



# Renal denervation evidence for uncontrolled hypertension

Ingrid Prkačin

Clinical Hospital Merkur, Zagreb, School of Medicine,  
University of Zagreb, Croatia  
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# The scope of the problem?



A US Food and Drug Administration advisory panel met to discuss the way forward for future trials of device-based therapies for hypertension.

"The importance of finding new ways to treat hypertension is underscored by the scope of the problem: hypertension affects more than 1 billion people globally"

US Food and Drug Administration Circulatory System Devices Panel Meeting. Clinical evaluation of antihypertensive devices. December 5, 2018.



# 1 IN 3 ADULTS WORLDWIDE SUFFER FROM HYPERTENSION<sup>1,2,3</sup>

<sup>1</sup>Ikeda N, et al. *Bull World Health Organ.* 2014;92:10-19C.

<sup>2</sup>Kearney PM, et al. *Lancet.* 2005;365:217–223.

<sup>3</sup>CDC *Vital Signs.* September 2012, NHANES 2003-2010



COMPLICATIONS  
OF  
HYPERTENSION  
ACCOUNT FOR  
**9.4 MILLION  
DEATHS  
WORLDWIDE/Y<sup>4</sup>**

**NEARLY 50% OF PATIENTS  
BECOME NON-ADHERENT  
TO MEDICATIONS WITHIN  
ONE YEAR<sup>5</sup>**

<sup>4</sup>Lim SS, et al. ...a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012 ; 380 (9859) : 2224-60.

<sup>5</sup>Jung O, et al. *J Hypertension*. 2013;31:766-774

# CONTROLLING HYPERTENSION IS CRITICALLY IMPORTANT

BLOOD PRESSURE CONTROL REDUCES THE RISK OF DEBILITATING SIDE EFFECTS

**10 mmHg DECREASE IN MEAN OFFICE SBP:**

**20%**

Reduction in relative risk of major cardiovascular events

**13%**

Reduction in relative risk of all-cause mortality

HF

Stroke

CHD

**-28%**

**-27%**

**-17%**

Ettehad D, et al. *Lancet*. 2016,387:957–967.



**PATIENT NON-ADHERENCE HAS REACHED EPIDEMIC PROPORTIONS**  
MANY PATIENTS CANNOT LIVE WITH POLYPHARMACY AND ABANDON IT

**SHOULD YOU  
BE LOOKING FOR  
ADDITIONAL, DIFFERENT TOOLS?**

NCHS, National Health and Nutrition Examination Survey. NCHS Fact Sheet, December 2017.



**1 IN 3 ADULTS WORLDWIDE SUFFER  
FROM HYPERTENSION**



**GIVE HYPERTENSION PATIENTS A NEW OPTION**

# Options for hypertension control



When overactive nerves cause higher sympathetic activity, it can lead to hypertension.

The Renal Denervation (RDN) procedure combats these nerves to help lower blood pressure.

We can lower blood pressure with RDN.

RDN is an **Interventional approach** to hypertension

# Options for hypertension control



RDN is an **Interventional approach** to hypertension

In RDN, energy is delivered to the **renal nerves** to help control blood pressure

## **The RDN procedure**

itself is approximately an hour long<sup>1</sup>

We can lower blood pressure with RDN.

<sup>1</sup>The Lancet, 2017

# Procedure



## Renal denervation

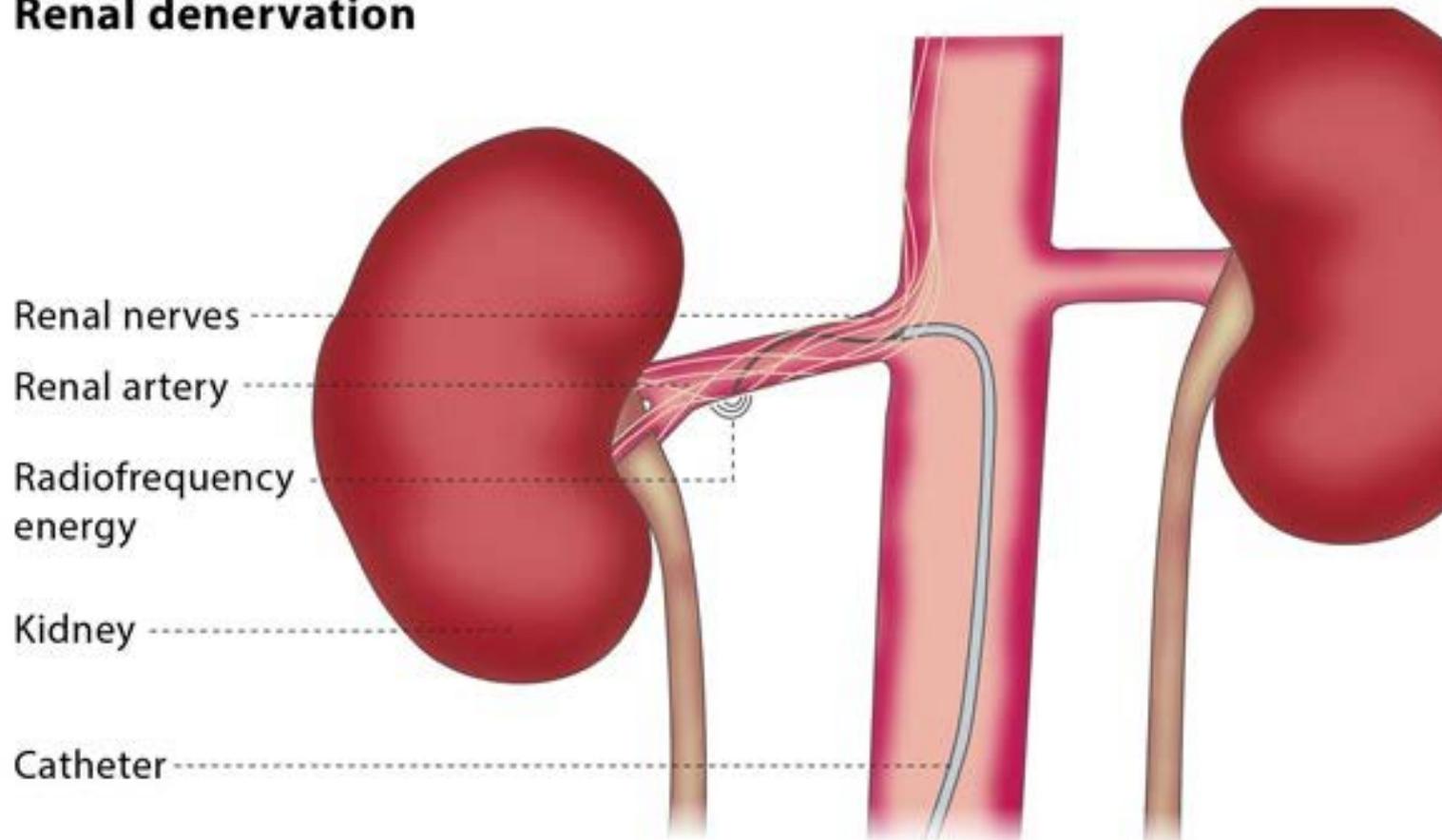


IMAGE 1. Renal denervation procedure. Source: <https://www.cirse.org/patients/ir-procedures/renal-denervation/>  
Accessed 20<sup>th</sup> Sep 2019



**SYMPPLICITY HTN-1 AND SYMPPLICITY HTN-2 CLINICAL TRIALS**  
**SHOWED SIGNIFICANT AND SUSTAINED BLOOD PRESSURE**  
**REDUCTION**

**Out to three years**

**Significant change in office BP**  
**compared to a medication.only group**

<sup>1</sup>Krum H et al. *The Lancet*. 2014;383:622–629.

SYMPPLICITY HTN-2 Investigators. *The Lancet*. 2010; 376: 1903-1909



## SYMPPLICITY HTN-3 **PRIMARY EFFICACY ENDPOINT**

**There was no significant difference in BP change at 6 months**

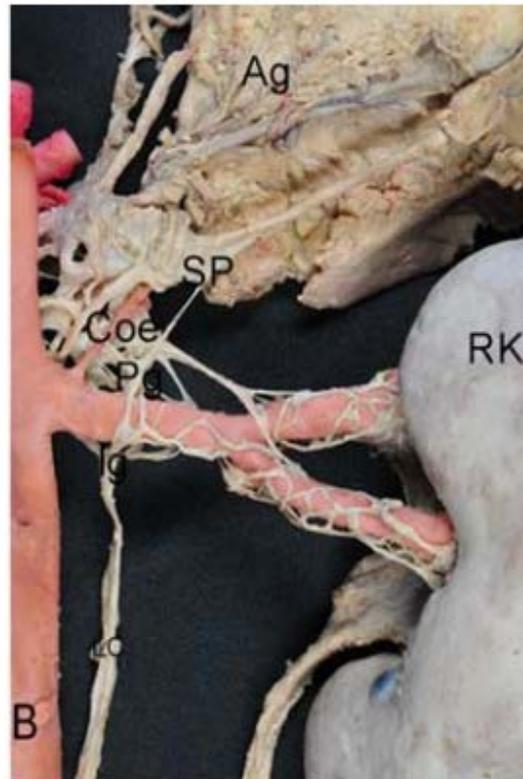
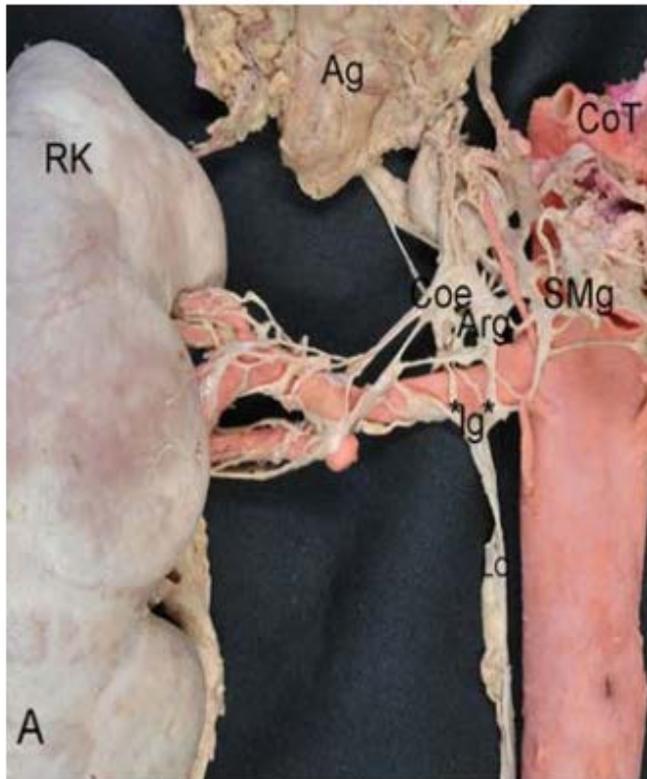
**The large BP change in the control group suggested that there were SIGNIFICANT SOURCES OF VARIATION that were not controlled in the trial**

1. DRUG CHANGES AND VARIABLE PT ADHERENCE
2. PATIENT POPULATION
3. PROCEDURAL EXPERIENCE AND VARIABILITY

Bhatt DL et al. *N Engl J Med.* 2014;370:1393–1401

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

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.



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.

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

# GLOBAL SYMPPLICITY REGISTRY



The Global SymPLICity Registry was designed to confirm the safety of the system in real-world data set representative of **Flex and SymPLICity Spyril** in a variety of patient populations.

GSR is the single largest **real-world study** of RDN patients.

The procedure was shown to be safe in this large patient set (197 patients) with **blood pressure reductions sustained out to 3 years in both office systolic blood** pressure as well as 24-hour ambulatory blood pressure monitoring (**ABPM**).

Mahfoud F, Three-year Safety and Efficacy in the Global SymPLICity Registry: Subgroup Analyses.  
EuroPCR 2019



Renal denervation (RDN) is indicated for use in patients with uncontrolled hypertension.

The use of RDN: in patients between 150 and 180 mmHg office blood pressure (or between 140 and 170 mmHg ABPM) who are on three and more antihypertensive medications.

[Global Symplicity Registry.](#)

# GLOBAL SYMPPLICITY REGISTRY SUBGROUP RESULTS

In GSR high-risk subgroups (diabetes, **elderly**, ISH, rHTN, CKD), RDN showed similar **consistent and meaningful long-term BP lowering effects between 10 to 20 mmHg reductions to 3 years.**

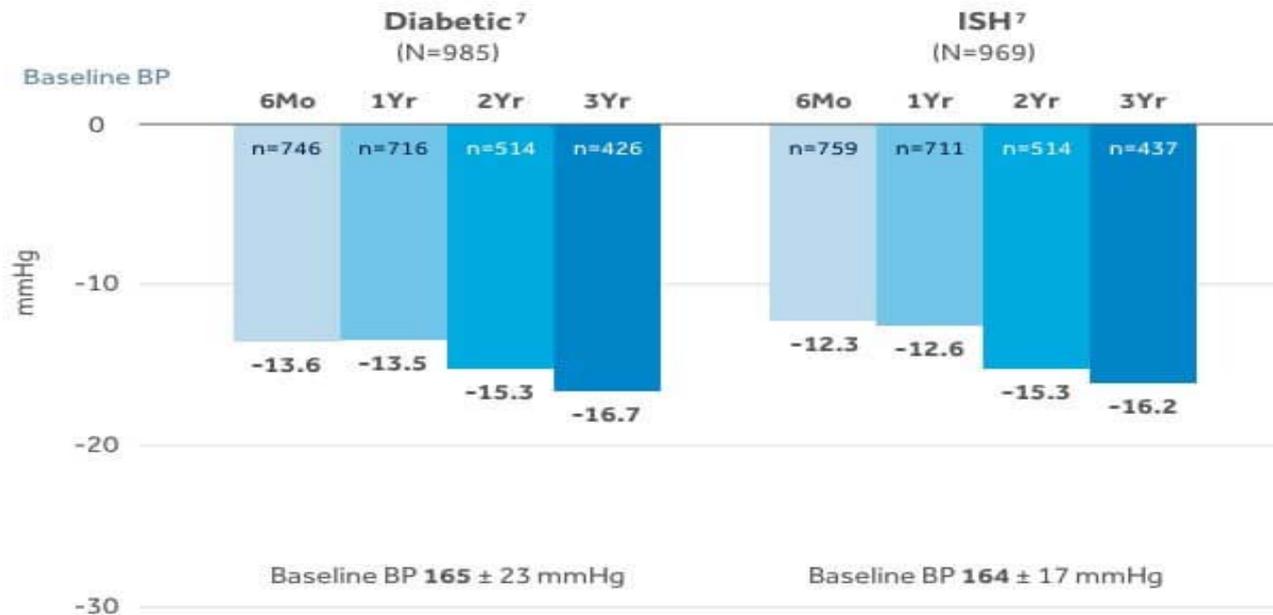
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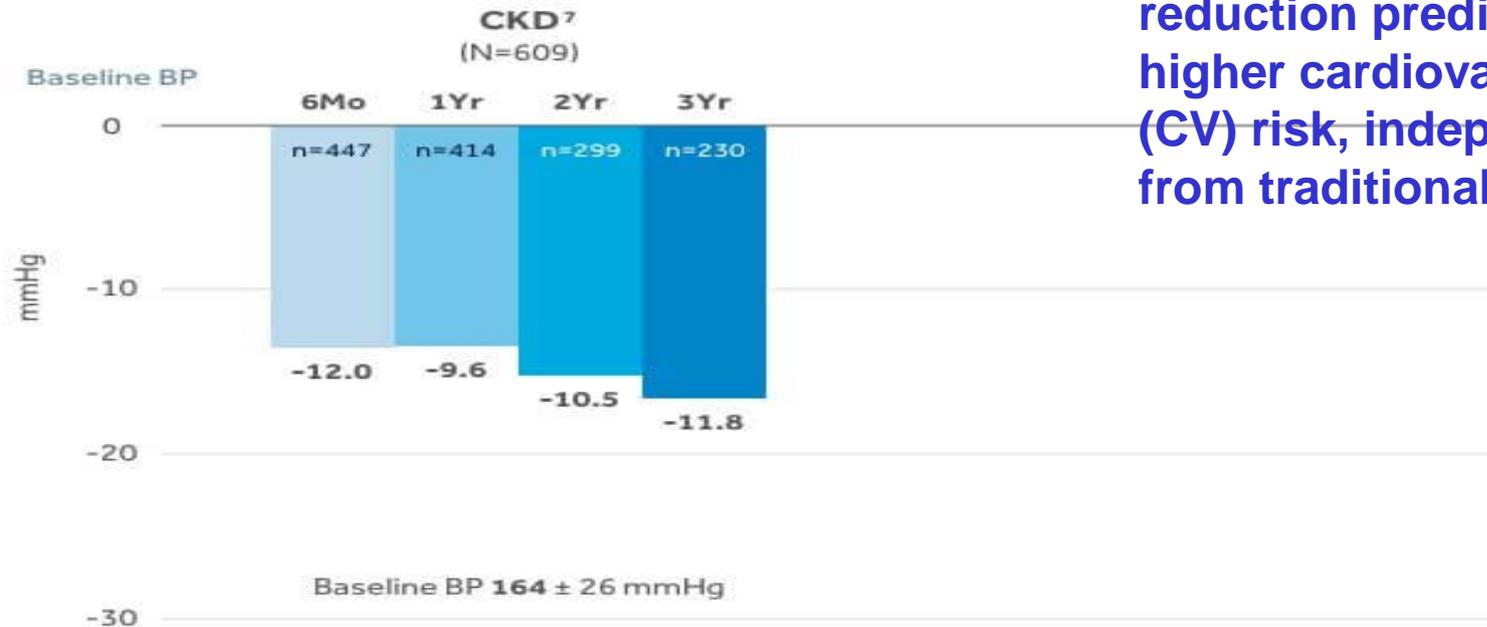
EuroPCR 2019



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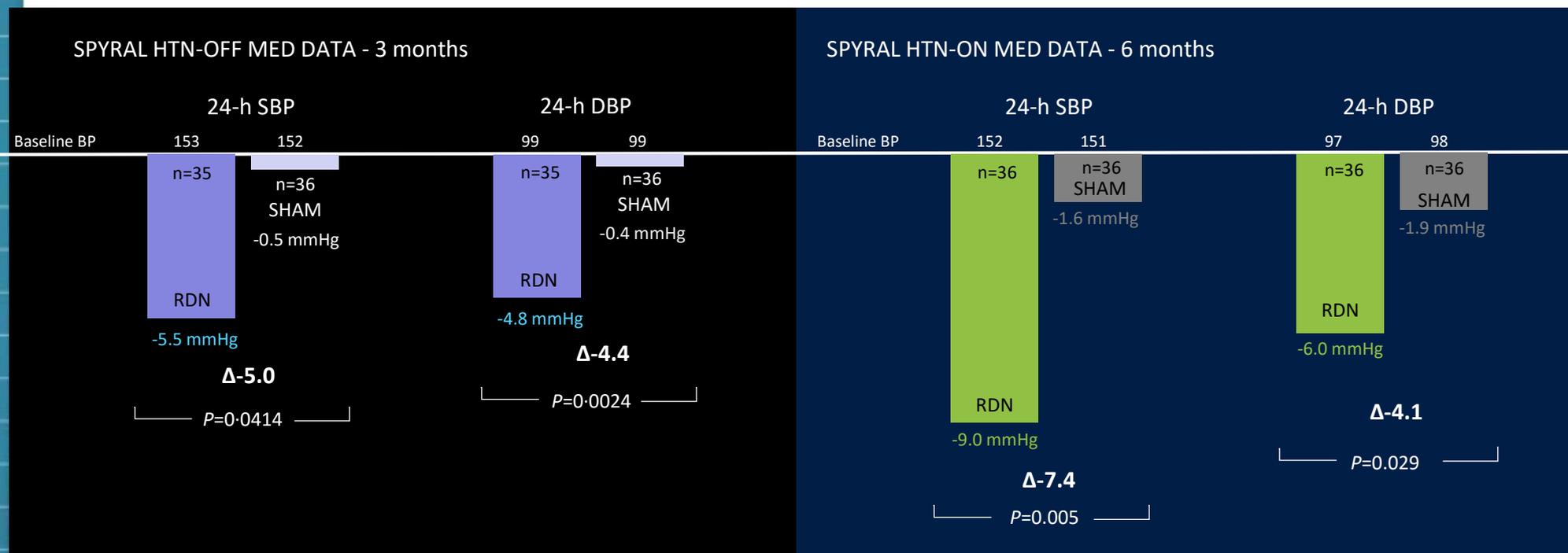
2019



The onset of eGFR reduction predict higher cardiovascular (CV) risk, independent from traditional CV risk

# RDN IS A MINIMALLY INVASIVE PROCEDURE THAT REDUCES BLOOD PRESSURE

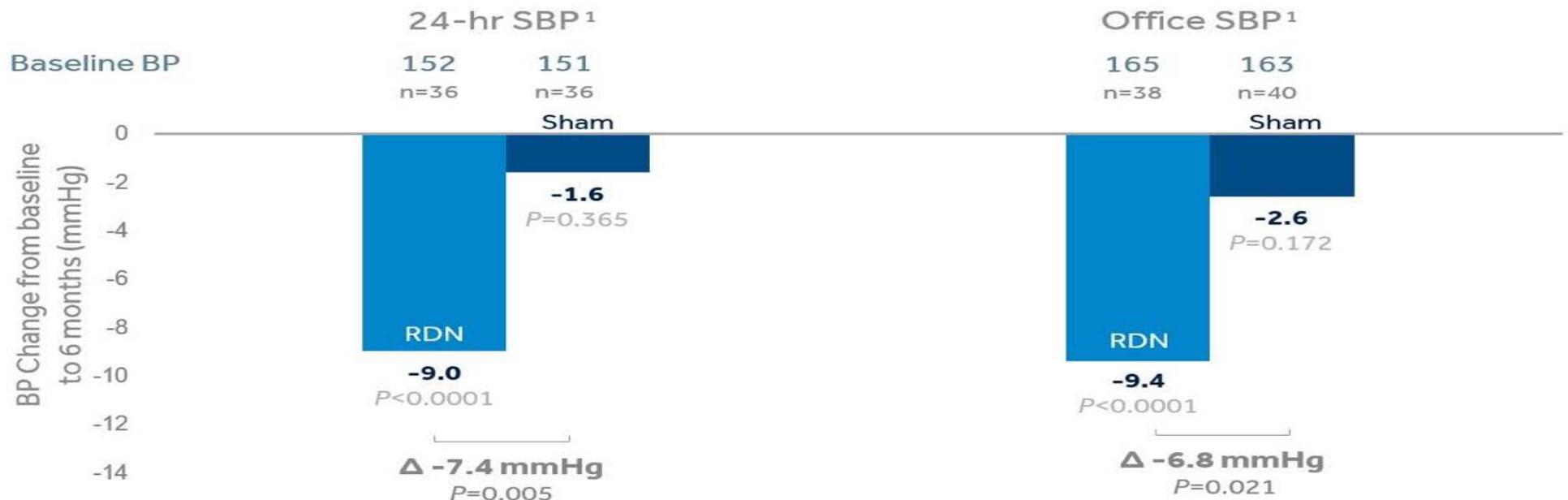
IT WAS PROVEN EFFECTIVE BOTH IN THE PRESENCE AND ABSENCE OF DRUGS IN PILOT STUDIES



## SPYRAL HTN-ON MED

This study was designed to evaluate the effect of renal denervation (RDN) in the presence of anti-hypertensive drugs, which may be considered representative of clinical practice where integrating drug and procedural strategies may be anticipated.

Ettehad D, Emdin CA, Kiran A, et.al., *Lancet* 2016; 387: 957-67



## SPYRAL HTN-ON MED

There were statistically significant reductions in 24-h ABPM and office systolic blood pressure between the RDN and sham groups. **The 24-h ABPM declined by 9.0 mmHg in the RDN group, resulting in a statistically significant difference with the sham control arm.**<sup>1</sup>

The RDN procedure demonstrated **safety**.

No cases of new or worsening renal failure, vascular complications, or other major adverse events were observed within 6 months post procedure.

<sup>1</sup> Ettehad D, Emdin CA, Kiran A, et al., *Lancet* 2016; 387: 957-67; <sup>2</sup>Townsend RR, et al. *Lancet*. 2017;390:2160–2170; <sup>3</sup>Kandzari DE, et al. *Lancet*. 2018;391:2346–2355.

# SPYRAL HTN-OFF MED

is a randomized sham-controlled study examining the effect of RDN on hypertensive patients who have been washed off of their medications or are medication naive. **The goal of this trial is to explore the effect of RDN alone (without drugs) and controlling for placebo effect and variable medication adherence.**

Townsend RR, et al. *Lancet*. 2017;390:2160–2170



## SPYRAL HTN-OFF MED

At three months, patients treated with RDN (n=37) saw **significant (p=0.02) reductions in both office blood pressure and 24-hour ambulatory blood pressure** compared with patients who received the sham procedure (n=36).<sup>4</sup>

These safety results were achieved even as a number of ablations were performed in the renal artery branches as well as the main artery. **The reductions in blood pressure seen with RDN in this trial correspond to an approximate 20% risk reduction in major cardiac events**

Townsend RR, et al. *Lancet*. 2017;390:2160–2170



RDN PATIENTS HAD STATISTICALLY LOWER SYSTOLIC BP IN THE “HIGH-RISK ZONE<sup>1</sup>” AT 3-MONTHS

## SPYRAL HTN-OFF MED

**RDN (N = 38)**

**Sham Control (N = 42)**

▪ In RDN difference was >10 mmHg.

In Sham Control difference was 2-3 mmHg

▪ **“High-risk zone” that occurs in the late night/ early morning period is usually associated with increased risk for stroke and cardiovascular events<sup>2,3</sup>**

1. Kario K et al, ACC 2018

2. Amodeo C, Blood Pressure Monit, 2014

3. Boggia J, The Lancet



# ESH POSITION STATEMENT ON GUIDELINES

Experts from the European Society of Hypertension (ESH) – including the interventional working group – published a position paper on catheter-based RDN technologies.

Schmieder R et al, European Society of Hypertension position paper on renal denervation 2018, Journal of Hypertension, 2018: 36.



From the ESH Position Statement,  
authors state that:

1. Evidence provides biologic proof that RDN works in lowering blood pressure (BP): “Sham subtracted reduction in ambulatory BP provides the clear message that **RDN is effective in lowering BP** in hypertensive patients without or with 1–3 antihypertensive medication.”

2. RDN provides clinically meaningful BP reductions: “**The 10-mmHg decrease in office BP** achieved in RDN trials, if maintained long term, would be **associated with a reduction in cardiovascular events by 25%.**”

Journal of Hypertension, 2018: 36.

From the ESH Position Statement, authors state that:

3. Evidence shows **RDN is safe**: “No major adverse events occurred in the three trials in the short term from 30 days to 6 months post procedure.”

4. Emphasis must be placed **on individualized treatment and patient preference** given the challenges with medication adherence: Discussions with the patient of treatment choice “needs to take the patient’s preference into account.”

Journal of Hypertension, 2018: 36.



# The value of guidelines



Guidelines are not static documents,  
rather iterative pieces  
that grow,  
and build on one another

The value of guidelines is determined by how effectively it is implemented into practice and how much morbidity and mortality are avoided through its applications.

# RENAL DENERVATION SYSTEM

EFFECTIVE  
BP REDUCTION



SAFE



ECONOMIC  
VALUE

*RDN's "always on" effect works in the presence and absence of medications, 24-hours a day<sup>1</sup>*

*RDN's "Excellent safety profile in clinical research and real-world registry*

*Lower BP correlates to reduced cardiovascular events and lower economic burden<sup>2</sup>*

<sup>1</sup>Kandzari et al, The Lancet 2018)

<sup>2</sup>FDA guidance document OMB Control Number 0910-0670

# Conclusion



Prevalence and incidence of CKD have risen by 87 and 89%, worldwide, over the last three decades. The onset of albuminuria has found to predict higher cardiovascular (CV) risk.

With RDN we can decrease albuminuria.

**RENAL DENERVATION=COMPLEMENTARY TOOL  
FOR SAFE CONTINUOUS BP REDUCTION**

# Conclusion



The RDN program is just rebeginning to translate the message of guideline to a language that resonates with patients, providers and public health officials

We can lower blood pressure with RDN,  
decrease albuminuria,  
Prevent eGFR reduction

# RDN in Croatia



According to the total population in Croatia, the RDN ratio is 1:20

From 2012-2018 **61** RDN procedures

41 with old method Flex Symplicity.

In Hospital Merkur 15 Flex RDN (pt. had chronic resistant hypertension more than 10 years with extremely high office values of blood pressure (min 190/120, max 300/180mmHg).

The majority of patients were female (11 vs. 4) with an average age of 61 years (range 47-76years).

# Results



- Renal denervation (Flex) procedure significantly reduced average 24h values of:
- **Systolic blood pressure** (170.93 vs. 144.21mmHg,  $p < 0.01$ , **15.63% reduction**)
- **Diastolic blood pressure** (100.92 vs. 85.93mmHg,  $p < 0.05$ , **14.86% reduction**)
- **MAP** (124.26 vs. 105.36mmHg,  $p < 0.01$ , **15.21% reduction**)
- The amount of **proteinuria after 3 months** showed a statistically insignificant decrease after RDN (0.43 vs. 0.16 g/L,  $p = 0.16$ )



THE YEAR 2019 marks the 500th anniversary of the death of one of the greatest minds in history. On May 2nd 1519 **Leonardo da Vinci** died.

The value of his scientific work took much longer to be recognised.

Science is often thus: ideas can take a long time to reach maturity, and they often do so through the coming together of people from around the globe.



# Thank You

[ingrid.prkacin@gmail.com](mailto:ingrid.prkacin@gmail.com)