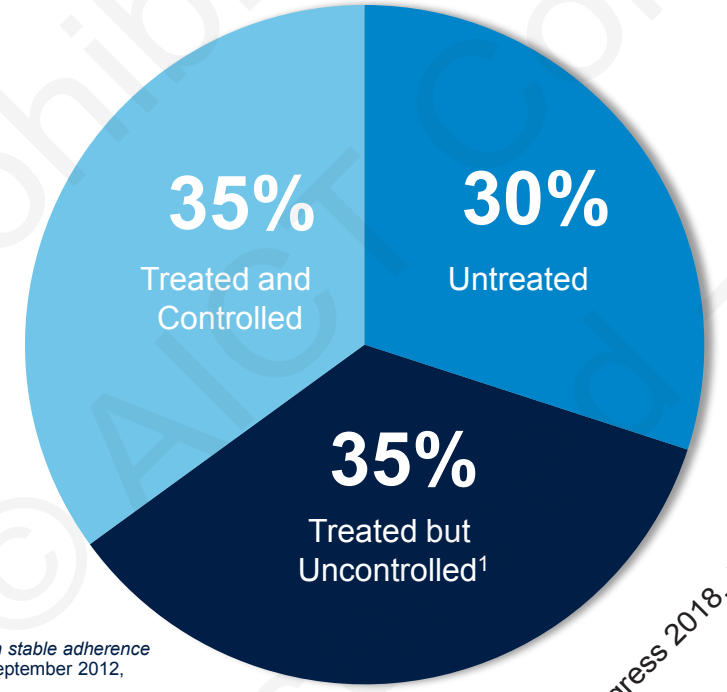
[1]30% claim – Jung O et.al., Journal of Hypertension. 2013, 31: 766-774.
[2]8.2% claim – Hutchins et.al., Circ Cardiovasc Qual Outcomes. 2015; 8. DOI:10.1161/CIRCOUTCOMES.114.001240
[3]50% claim – Jung O et.al., Journal of Hypertension. 2013, 31: 766-774

HYPERTENSION IS THE SINGLE LARGEST CONTRIBUTOR TO DEATH

HTN is estimated to have **added $18.6B in avoidable costs**[1] to the US health care[2] system alone



Avoidable costs include emergency, hospital, and outpatient visits that could be avoided with stable adherence

[1]Uncontrolled defined as ≥140 mm Hg systolic or ≥ 90 mm Hg diastolic. CDC Vital Signs September 2012, NHANES 2003–2010

[2]*Investigational Use Only in the USA*

[3]Kearney PM et al. *The Lancet*. 2005;365:217–223.

[4]World Health Organization. World Health Report 2002: Reducing risks, promoting healthy life. Geneva, Switzerland.

[5]Messerli FH et al. *The Lancet*. 2007;370:591–603.

HYPERTENSION REMAINS A MAJOR HEALTH BURDEN

1 IN 3 ADULTS HAVE HYPERTENSION[3]

1B PEOPLE WORLDWIDE[4]

1.6B BY 2025[5]

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ADEHERENCE TO MEDICATION: PATIENTS ARE SHOWING THEIR PREFERENCE

ACTIONS SPEAK LOUDER THAN WORDS!

For every 100 prescriptions written…

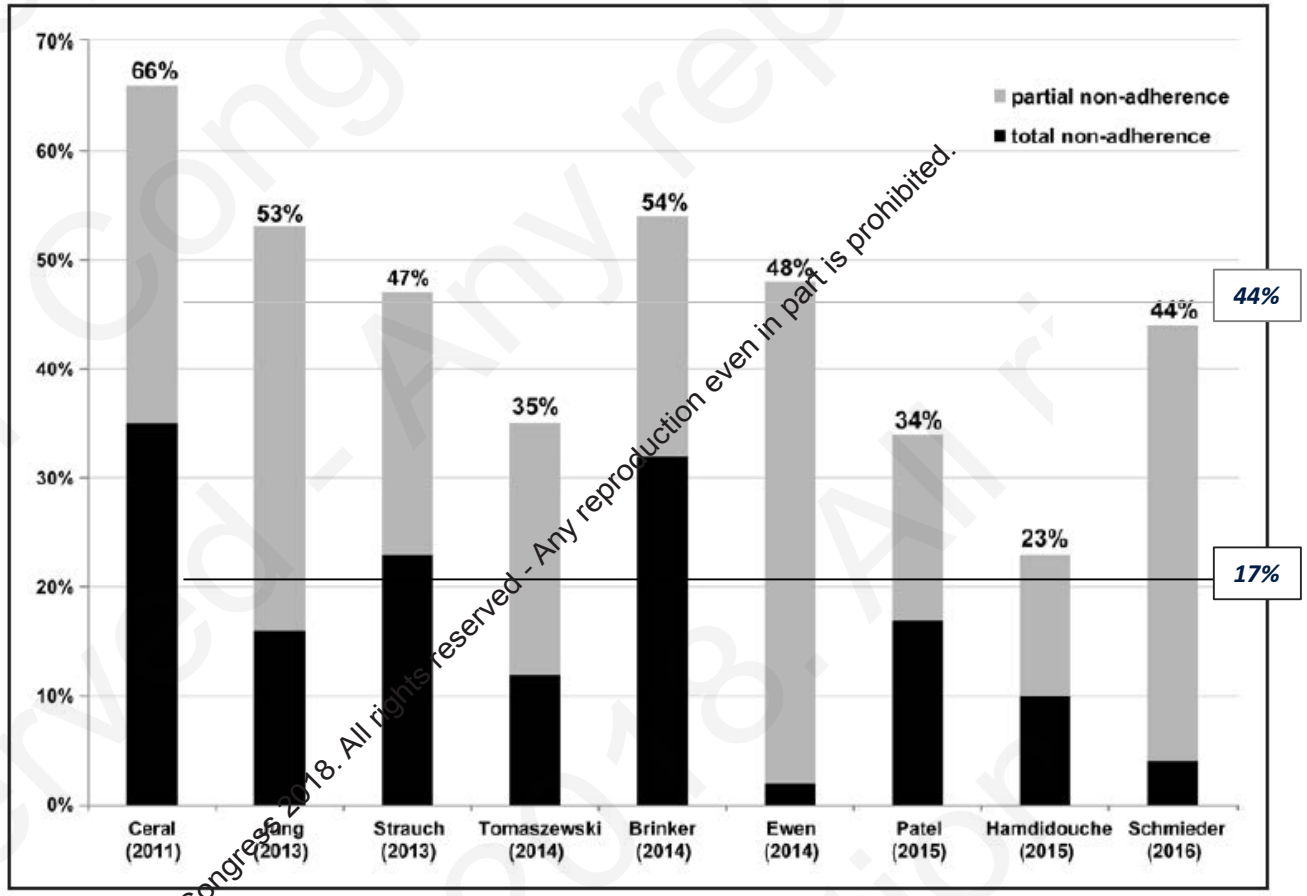
50 Rx picked-up

25 Taken properly

15 Rx re-filled

National Association of Chain Drug Stores Pharmacies: Improving Health, Reducing Costs. July 2010. Based on IMS Health data.

PROPORTION OF POOR OR NONADHERENCE ACCORDING TO DRUG MONITORING IN DIFFERENT COHORTS OF PATIENTS WITH APPARENTLY RESISTANT HYPERTENSION.



Elena Berra et al. Hypertension. 2016;68:297-306

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RECENT 4,000-PT STUDY TO IMPROVE ADHERENCE SHOWED MINOR BENEFIT

STIC2IT: STUDY OF TELE-PHARMACY INTERVENTION FOR CHRONIC DISEASES

STIC2IT: Results of the Study of a Tele-pharmacy Intervention for Chronic Diseases to Improve Treatment Adherence

Purpose: Investigation into a tele-pharmacy intervention to improve medication adherence.

Trial Design: randomized trial of patients with poor control and/or medication adherence with either HTN, diabetes, or hyperlipidemia. 14 primary care practices randomized to the tele-pharmacy intervention or routine care. The intervention involved pharmacist communication and feedback with the patient via phone, text, and mail and with their physician. 1 year f/u.

Primary Endpoint: adherence to medications.

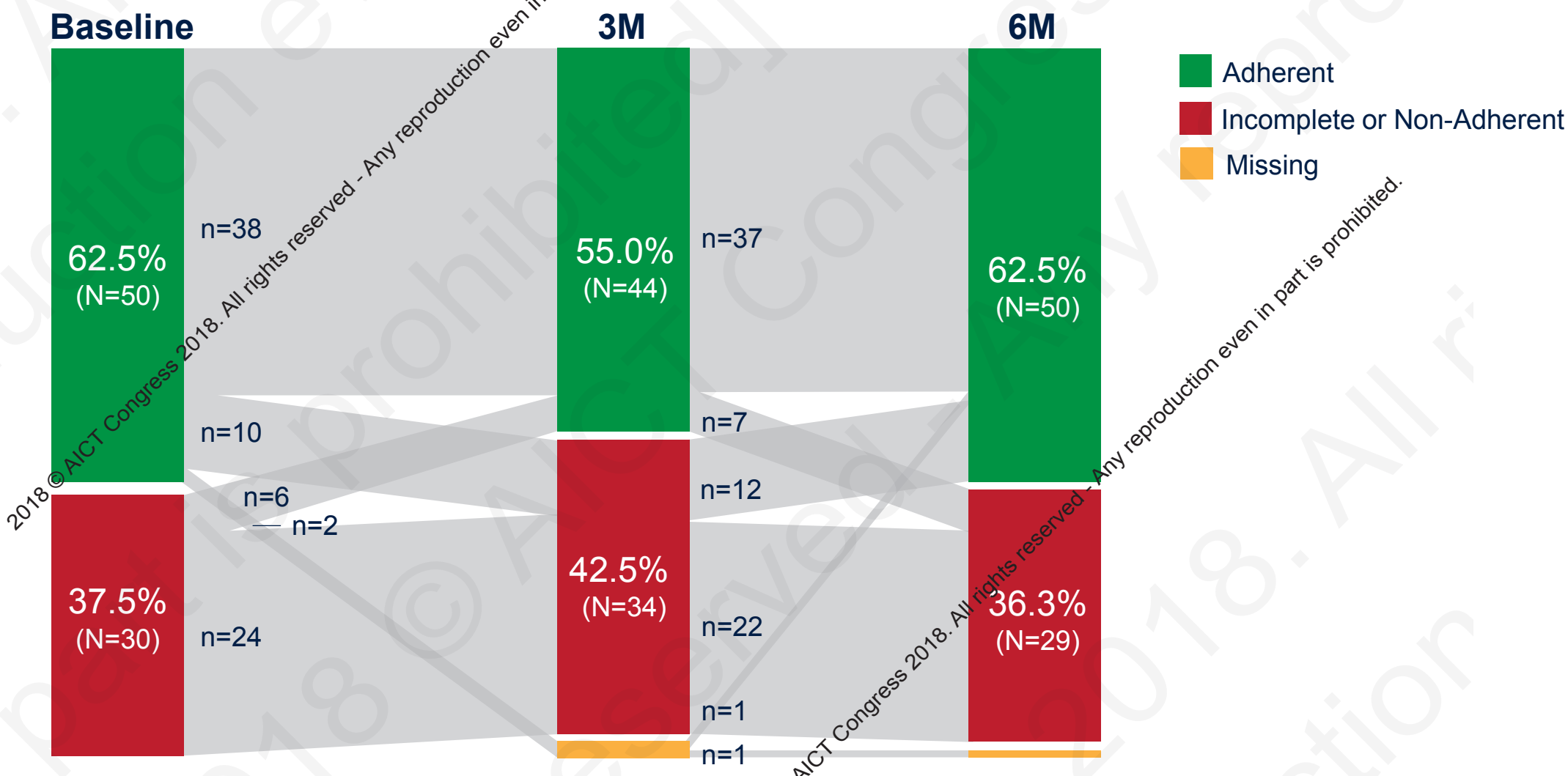
	Usual Care	Intervention	
Adherence	42.1%	46.2%	% Improvement 4.7% intention to treat 10.4% as treated
Disease Control – all conditions	23.4%	23.4%	P=0.98

Conclusion: Tele-pharmacy Intervention improved adherence to medication, but did not improve clinical outcomes.

Kumar et al., presented at AHA 2017

SPYRAL HTN – ON MED

Medication Adherence



Drug testing of urine and serum by tandem HPLC and mass spectroscopy. Medication adherence defined as detectable levels of all prescribed antihypertensive medications at each follow-up visit and includes cases in which an extra antihypertensive medication was also detected.

Kandzari D, et al, *Lancet*. 2018;391:2346-2355.

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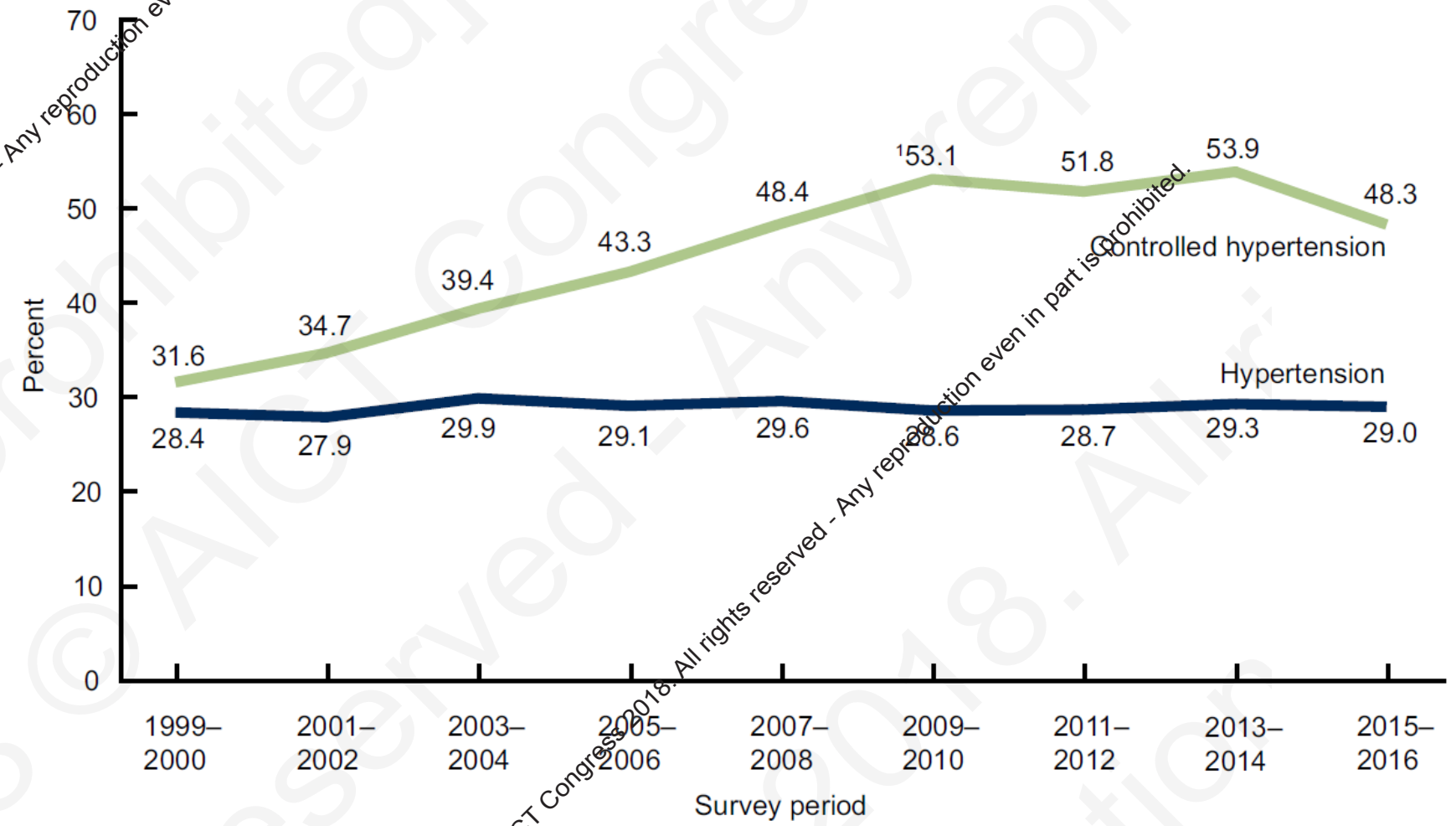
LIFELONG POLYPHARMACY IS FAILING AS A STRATEGY TO IMPROVE HYPERTENSION CONTROL

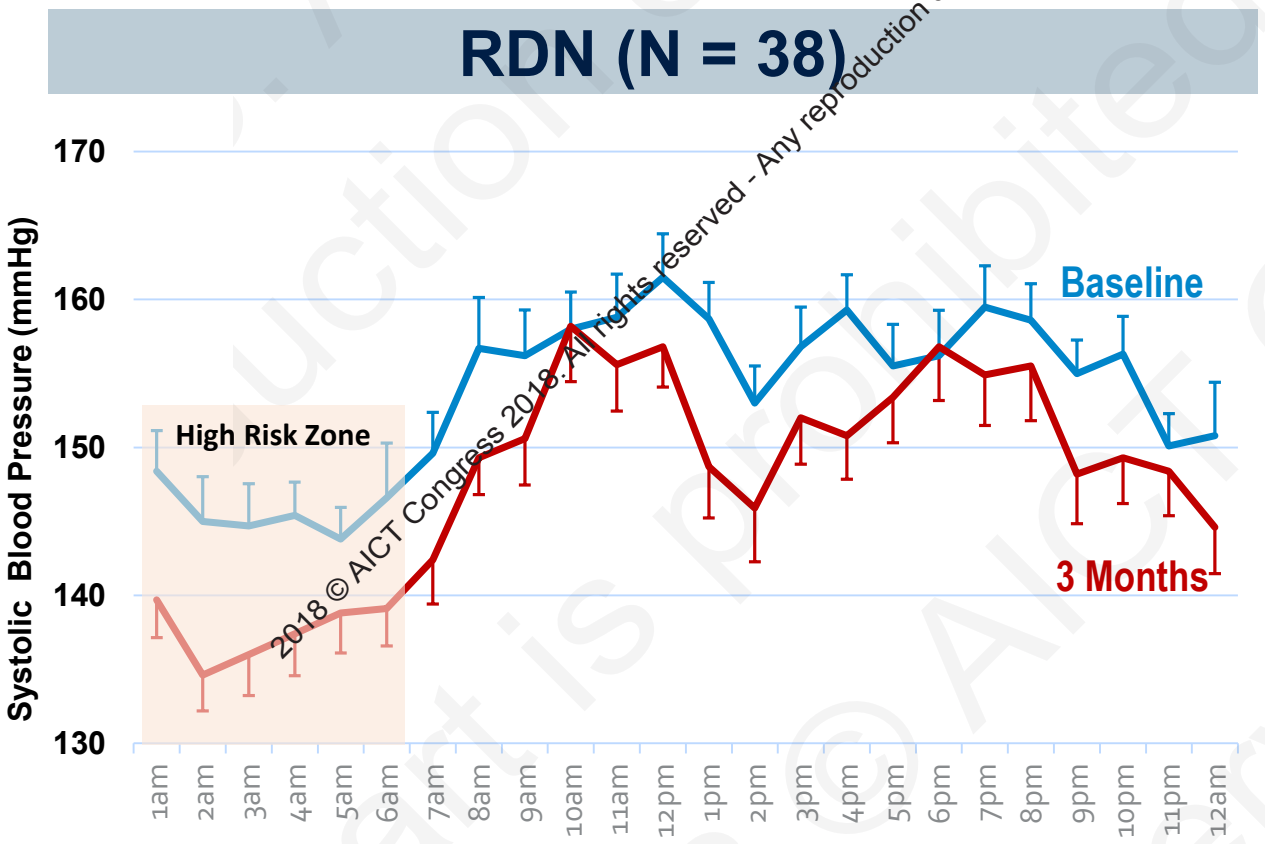
- Overall hypertension control rates have plateaued at about **50%**, despite improvement from 1999–2010[1].

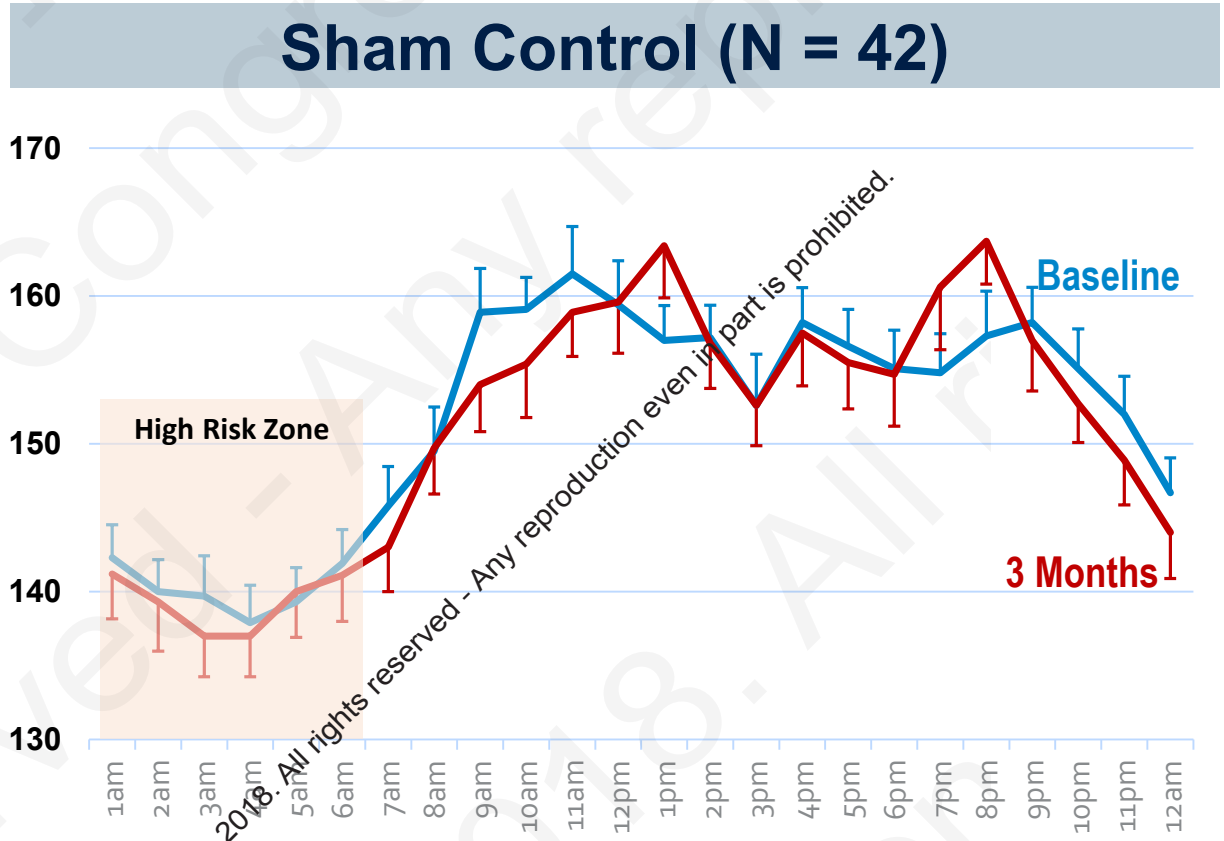


[1] NCHS, National Health and Nutrition Examination Survey

SPYRAL HTN-OFF MED **RDN IS "ALWAYS ON"**

RDN PATIENTS HAD STATISTICALLY LOWER SYSTOLIC BP IN THE "HIGH-RISK ZONE[1]" AT 3-MONTHS





- "High-risk zone" that occurs in the late night/ early morning period is usually associated with increased risk for stroke and cardiovascular events[2,3]

1. Kario K et al, ACC 2018
2. Amodeo C, Blood Pressure Monit, 2014
3. Boggia J, The Lancet, 2007

Graphs based on actual clock times. Similar results were observed when 24-hour BP patterns were normalized to patient reported time of waking.

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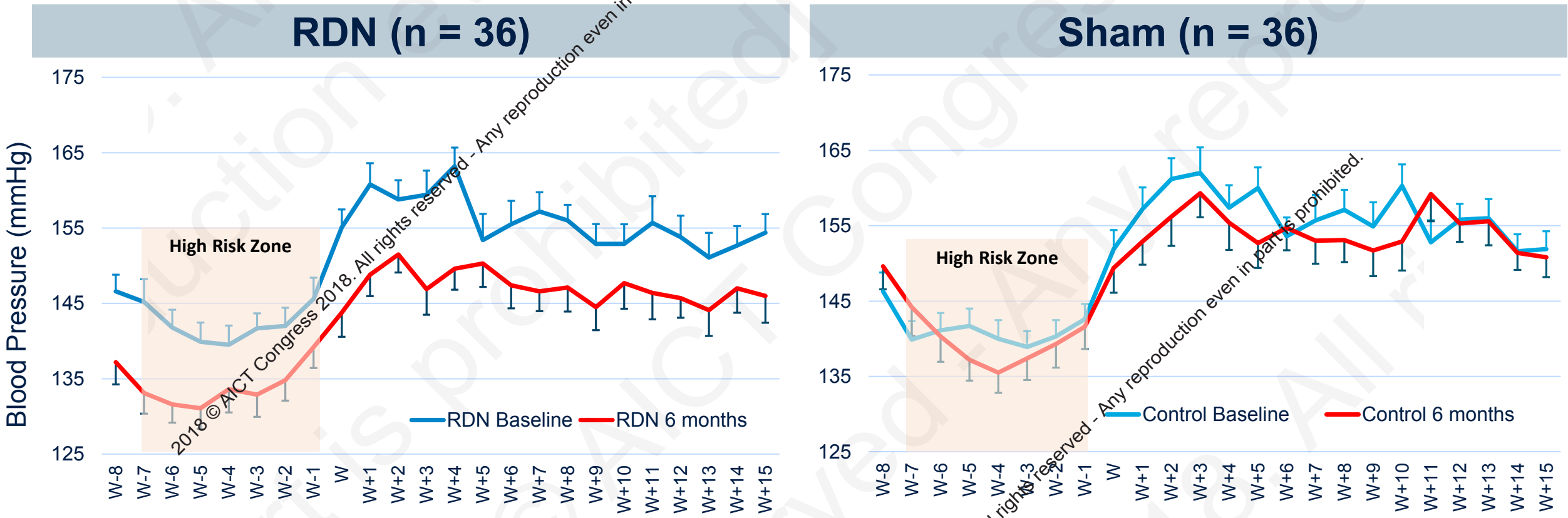
SPYRAL HTN-ON MED FURTHER PROOF OF RDN'S "ALWAYS ON" EFFECT

RDN PATIENTS SHOWED LOWER 24-HOUR SYSTOLIC BP, INCLUDING IN THE HIGH-RISK ZONE[1]



- "High-risk zone" that occurs in the late night/ early morning period is usually associated with increased risk for stroke and cardiovascular events[2,3]

[1]Kandzari et al, PCR 2018
[2]Amodeo C, Blood Pressure Monit, 2014
[3]Boggia J, The Lancet, 2007

W = Wake time reported by patients; otherwise set to 7:00AM for those patients not reporting

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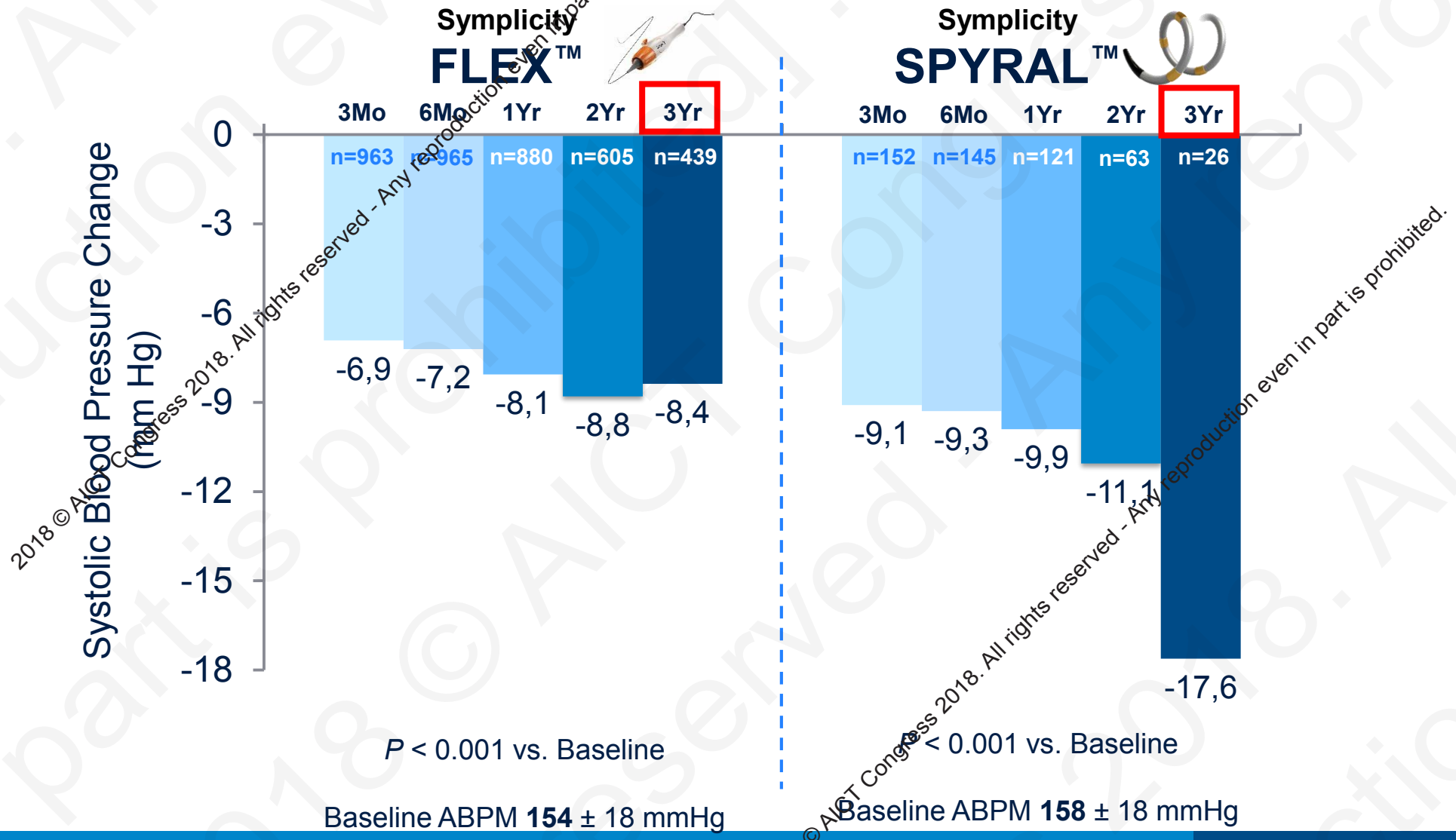
GLOBAL SIMPLICITY REGISTRY

24-Hr Systolic Blood Pressure



SPYRAL HTN – ON MED NO MAJOR ADVERSE EVENTS AT 6 MONTHS

Adverse event (number of events)	RDN (n = 38)	Sham Control (n = 42)
Death	0	0
New myocardial infarction	0	0
Major bleeding (TIMI[1])	0	0
New onset end stage renal disease	0	0
Serum creatinine elevation >50%	0	0
Significant embolic event resulting in end-organ damage	0	0
New renal artery stenosis > 70%	0	0
Vascular complications	0	0
Hospitalization for hypertensive crisis/emergency	0	0
New stroke	0	0

Kandzari et al, PCR 2018

[1]TIMI definition: intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure)

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SPYRAL HTN
Global Clinical Trial Program

First Phase: 2 Parallel Proof of Concept Trials

24 Global Sites

SPYRAL HTN–OFF MED

- Sham RCT (1:1)
- Main body and branch ablation
- Drug naïve or discontinuation of antihypertensive medications
- Drug testing for absence of medications
- Compare 24-Hr BP change at 3 months
- All cases proctored for standardisation

SPYRAL HTN–ON MED

- Sham RCT (1:1)
- Main body and branch ablation
- Stable on 1–3 medications, no maximum tolerated dose requirement
- Drug testing for prescribed medications
- Compare 24-Hr BP change at 6 months
- All cases proctored for standardisation

Second Phase

SPYRAL HTN Pivotal Study

- Based on OFF/ON trial results

Kandzari DE, et al. *Am Heart J*. 2016 Jan;171(1):82-91.

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SUMMARY

- **Renal denervation is effective** and may help fulfill a key global unmet need for inadequate blood pressure control with currently available treatment options
  - Three new prospective, randomized sham-controlled trials showed **clinically meaningful reductions** in blood pressure in both the presence and absence of antihypertensive drug treatment
  - Blood pressure reductions following renal denervation were present **throughout the day and night** ("always on" effect)
  - Renal denervation demonstrated sustained reductions in blood pressure out to 3 years post-procedure, in a real world population registry

- **No major safety events occurred** despite a more complete denervation procedure that extended into renal artery branch vessels

- Future trials should focus on further confirming therapy safety and efficacy, identifying optimal treatment populations and care-pathways

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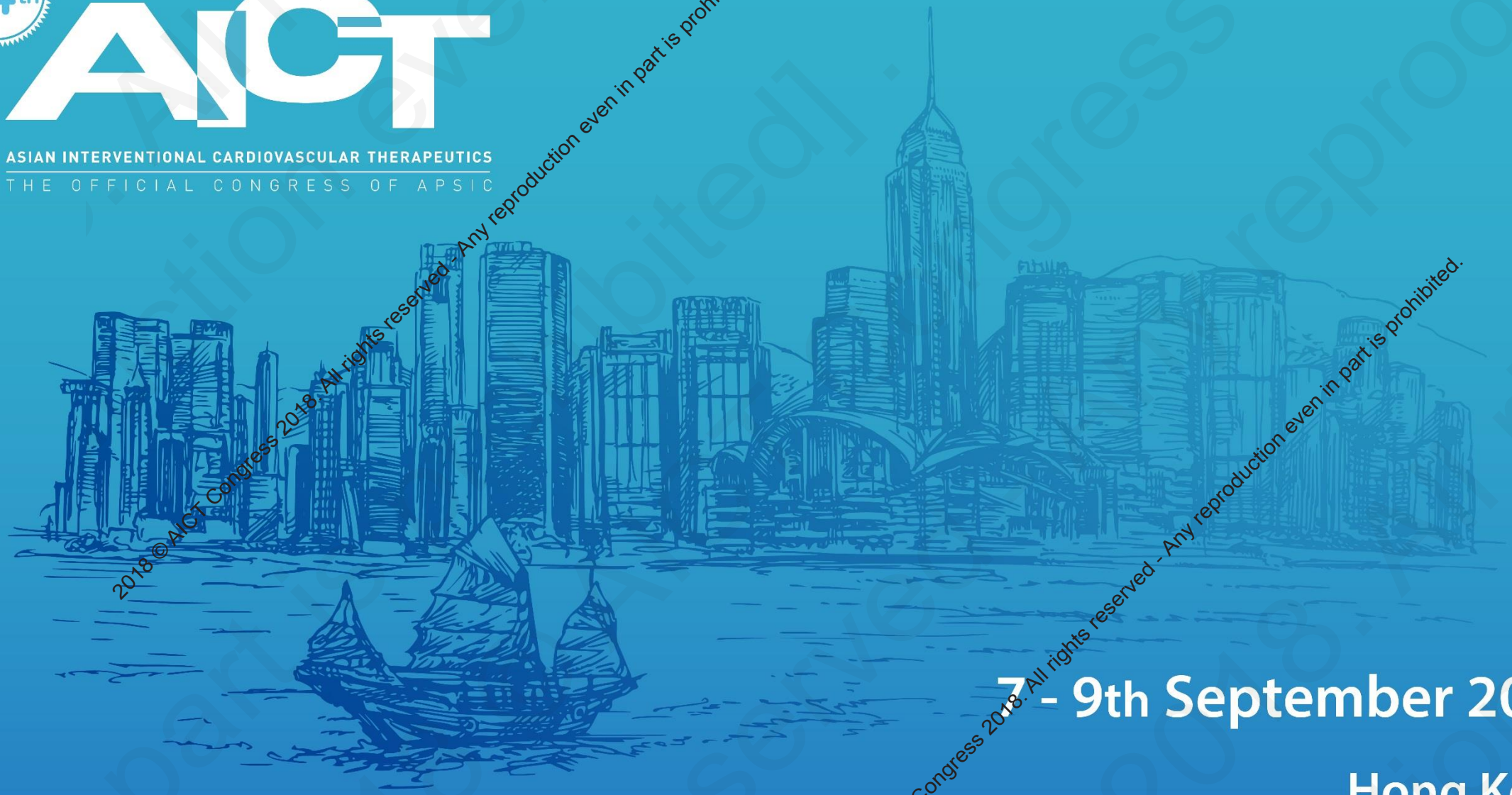
ASIAN INTERVENTIONAL CARDIOVASCULAR THERAPEUTICS

THE OFFICIAL CONGRESS OF APSIC



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