



UNIVERSITA' DEGLI STUDI DI TORINO
DIPARTIMENTO DI SCIENZE MEDICHE
CATTEDRA MEDICINA INTERNA
CENTRO IPERTENSIONE ARTERIOSA
AO CITTA' SALUTE E SCIENZA
TORINO

Renal denervation for refractory hypertension hype or hope?

Franco Veglio

Torino, 26 Ottobre 2012

DEFINIZIONI **ESH-JNC-AHA-BHS**

➤ **IPERTENSIONE PSEUDO RESISTENTE:**

mancato controllo pressorio, nonostante terapia in pazienti che non hanno ipertensione resistente

➤ **IPERTENSIONE RESISTENTE:** PAOS e/o PAOD $\geq 140/90$ mmHg (o $130/80$), nonostante terapia con almeno tre farmaci a dosaggio pieno incluso un diuretico.

Fattori ASSOCIATI: farmaci, eccessiva assunzione di sale o alcool, obesità, ipertensione secondaria ,OSAS.

NON MODIFICABILI: **IPERTENSIONE RESISTENTE VERA**

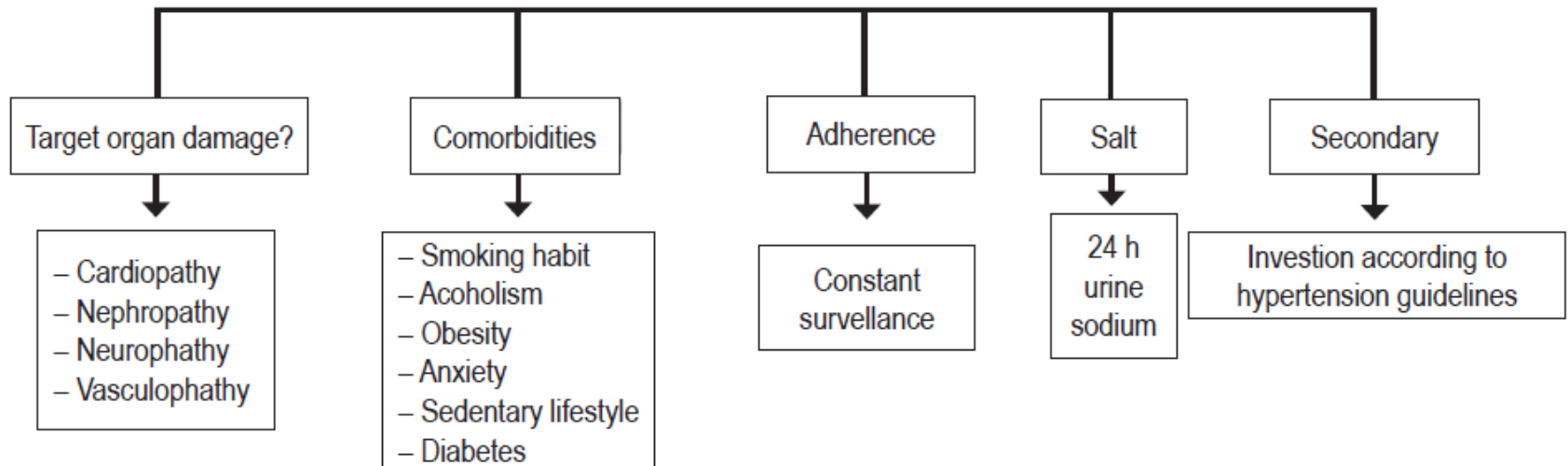
Resistant Hypertension Algorithm 2012

Suspected Resistant Hypertension

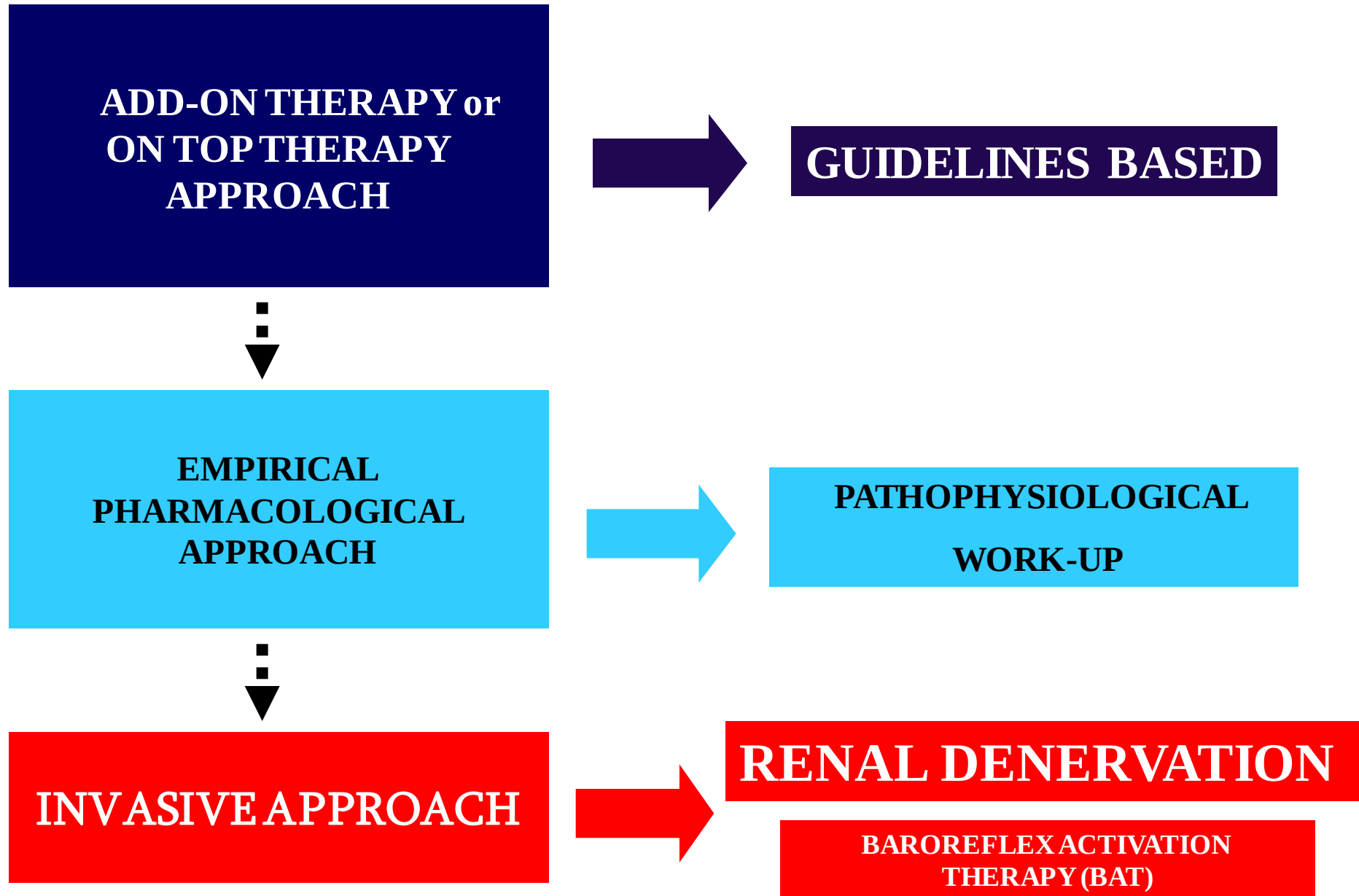
Exclude pseudo-resistance

- Adherence to therapy (pharmacological and non-pharmacological)
- Inadequate dosage

Exclude white coat effect
ABPM

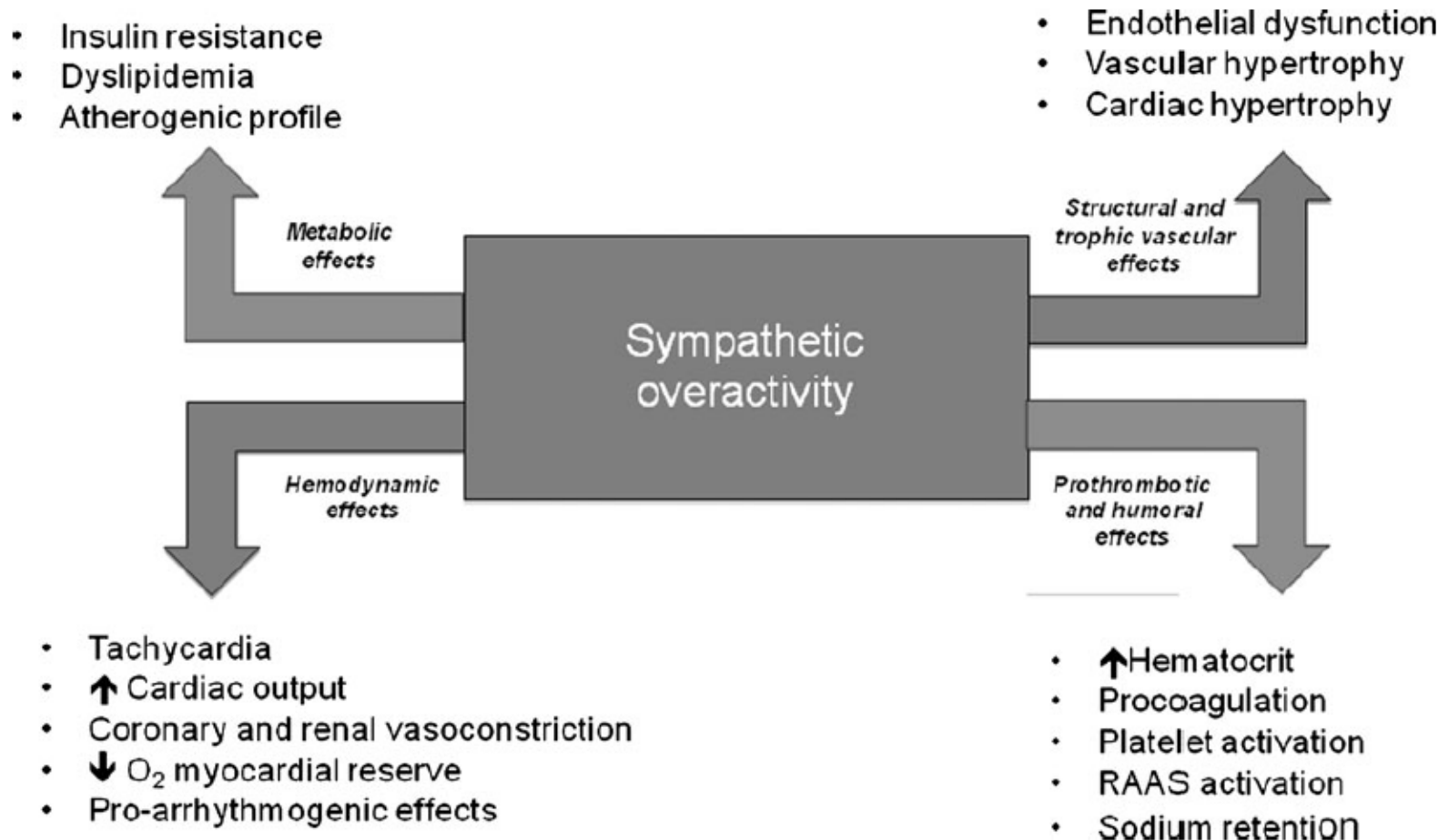


CLINICAL STRATEGIES IN RESISTANT HYPERTENSION



Renal Denervation Background

Sympathetic Cardiovascular Drive in Human Hypertension



Concept Validated by Surgical History

THE EFFECTS OF PROGRESSIVE SYMPATHECTOMY ON BLOOD PRESSURE

BRADFORD CANNON

From the Laboratories of Physiology in the Harvard Medical School

Received for publication March 24, 1931

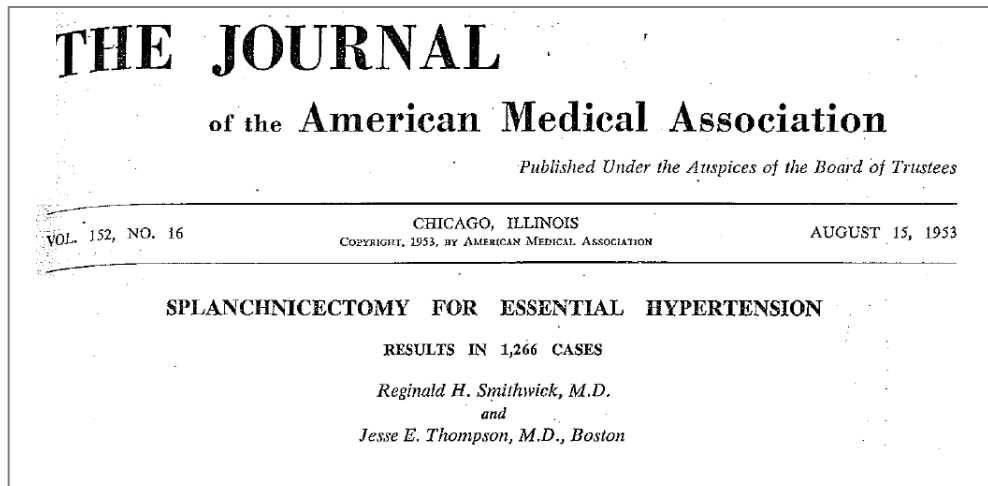
THE BRITISH JOURNAL OF SURGERY

1952

SYMPATHECTOMY IN THE TREATMENT OF BENIGN AND MALIGNANT HYPERTENSION*

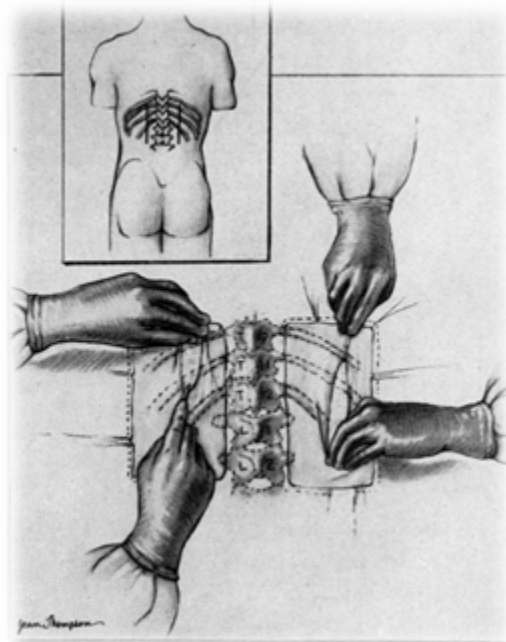
A REVIEW OF 76 PATIENTS

By C. J. LONGLAND AND W. E. GIBB



Effective, but significant morbidity

Sympatectomia: un vecchio concetto



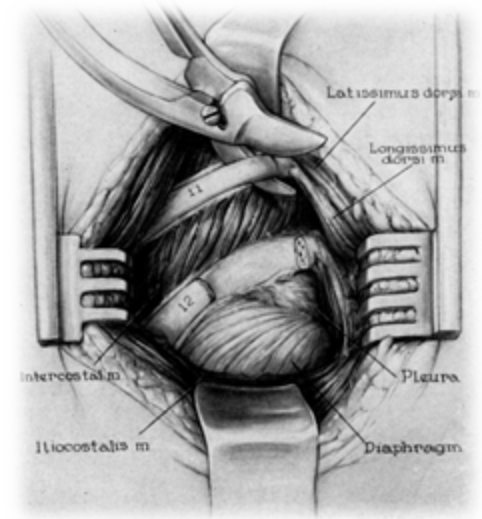
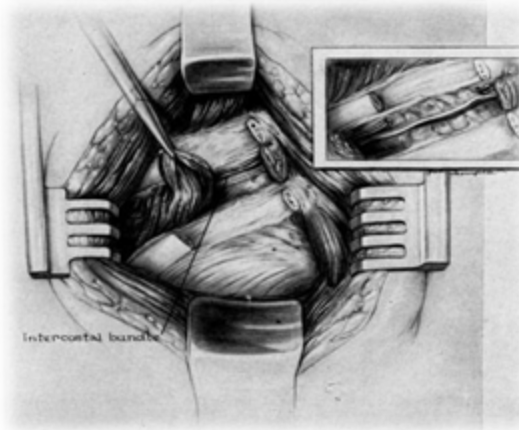
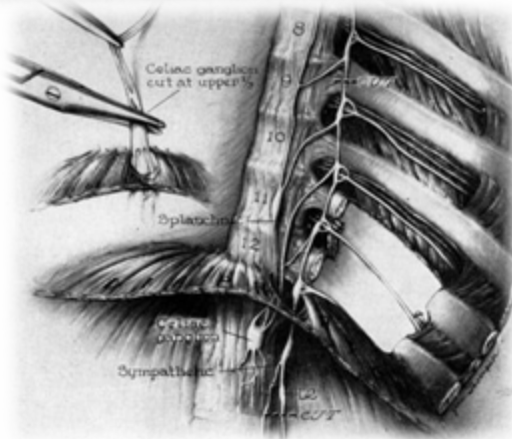
THE MEDICAL AND SURGICAL TREATMENT OF HYPERTENSION*†

F. L. REICHERT, V. RICHARDS, E. HOLMAN, A. L. BLOOMFIELD,
T. ADDIS, D. A. RYTAND, AND J. K. LEWIS

SAN FRANCISCO, CALIFORNIA

FROM THE DEPARTMENTS OF SURGERY AND MEDICINE, STANFORD UNIVERSITY SCHOOL OF MEDICINE,
SAN FRANCISCO, CALIFORNIA

† Read at the 4th Congress of the Pan-Pacific Surgical Association, Honolulu, T. H.,
September 2, 1948.



Linee Guida di Consenso sulla Denervazione Renale

United Kingdom¹

Joint Societies Statement on Renal Denervation for Resistant Hypertension.
The Joint UK Societies' Consensus Statement on
Renal Denervation for Resistant Hypertension.



Steering Group: Mark Caulfield¹ (Chair), Mark de Zeeuw², Trevor Cleveland³, David Collier⁴, John Deanfield⁵, Huon Gray⁶, Charles Knight⁷, Melvin Lobo⁸, Matthew Matson⁹, Jon Moss¹⁰, Neil Poulter¹¹, Iain Simpson¹², Charles Tomson¹³, Bryan Williams¹⁴.

On behalf of the British Hypertension Society¹, the British Cardiovascular Intervention Society², the British Society for Interventional Radiology³, National Institute for Clinical Outcomes Research⁴, the British Cardiovascular Society⁵, and the Renal Association⁶.

This statement was developed with the guidance and advice from patients who had undergone this procedure at Barts and The London NIHR Cardiovascular Biomedical Research Unit and are members of the Patients and Public Engagement Group. The Joint UK Societies wish to express their thanks to Mr John Bold and Mr Anthony Henry.

This statement is intended to be read alongside NICE IP 418.
<http://guidance.nice.org.uk/IP418>

Issue 1: Live on web 26th January 2012
Final version.

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<http://www.whtr.qmul.ac.uk/index.html>

Germany²

REVIEW ARTICLE

Treatment Strategies for Resistant Arterial Hypertension

Felix Mahfoud¹, Frank Himmel², Christian Ukena, Herbert Schunkert,
Michael Böhm, Joachim Weil

SUMMARY

Background: Resistant hypertension is defined as blood pressure above the target range set by current guidelines despite the concurrent use of three or more antihypertensive drugs of different classes, including a diuretic, at their maximum or highest tolerated doses. This problem affects 5% to 15% of all hypertensive patients and is thus commonly seen by both primary care physicians and specialists.

Methods: Review of current guidelines and pertinent literature revealed by a selective Medline search.

Results: The treatment of resistant hypertension is multifactorial, involving systematic identification of secondary causes of hypertension as well as the exclusion of spurious and/or inadequate treatment. Non-pharmacological treatment includes weight loss, dietary salt restriction, exercise, and abstinence from alcohol. Drug treatment consists of an individualized combination of antihypertensive agents with different mechanisms of action. Activation of the sympathetic nervous system is considered to be a major element in the pathogenesis of resistant hypertension; a new interventional treatment, a selective denervation of the renal sympathetic nerves, results in clinically relevant and sustained blood pressure reduction in ca. 50% of the patients undergoing the procedure (a meta-analysis of office systolic blood pressure by 32 mm Hg and by 12 mm Hg at six months; $p < 0.001$). Among the 200 patients who underwent this procedure in the setting of published studies, 5 had complications. These included pseudoaneurysm of the femoral artery and dissection of the renal artery during the introduction of the catheter.

Conclusion: The treatment of resistant hypertension is interdisciplinary and multifactorial. The new and promising option of interventional renal sympathetic denervation can be considered for patients whose high blood pressure is inadequately controlled with medication.

► **On this site:**
Mahfoud F, Himmel F, Ukena C, Schunkert H, Böhm M, Weil J. Treatment strategies for resistant arterial hypertension. Dtsch Arztebl Int 2011; 108(43): 725–31. DOI 10.3238/arztebl.2011.0725

Article for review: Mahfoud F, Himmel F, Ukena C, Schunkert H, Böhm M, Weil J. Treatment strategies for resistant arterial hypertension. Dtsch Arztebl Int 2011; 108(43): 725–31. DOI 10.3238/arztebl.2011.0725

10th authors contributed equally to the preparation of this manuscript.

Dtsch Arztebl International | Dtsch Arztebl Int 2011; 108(43): 725–31

MEDICINE

W Polscelin Poland

Kardiologia Polska
2011; 62: 11, 1208–1211
ISSN 0022-9032

Stanowisko grupy ekspertów w sprawie zabiegów przeszłkowej denervacji nerek w leczeniu nadciśnienia tętniczego w Polsce

Catheter-based renal sympathetic denervation for the treatment of
resistant arterial hypertension in Poland – experts consensus statement

Adam Witkowski¹, Andrzej Januszewicz², Jacek Imieła³, Krzysztof Narkiewicz⁴, Grzegorz Opolski⁵,
Olgierd Rowiński⁶, Jerzy Sadowski⁷, Dariusz Dudek⁸, Leszek Brylowski⁹, Robert J. Gell¹⁰,
Marcin Adamczak¹¹, Stefan Grajek¹², Jacek Kądziera¹³, Aleksander Proch¹⁴, Maciej Nowicki¹⁵

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WSTĘP

Dnia 15 czerwca 2011 r. w Warszawie odbyło się spotkanie ekspertów w dziedzinie kardiologii, hipertensjologii, nefrologii, chorób wewnętrznych, radiologii i kardiologii polskiej oraz zabiegów przeszłkowej (przezskórnego) denervacji nerek (PND) w leczeniu opornego nadciśnienia tętniczego (ONT). Celem spotkania było zapoznanie się z aktualnym stanem wiedzy na temat metod diagnostyki i terapii prawdziwego opornego nadciśnienia tętniczego, ocenie roli i znaczenia zabiegów PND w leczeniu ONT, próbie zdefiniowania kwalifikacji grupy docelowej pacjentów z ONT w Polsce, którzy mogliby zostać poddani zabiegowi PND, oraz omówienie strategii postępowania mającego na celu wprowadzenie zabiegów PND „do kliniki” świadcząc gwarantowanych w Polsce.

DEFINICJA, WYSTĘPOWANIE, DIAGNOSTYKA I FARMAKOTERAPIA ONT

Zagadnienie ONT jest w ostatnich latach problemem o rosnącym znaczeniu klinicznym, m.in. ze względu na stosunkowo wysoką częstość występowania w populacji chorych na nadciśnienie tętnicze. Należy odnotować, że w ostatnich latach liczba opracowań dotyczących zagadnienia, które ukażą się na łamach czasopism medycznych, znacząco po-

głębia wiedzę o częstości występowania, przyczynach i następstwach ONT. Obecnie najczęściej stosowana tradycyjna definicja określa ONT jako sytuację, w której mimo stosowania w odpowiednich dawkach i we właściwym sekwencji co najmniej 3 leków hipotensyjnych, z wykorzystaniem diuretyku, nie udaje się obniżyć ciśnienia tętniczego do pożądanych wartości (1–4).

Należy jednak odnotować, że ostatnio zaprezentowano inne określenie, zgodnie z którym opisano na terapię oznacza konieczność przypięcia 4 i więcej leków hipotensyjnych w celu zapewnienia kontroli ciśnienia tętniczego. Badania przeprowadzone w Stanach Zjednoczonych i w Europie wskazują na skuteczność zabiegów PND w leczeniu ONT w populacji chorych z nadciśnieniem tętniczym (1–4).

Ważnym ONT osiągnięciem postępowania jest zastosowanie metody zabiegowej opartej na wyizolowaniu i denervacji nerwów autonomicznych (1–4).

W badaniach ONT osiągnięciem postępowania jest zastosowanie metody zabiegowej opartej na wyizolowaniu i denervacji nerwów autonomicznych (1–4).

Adres do korespondencji:

prof. dr hab. n. med. Adam Witkowski, Klinika Kardiologii i Angiologii, Instytut Kardiologii, ul. Aleja 42, 04-628 Warszawa, tel.: +48 22 34 34 127, fax: +48 22 34 34 556, e-mail: witek@onkard.pl

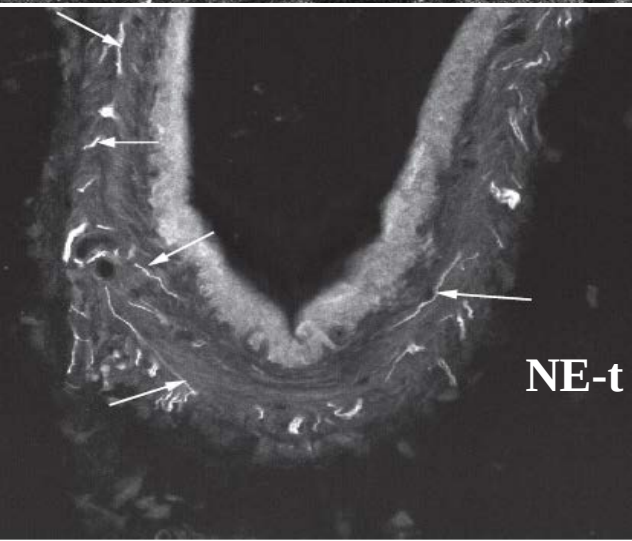
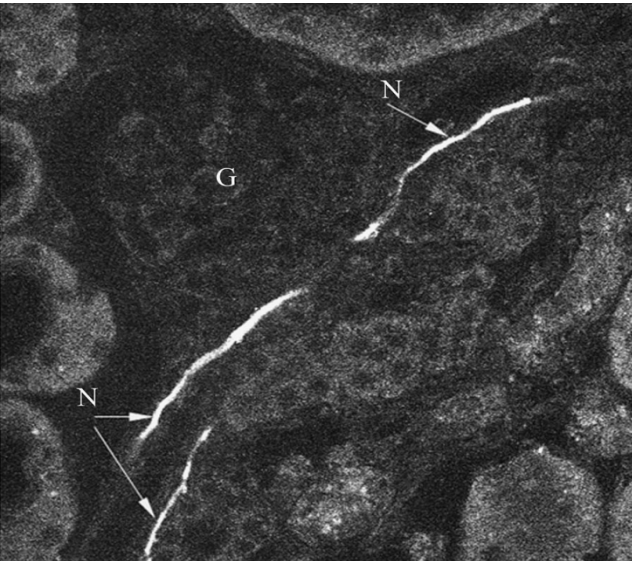
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www.kardiologia.polska.pl

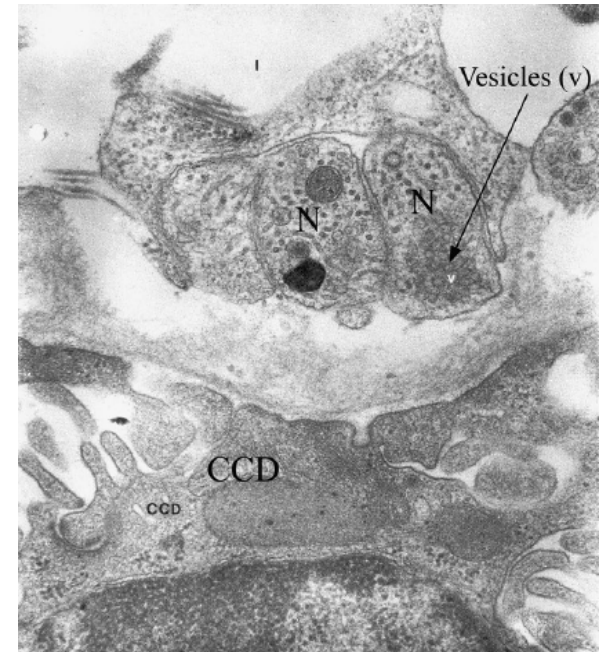
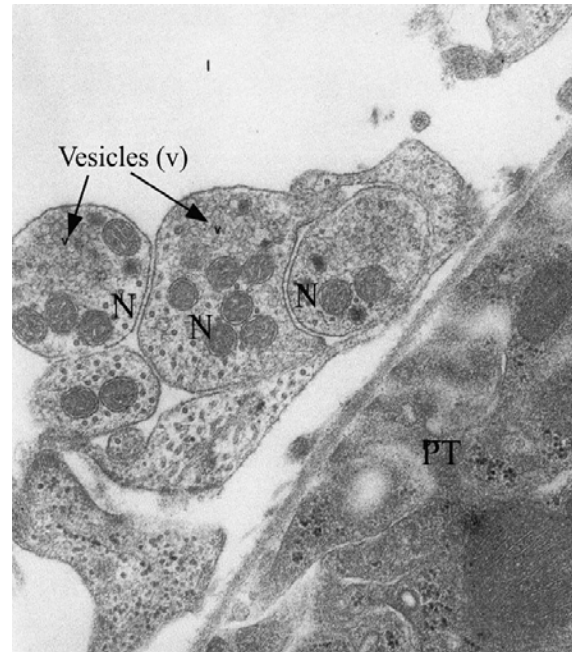
1. Caulfield M et al. Available at <http://www.bhsoc.org/docs/Joint-UK-Societies-Summary-on-Renal-Denervation.pdf>;
2. Mahfoud F et al. *Dtsch Arztebl Int.* 2011;136:2418;
3. Witkowski A et al. *Kardiologia Polska.* 2011;69:1208-1211.

Renal sympathetic nerve endings

Sympathetic nerve fibers (N)



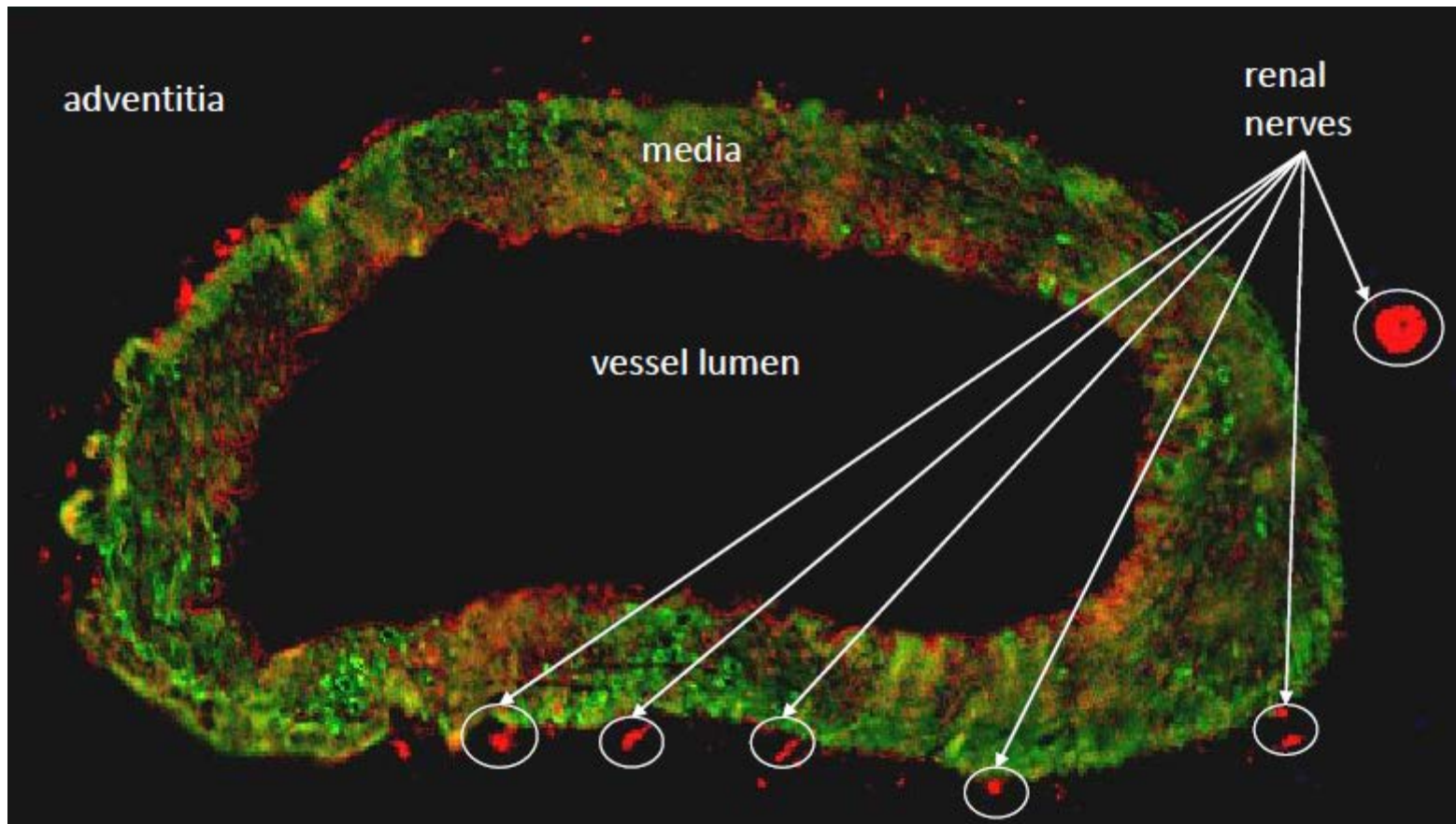
Sympathetic nerves terminals



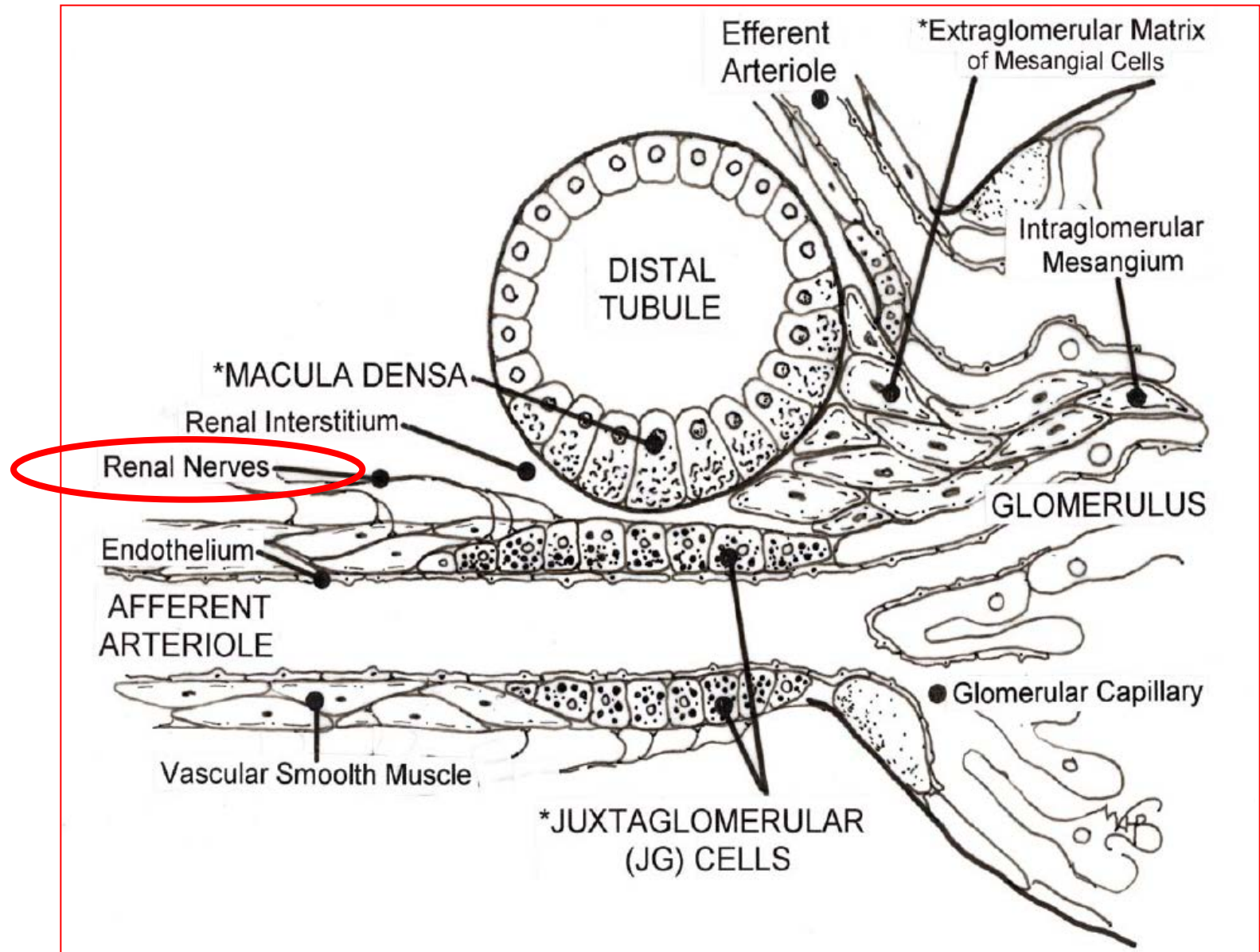
Sympathetic nerve fibers

SYMPATHETIC ANATOMY

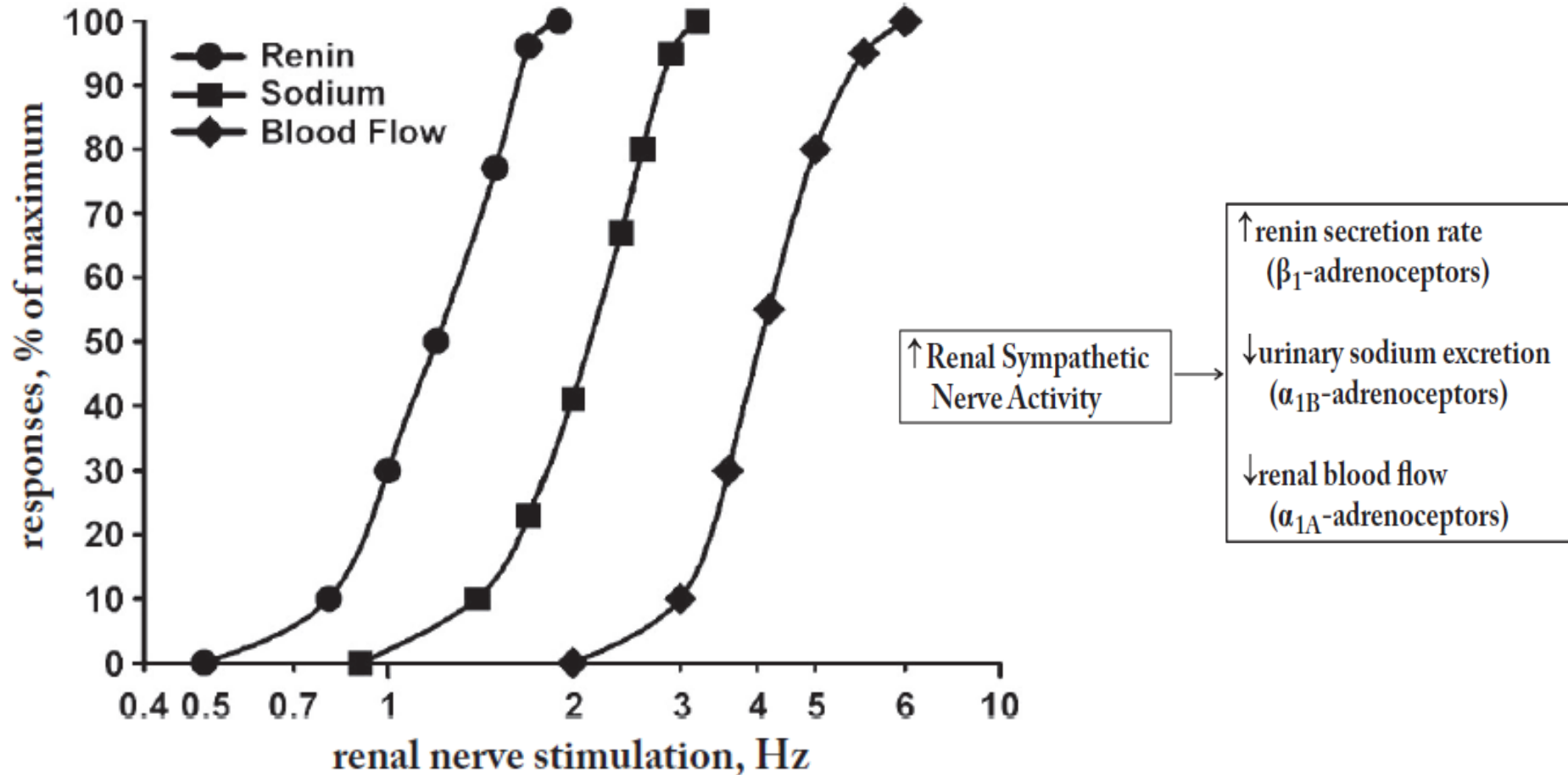
NERVES IN ADVENTITIA OF RENAL ARTERY



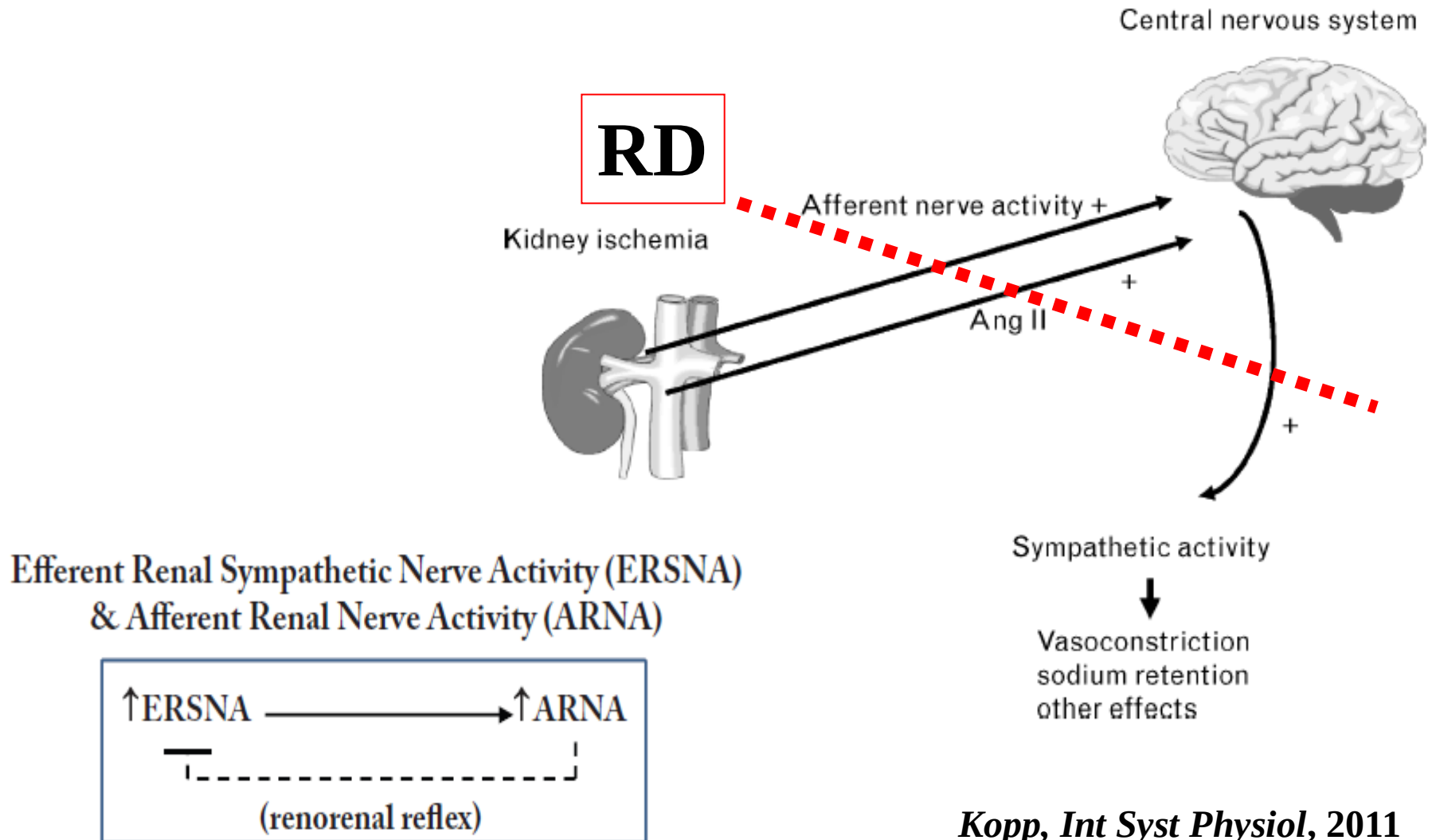
Anatomical juxtaposition of the juxtaglomerular apparatus



Surrogate of Neural renal function



RENORENAL REFLEX



Interventional Hypertension Renal Denervation Systems

ESH Position Paper: Renal denervation an interventional therapy of resistant hypertension

- **First step:** Exclude
 - False resistant hypertension (pseudoresistance) by using 24 h ambulatory blood pressure monitoring (ABPM) and home BP monitoring.
 - Secondary arterial hypertension
 - Causes which maintain high BP values and might be removed (obstructive sleep-apnea, high salt intake, BP raising drugs, severe obesity)
- **Second step:** Optimize antihypertensive treatment with at least three (or better four) tolerated drugs including a diuretic and an antialdosterone drug
- **Third step:** Consider anatomic contraindications due to unresolved safety issues (avoid RDN in case of multiple renal arteries, main renal artery diameter of less than 4mm or main renal artery length less than 20mm, significant renal artery stenosis, previous angioplasty or stenting of renal artery). Likewise, eGFR should be $> 45 \text{ ml/min/1.73m}^2$
- **Overall:**
 - Perform the procedure in very experienced hospital centers, such as hypertension excellence centers
 - Use devices which have demonstrate efficacy and safety in clinical studies

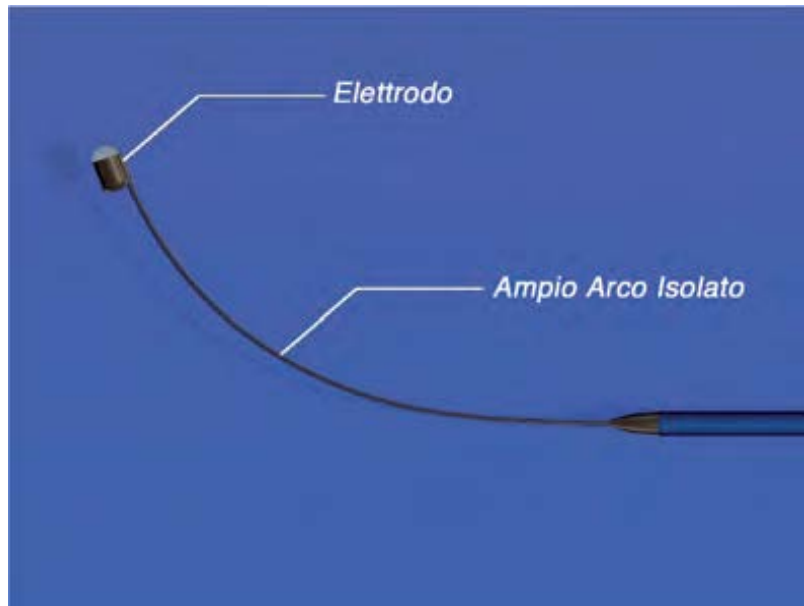
ESH Position Paper: Renal denervation

Anatomical Contraindications

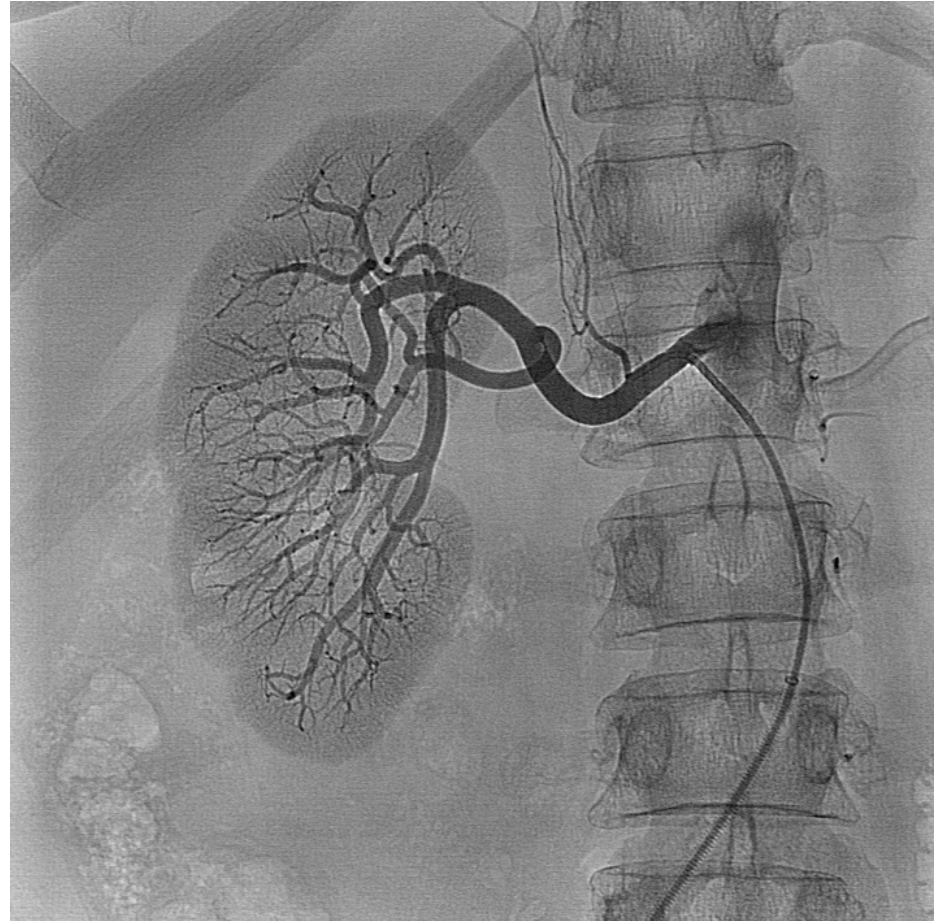
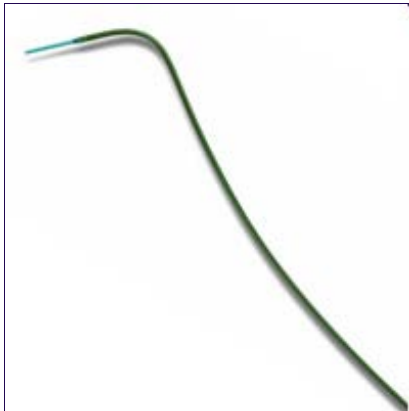
- Multiple renal arteries,
- Main renal artery diameter of less than 4mm or main renal artery length less than 20mm,
- Significant renal artery stenosis,
- Previous abdominal aortic grafts, angioplasty or stenting of renal artery



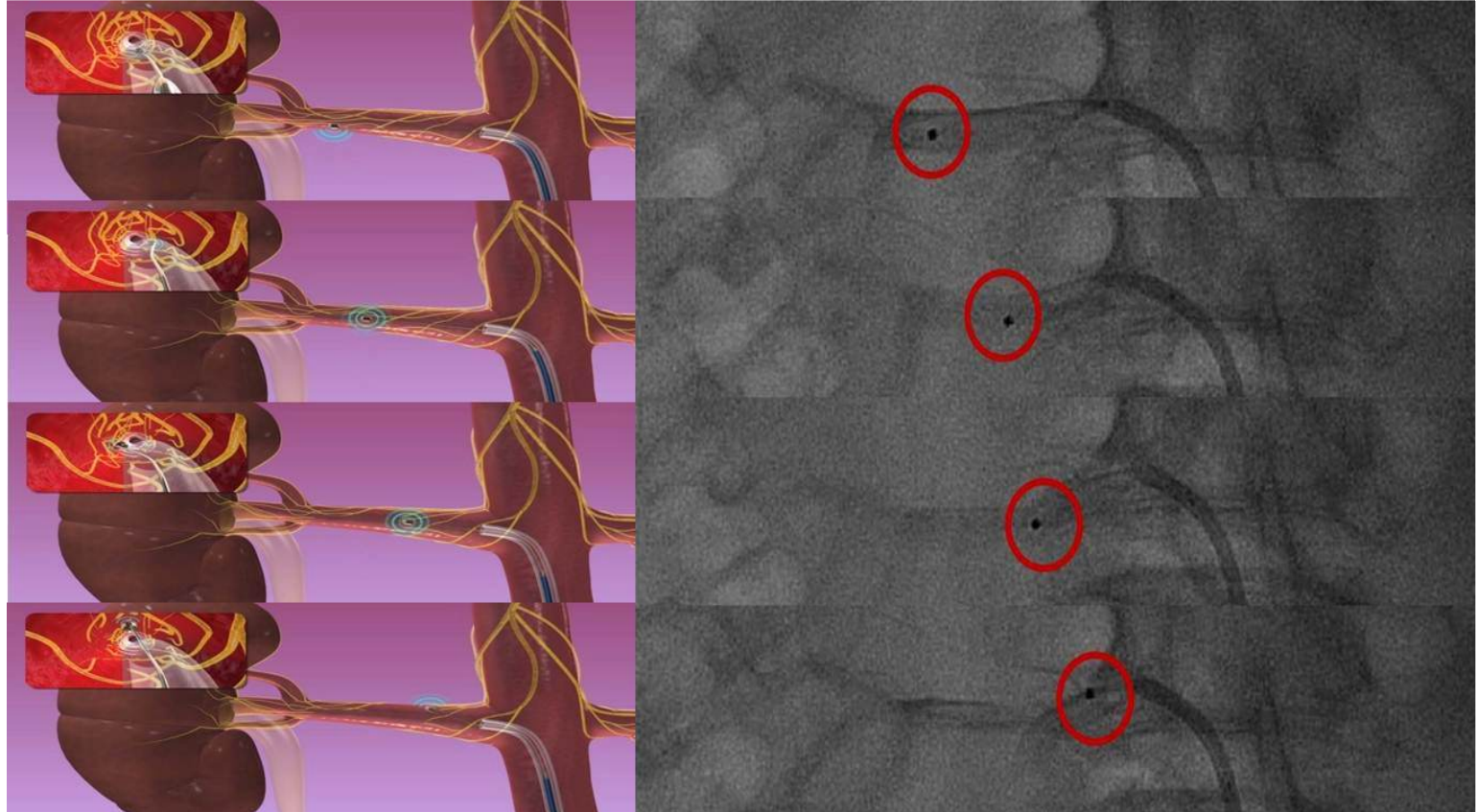
Medtronic Symplicity™ Point-by-Point Approach



Posizionamento del catetere guida in arteria renale

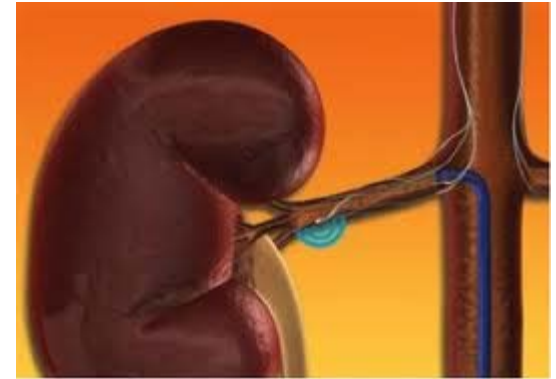


PROCEDURA DI RF RENALE



Serie di ablazioni endovascolari con intervalli di retrazione di circa 5 mm e di rotazione di circa 45° del catetere Symplicity

DATI OPERATIVI



$53,3 \pm 15,3$ min. (range 45 - 70)

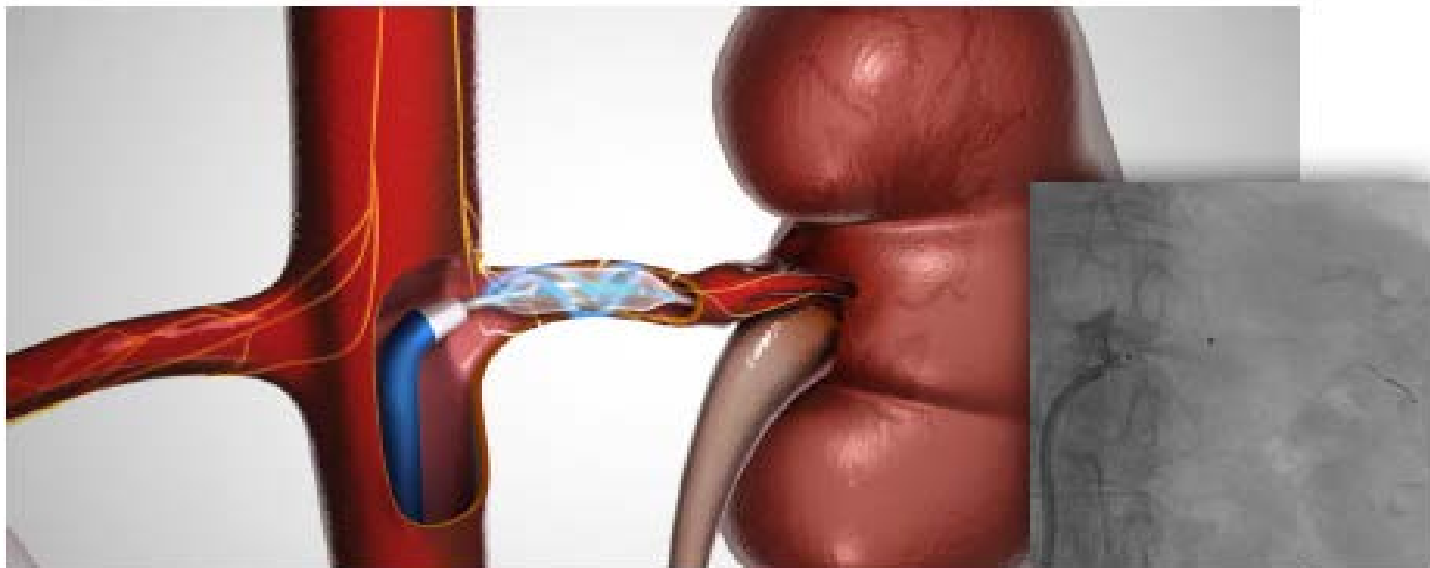
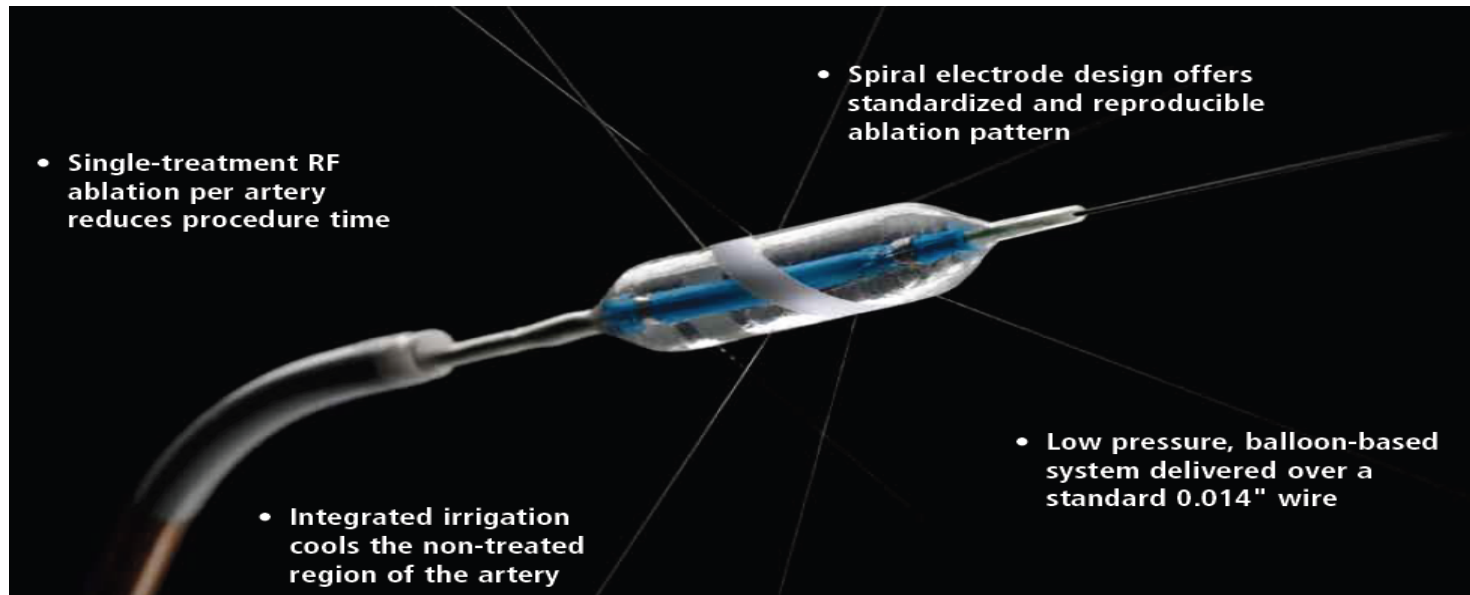
$105 \pm 22,9$ ml (range 85 – 130 ml) mdc Iomeron 300

2500 UI EBPM i.a. $\pm$ boli 2500 UI sec. ACT

200 μ g di Nitroglicerina selettivi in a. renale a bolo

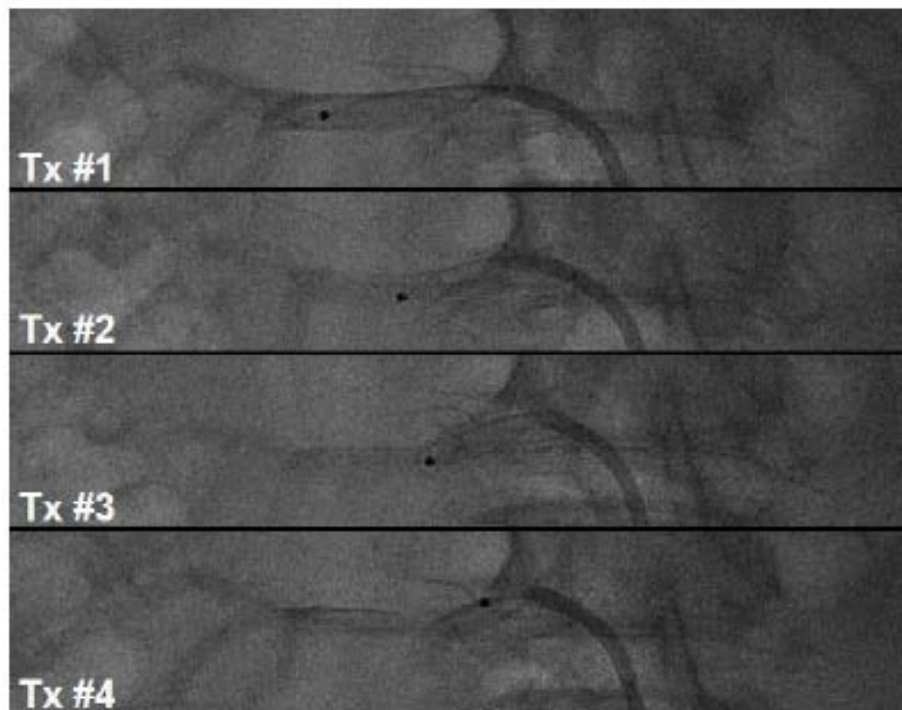
8,3 ablazioni con RF per arteria (range 6-11)

The Covidien OneShot™ renal denervation system

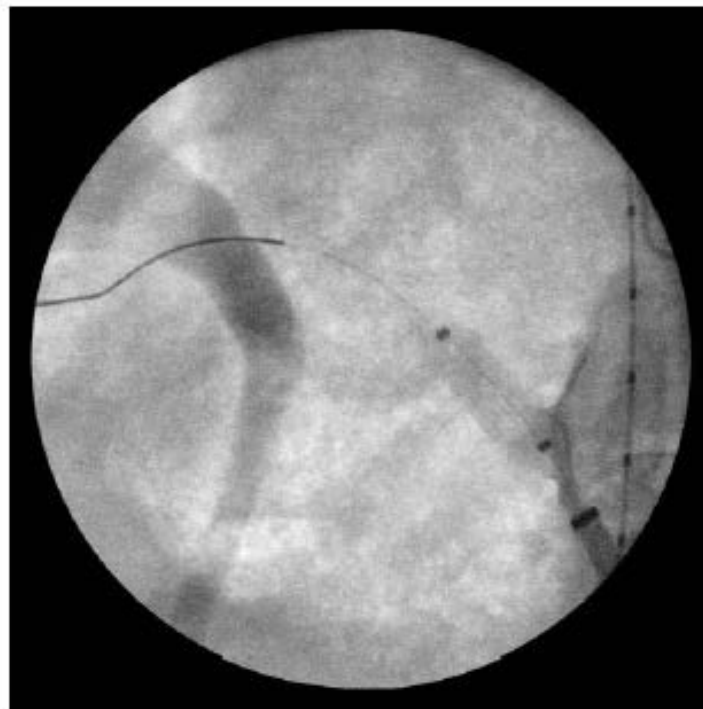


Fluoroscopy Images During Renal Denervation

Medtronic Symplicity™ point-by-point based treatment



Covidien OneShot™ balloon based treatment



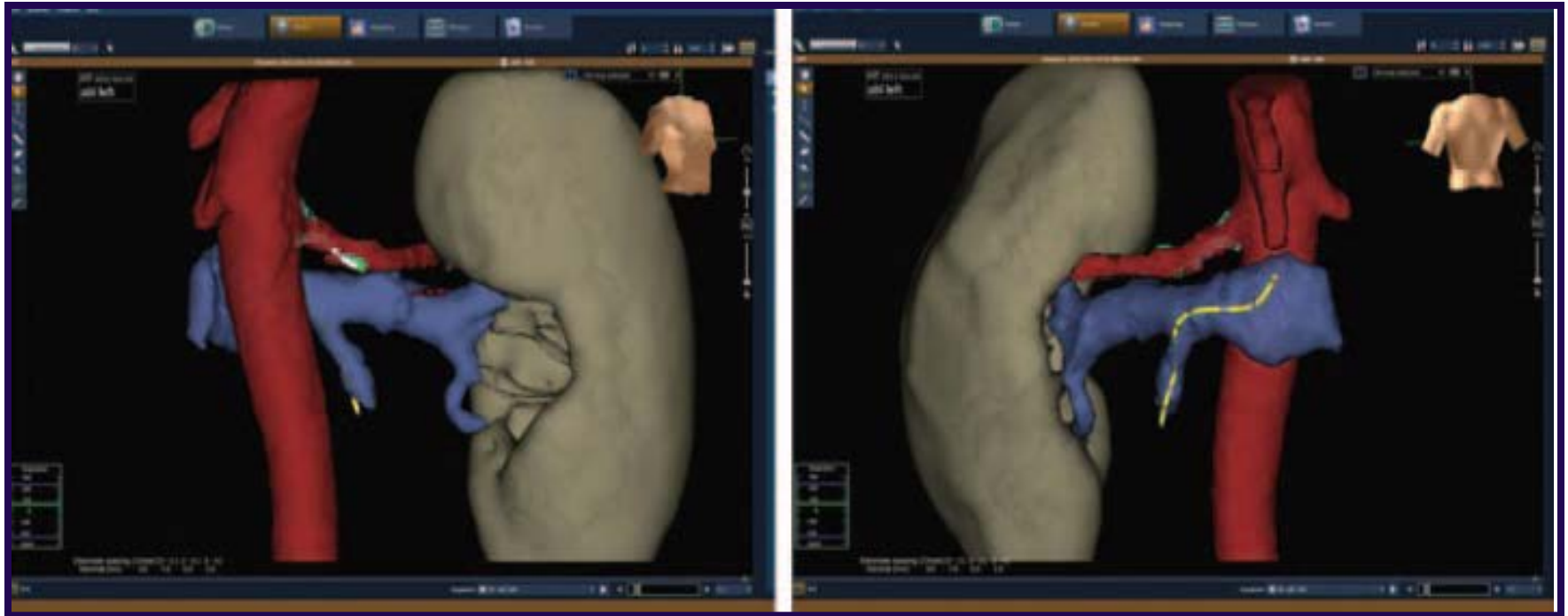
ENLIGHTEN™ Multi-Electrode System



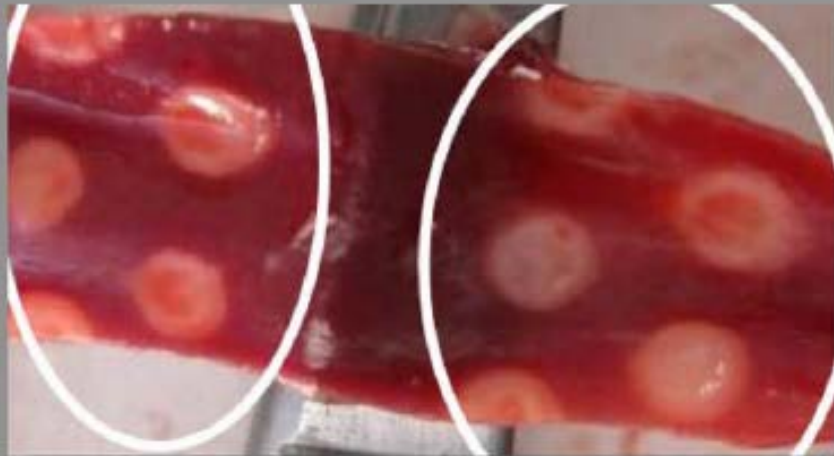
Multi-electrode catheter ablation system



Cooled tip 7F quadripolar radiofrequency ablation (IBI/St Jude) catheter



RENAL DENERVATION

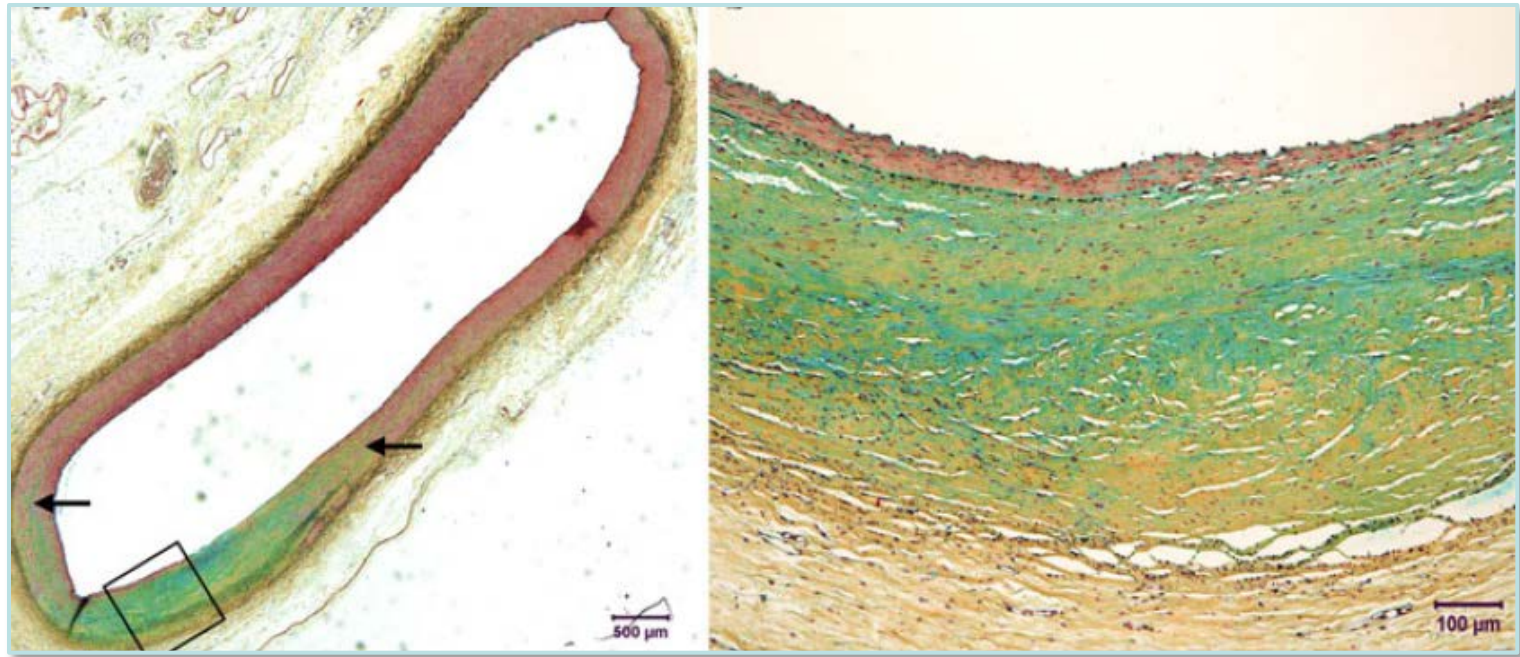


Acute



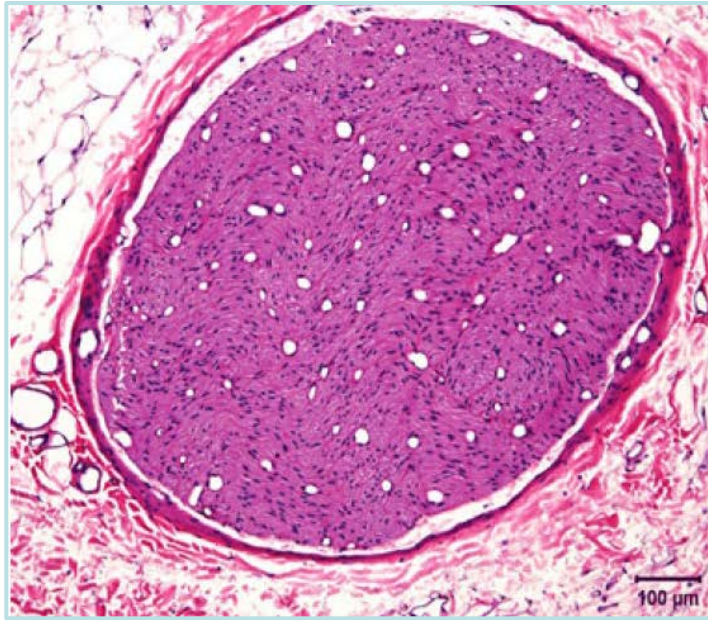
One Month

Six Month Post-Renal Denervation Histology (Porcine Model)

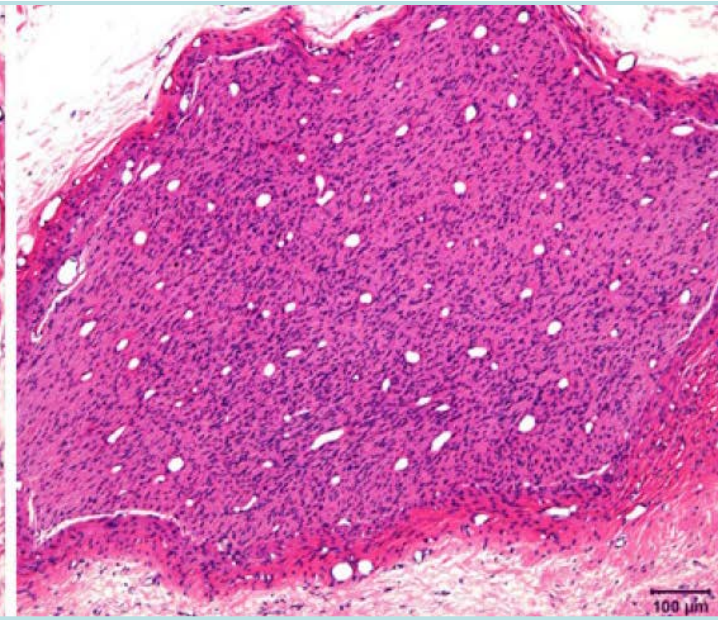


Six Month Post-Renal Denervation Nerve Histology (Porcine Model)

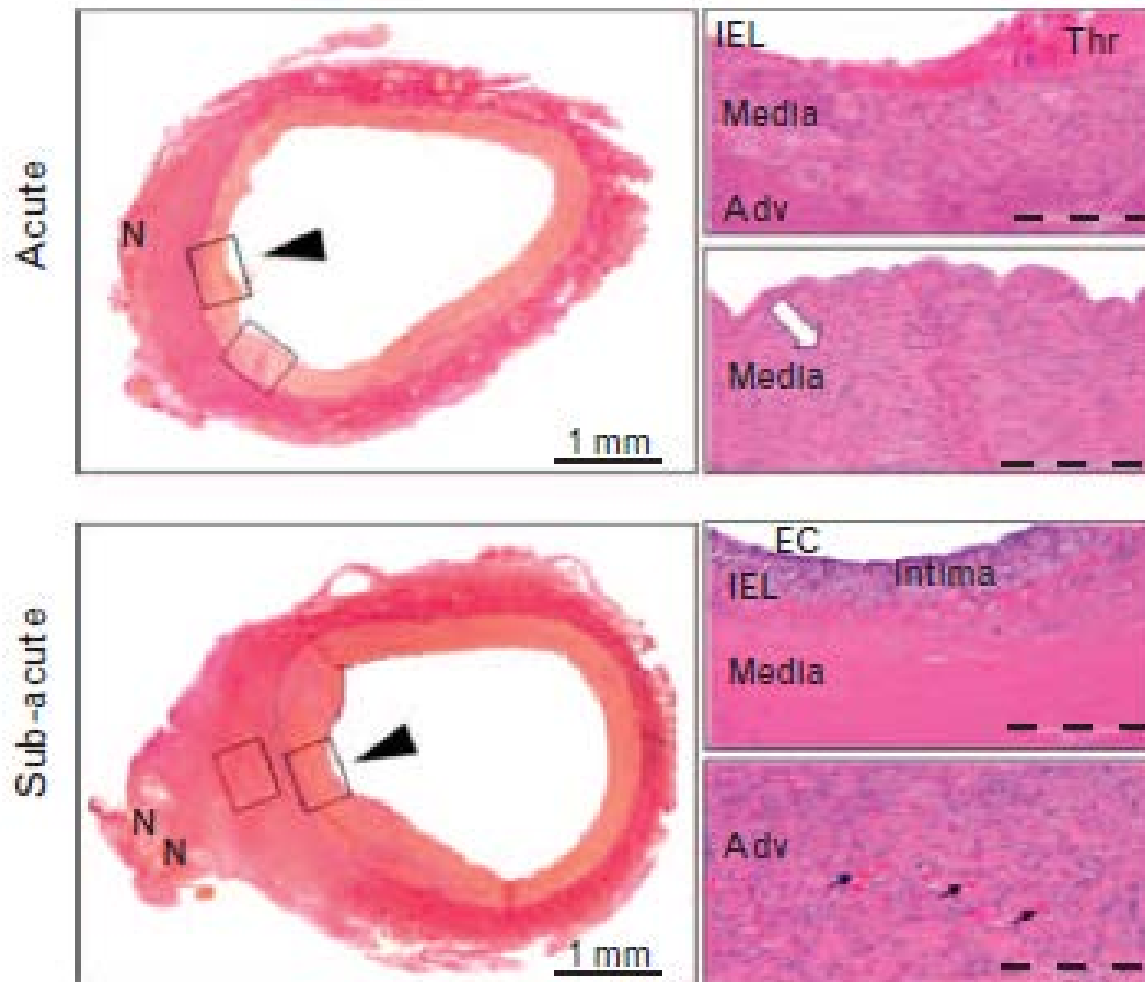
Nerve from Untreated Vessel



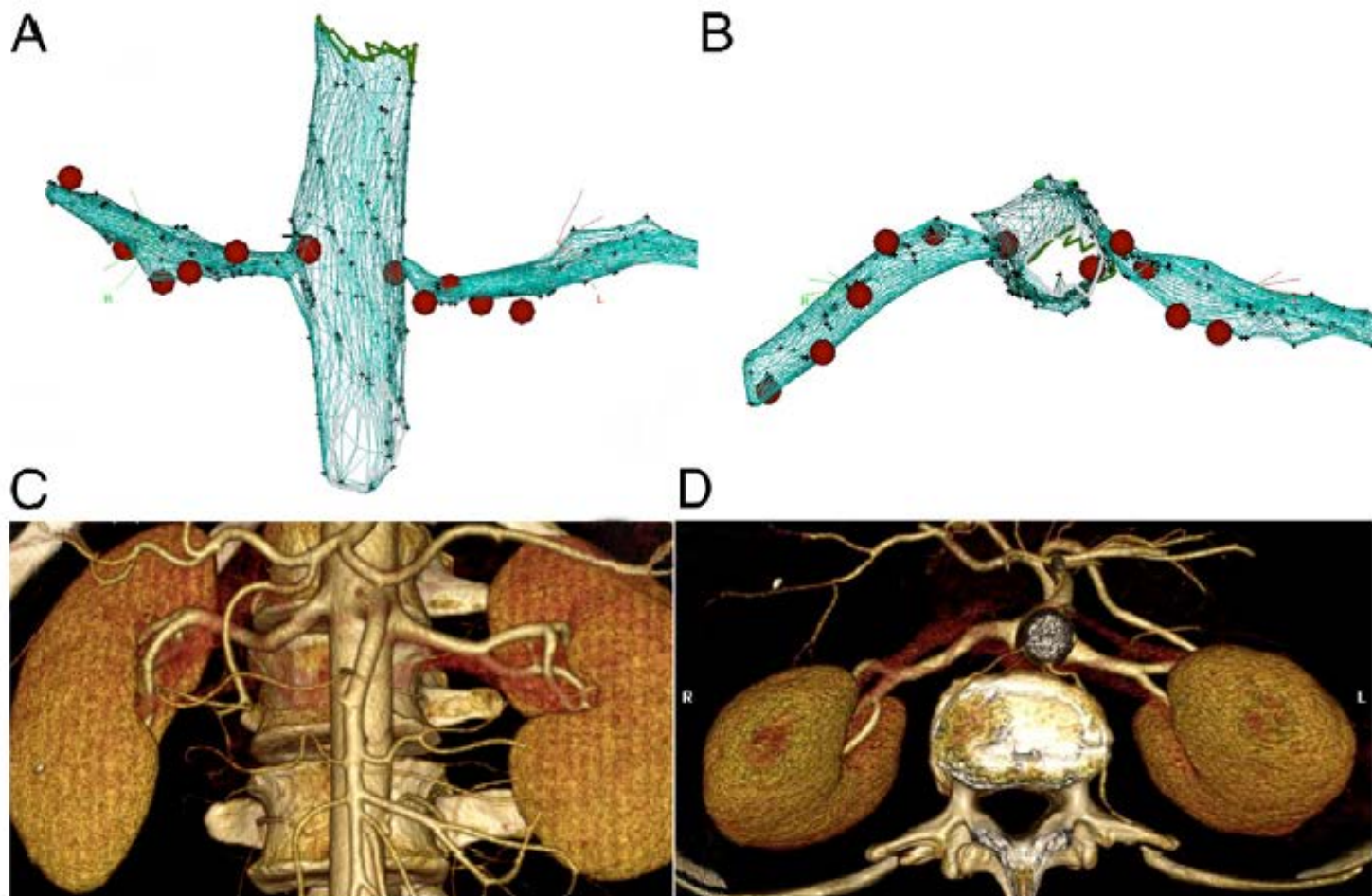
Nerve from Treated Vessel



Porcine histological cross-sections of the treated renal arteries

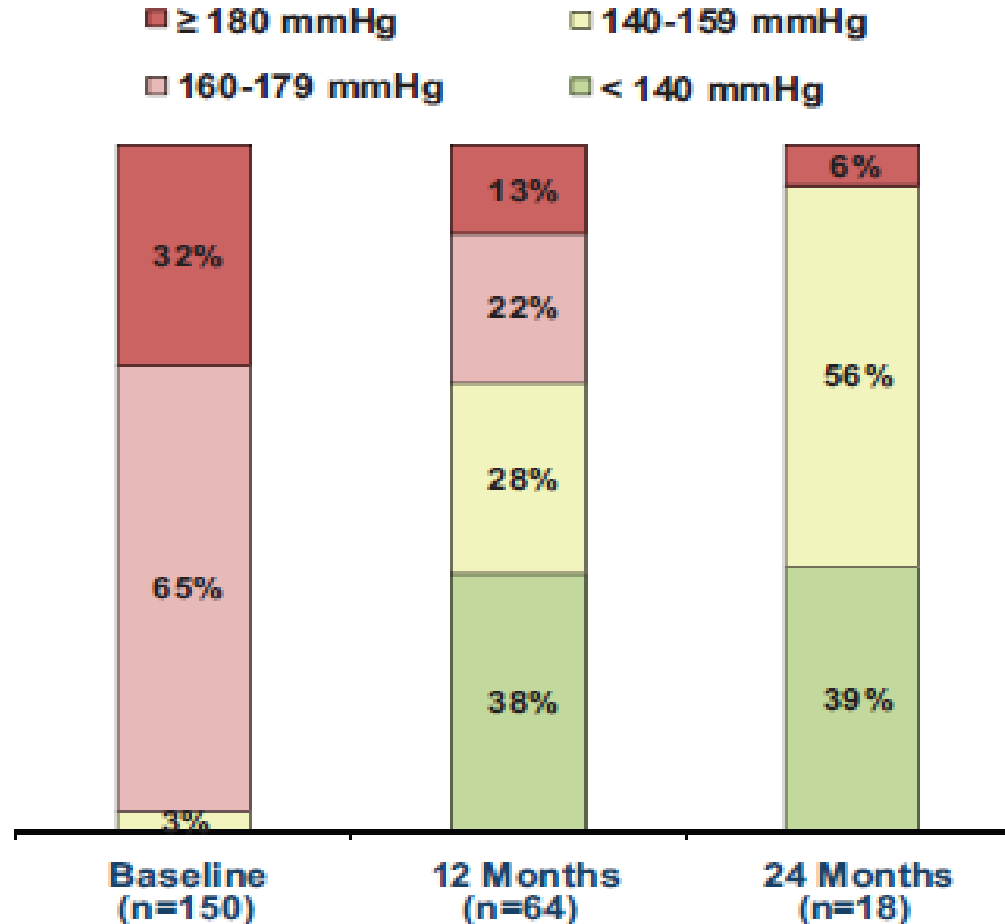


Imaging of Renal Arteries Before and After Ablation



Symplecity HTN-1

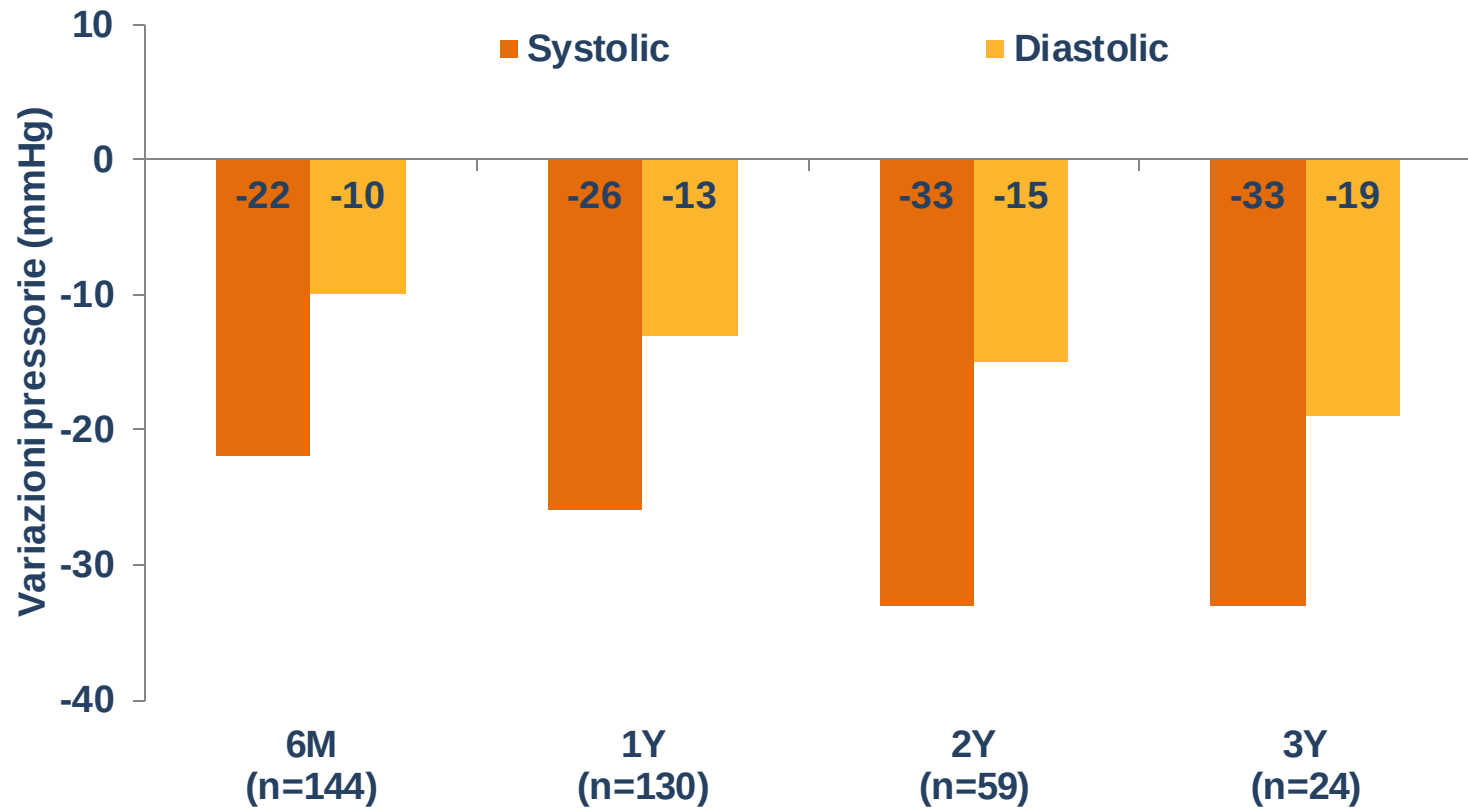
24-Month Renal Denervation



Interventional Studies

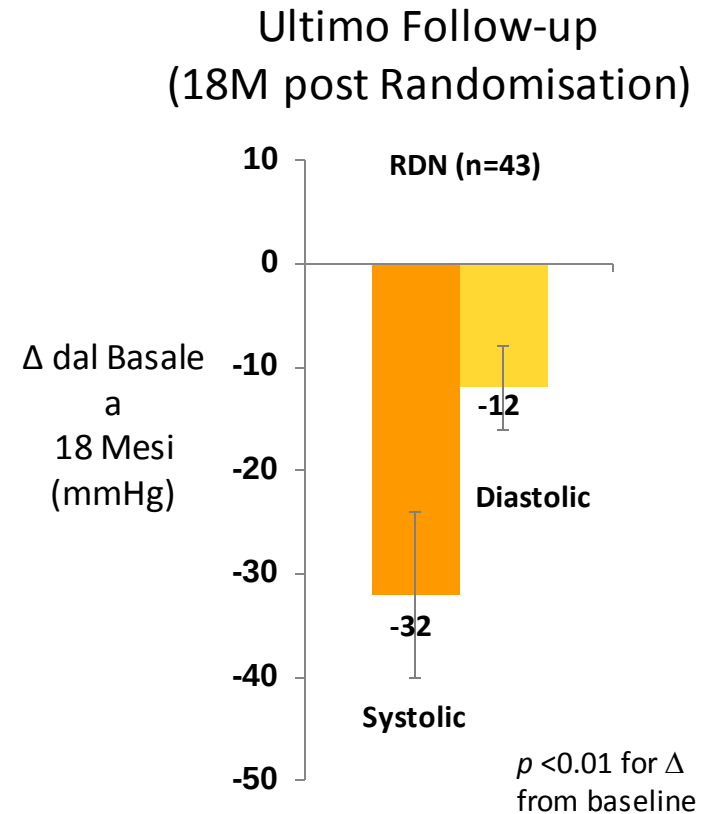
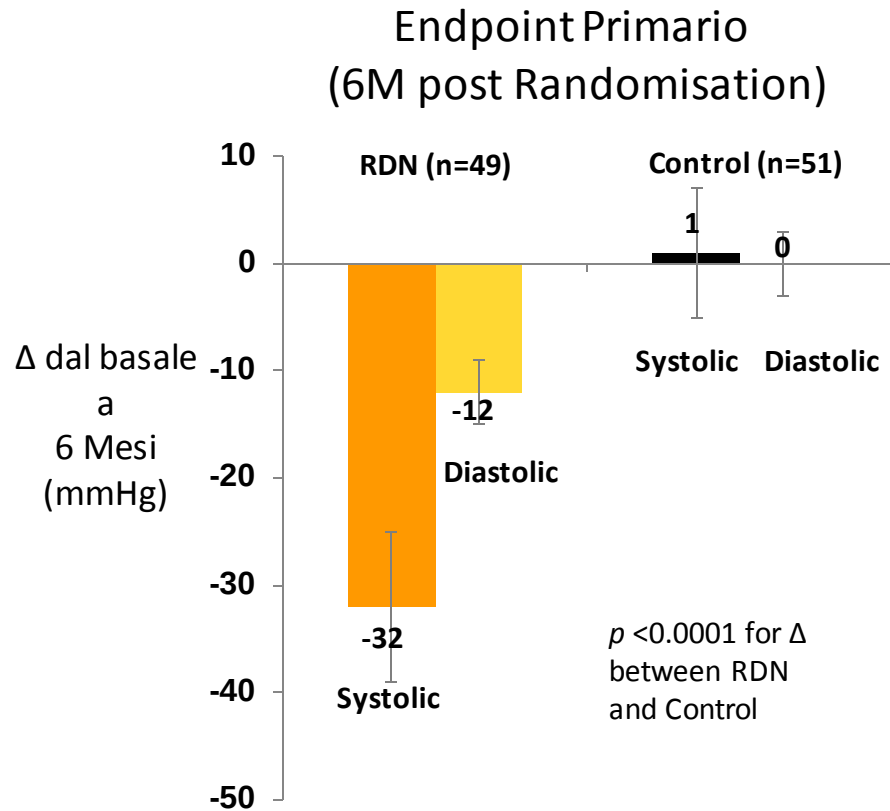
Hypertension Renal Denervation

SymPLICity HTN-1: follow up a 3 anni



$p < 0.01$ differenze significative per tutti i FU rispetto al valore di baseline

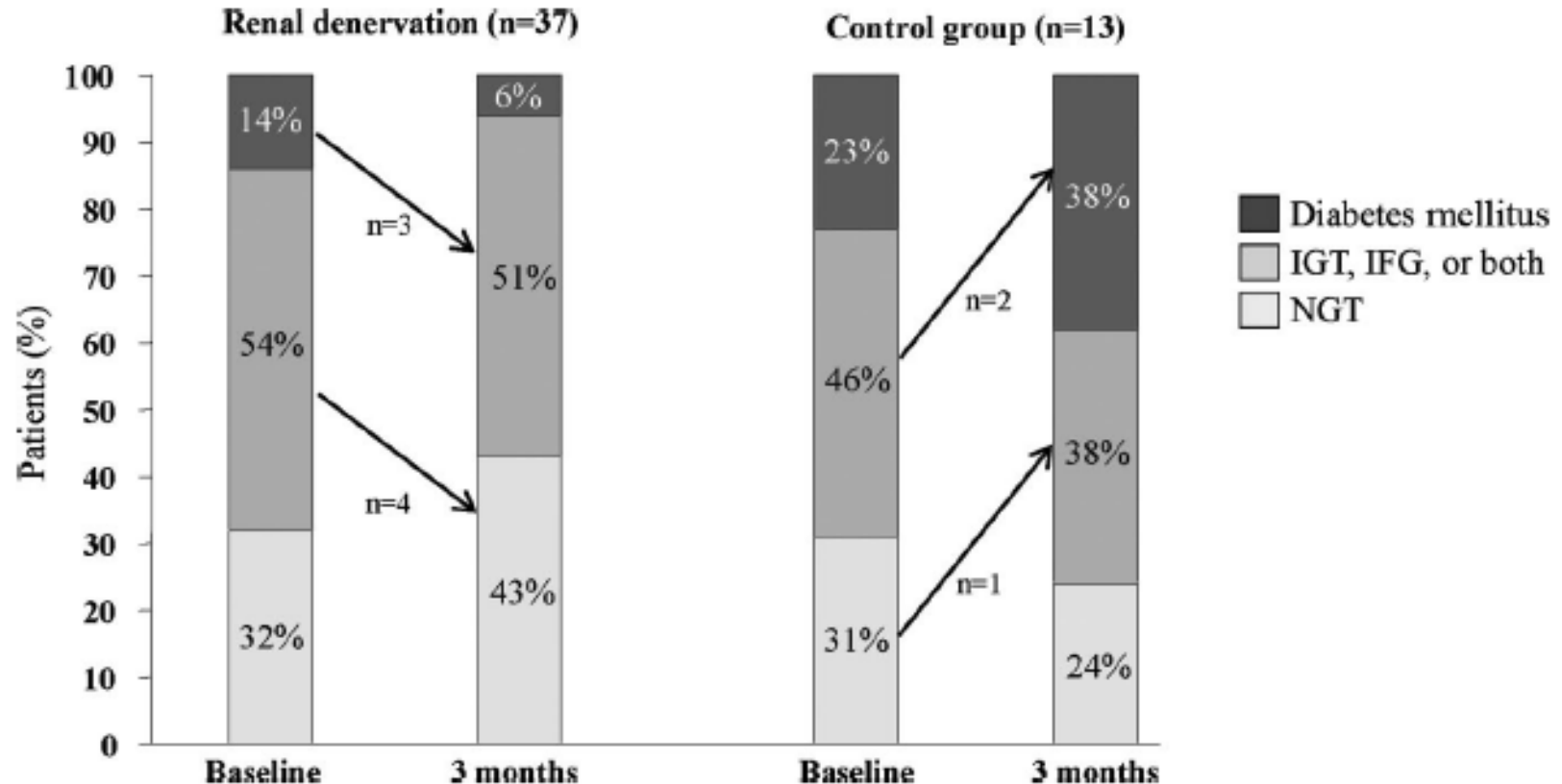
Symlicity HTN-2: Controllo a 18 mesi



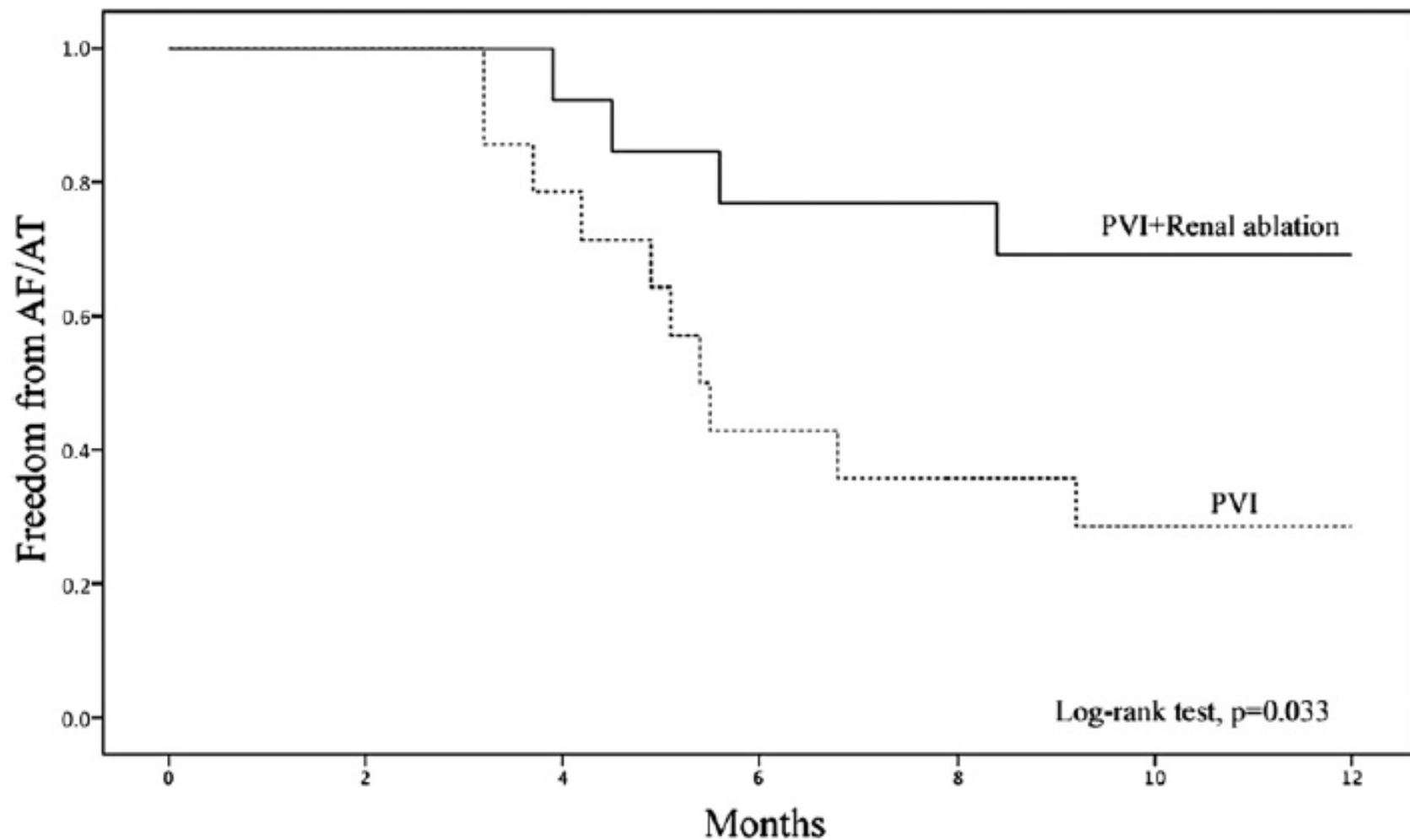
Primary Endpoint:

- >80% of RDN patients had ≥ 10 mmHg reduction in SBP
- 5 patients had ≤ 5 mmHg reduction in SBP

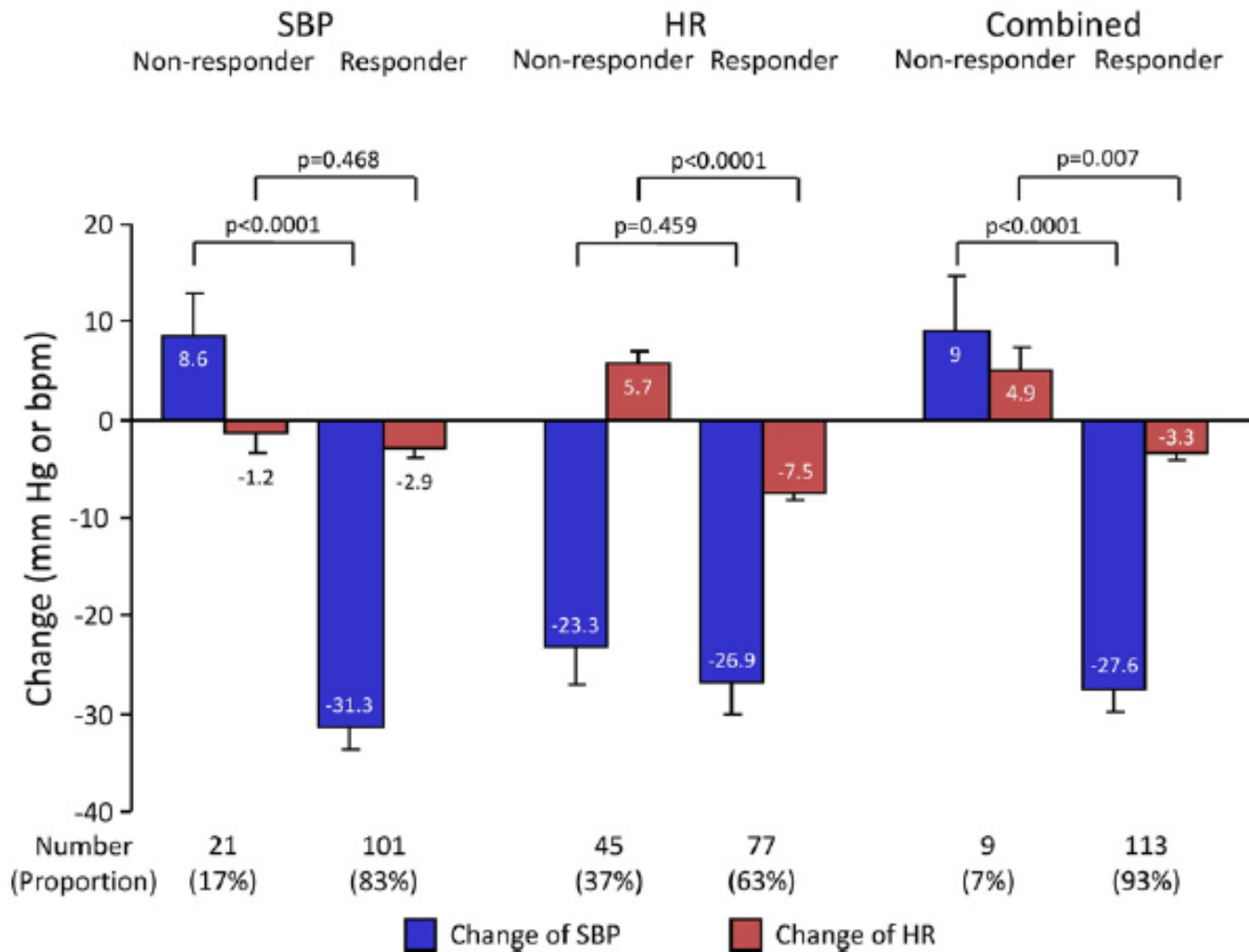
Renal Denervation Improves Glucose Metabolism



Incidence of AF Recurrences in Patients With and Without Renal Artery Denervation



Effects of renal sympathetic denervation on SBP and heart rate

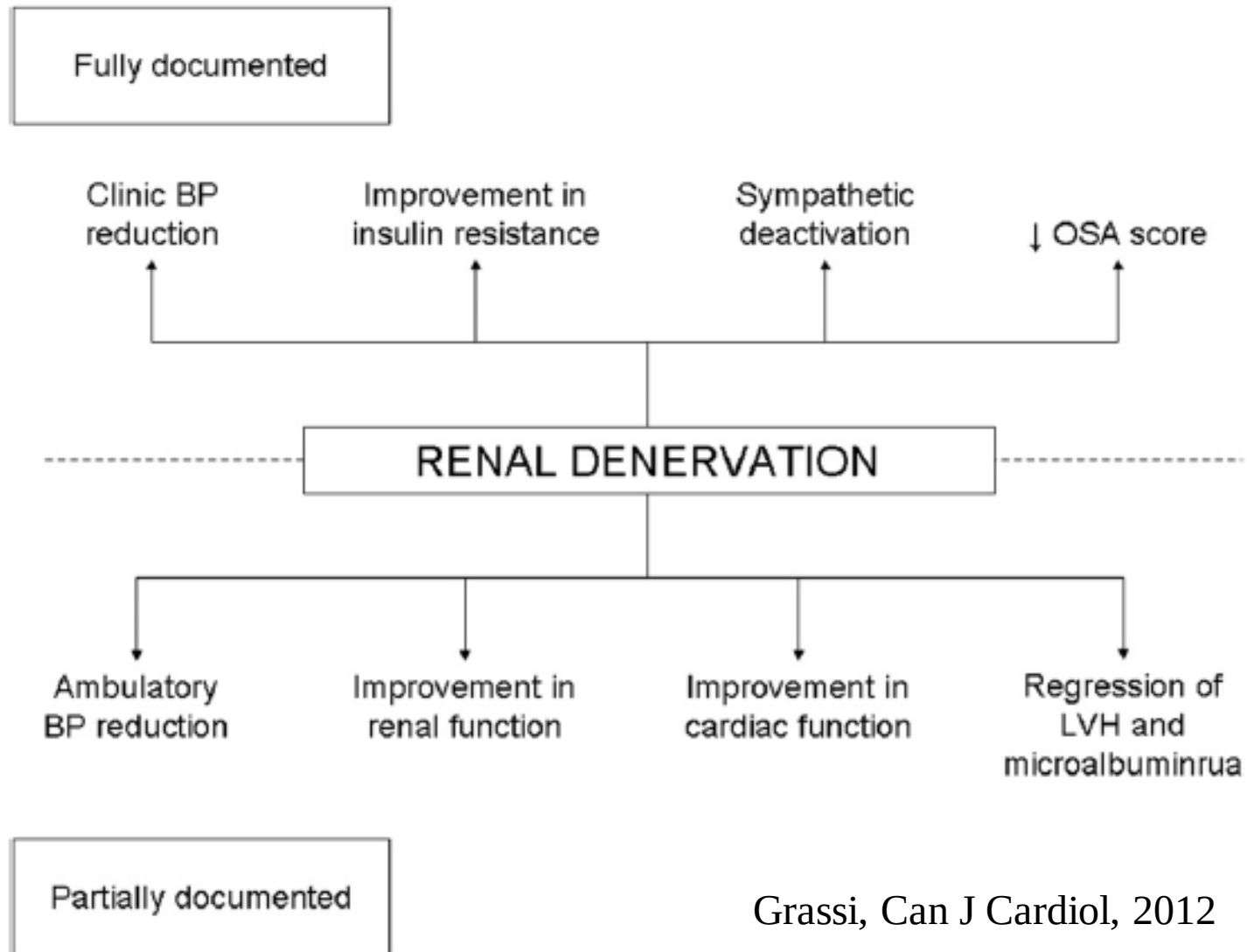


RENAL DENERVATION TRIALS in progress

The **RHAS** (Renal Hypertension Ablation System) OneShot

EnligHTN three months study

Perspectives of renal denervation

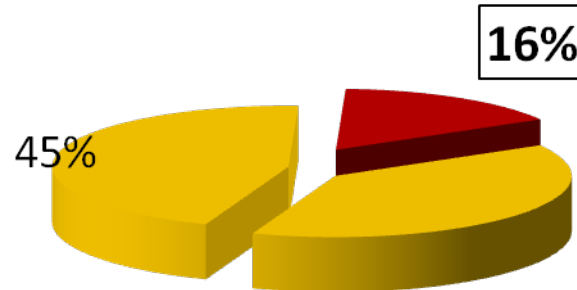


IPERTENSIONE RESISTENTE

Centro Ipertensione Torino

Pz totali = 9874

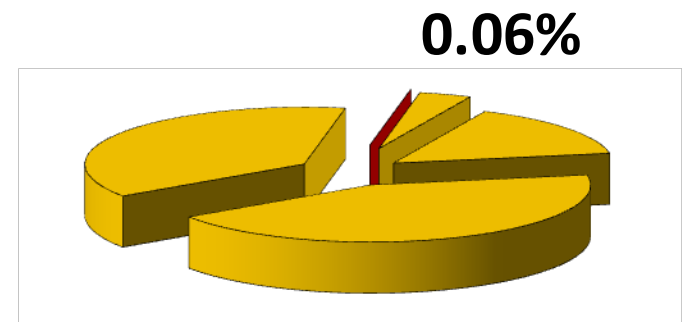
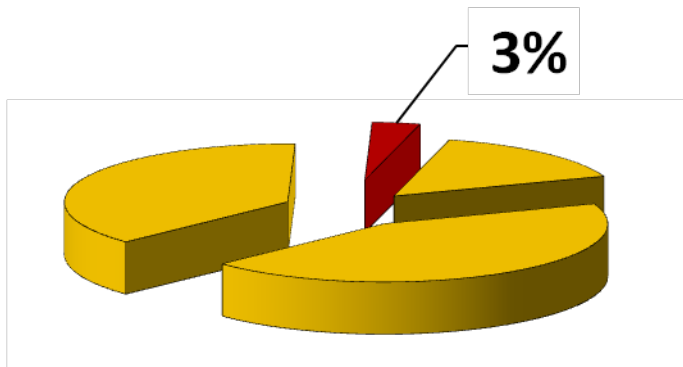
RESISTENTI (n=1520)



VERI RESISTENTI (n=357)

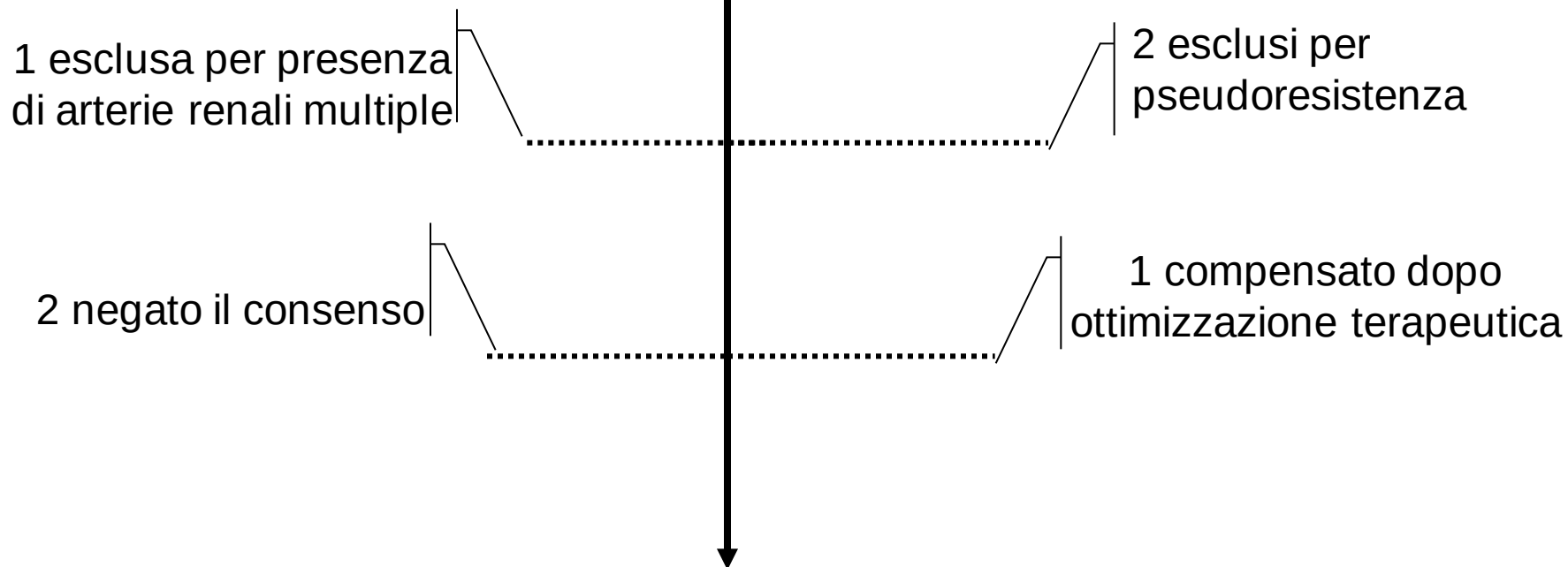


12 CASI ELEGGIBILI



CASISTICA 2011/12 CENTRO IPERTENSIONE TORINO

12 pazienti eleggibili (9 ♀, 3 ♂)



5 pazienti sottoposti a denervazione nel 2011-2012 (5 ♀)
1 paziente candidata a denervazione ottobre 2012

PROTOCOLLO OPERATIVO - TORINO

Valutazione eleggibilità del paziente iperteso resistente

SI

Esami ematochimici +microalbuminuria,sodiuria
PRA, Aldo, NM-M, eventuale test gravidanzaa)

Conferma di ipertensione resistente →

ABPM 24 ore

ANGIO TC o RM renale

Studio ecocardiografico – Pulse wave velocity-BRS

FOLLOW UP
CENTRO IA

INTERVENTO DI DENERVAZIONE RENALE
- Radiologia interventistica -

SI

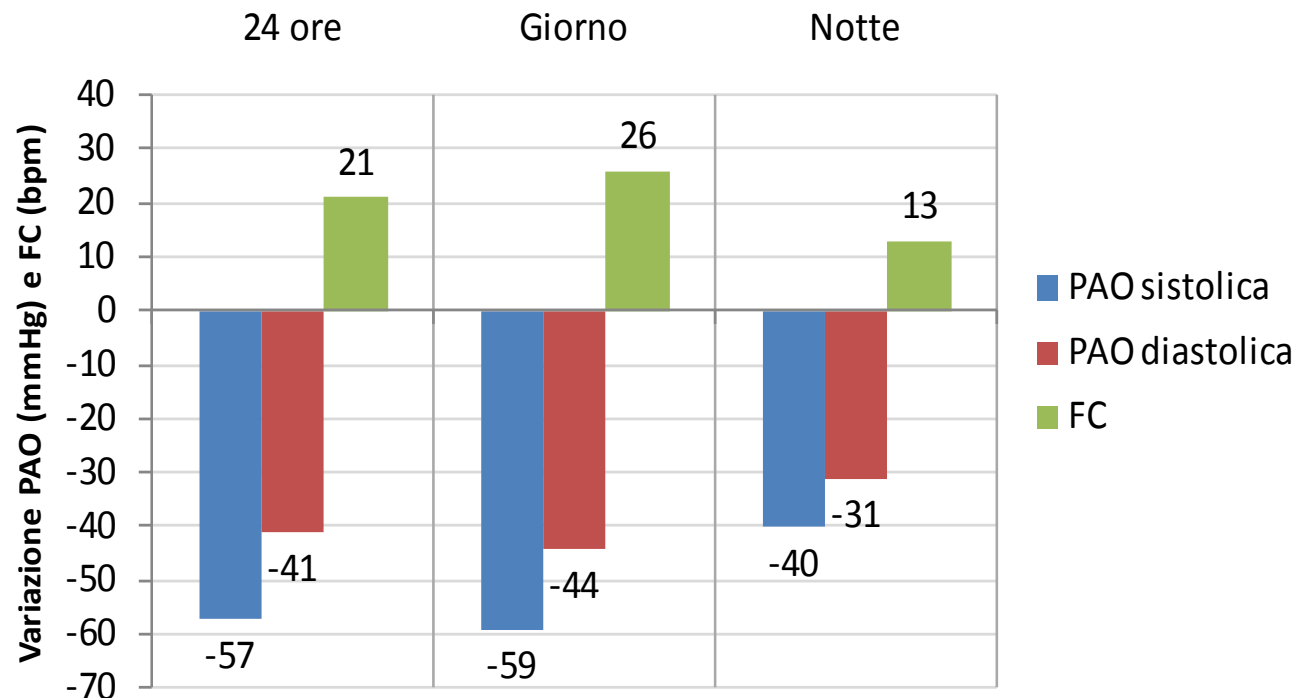
CARATTERISTICHE CLINICHE PAZIENTI

	Paziente 1	Paziente 2	Paziente 3	Paziente 4	Paziente 5
Età e sesso	44 ♀	40 ♀	49 ♀	52 ♀	50 ♀
PAO office (mmHg)	205/130	225/135	250/160	210/115	220/140
N. farmaci	10	11	12	7	13
BMI (Kg/m2)	32,7	31,2	29	21	22,4
DM	no	sì	no	no	no
Ictus	sì	sì	no	no	no

OUTCOME A BREVE

	Paziente 1	Paziente 2	Paziente 3	Paziente 4	Paziente 5
DENERVAZIONE	SI BILAT	SI BILAT	NO	SI BILAT	SI BILAT
Complicanze operatorie/ Post/ Operatorie	No/no	No/no	Dissecazione a. renale/no	No/no	Pseudoaneurisma a.fem/no
Ipotensione post intervento	No	Si marcata	Si moderata	No	No
Dolore	8/10	9/10	10/10	3/10	8/10
Terapia dolore	Morfina+ paracetamolo	Morfina+ paracetamolo	Morfina+ paracetamolo	paracetamolo	Morfina+ paracetamolo
Degenza (giorni)	3	4	7	3	3

Denervazione renale: follow-up 6 mesi



MSVAlt basale $76 \text{ g/m}^{2,7}$



MSVAlt a sei mesi $55 \text{ g/m}^{2,7}$

Riepilogo dati ricovero

Stato Cartella: Sola lettura	S.C.: 2666-Medicina Interna 4	
Cartella N°: 2011046122	Tipo di episodio: Ricovero Ordinario	
Assistito: ZANINI MARIA LORENZA	Data di Nascita: 30/06/1959	Sesso: Femmina
Data di accettazione: 15/11/2011	Data di dimissione: 18/11/2011	GG Degenza: 3
Condizione di dimissione: 2-Ordinaria	DRG: 120 - Altri int. su app. circolatorio	MDC: 05: 05-Mal. e dist. sis.cardiocircol
Categoria DRG: C: C - peso > 2.0	Peso DRG: 3,1099	N.ro di calcoli: 8
Tipo DRG: Chirurgico	Primo calcolo: 24/11/2011	Ultimo calcolo: 14/12/2011

Diagnosi		
Progr.	Data	Codice Descrizione
1	24/11/2011	4010 IPERTENSIONE ESSENZIALE MALIGNA
2	24/11/2011	40490 CARDIONEFROPATIA IPERTENSIVA NON SPECIFICATA SENZA INSUFFICIENZA CARDIACA E CON PATOLOGIA RENALE CRONICA DALLO STADIO I ALLO STADIO IV, O NON SPECIFICATA
3	24/11/2011	3004 DISTURBO DISTIMICO
	15/11/2011	Accettazione ipertensione resistente

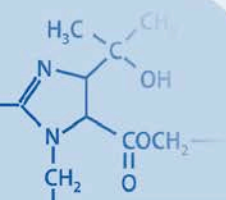
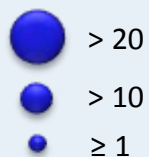
Procedure		
Progr.	Data	Codice Descrizione
1	16/11/2011	0525 SIMPATECTOMIA PERIARTERIOSA
2	16/11/2011	8845 ARTERIOGRAFIA DELLE ARTERIE RENALI
3	16/11/2011	9926 INIEZIONE DI TRANQUILLANTI
4	16/11/2011	9918 INIEZIONE O INFUSIONE DI ELETROLITI
5	15/11/2011	8744 RADIOGRAFIA DEL TORACE DI ROUTINE, SAI
6	15/11/2011	8952 ELETTROCARDIOGRAMMA

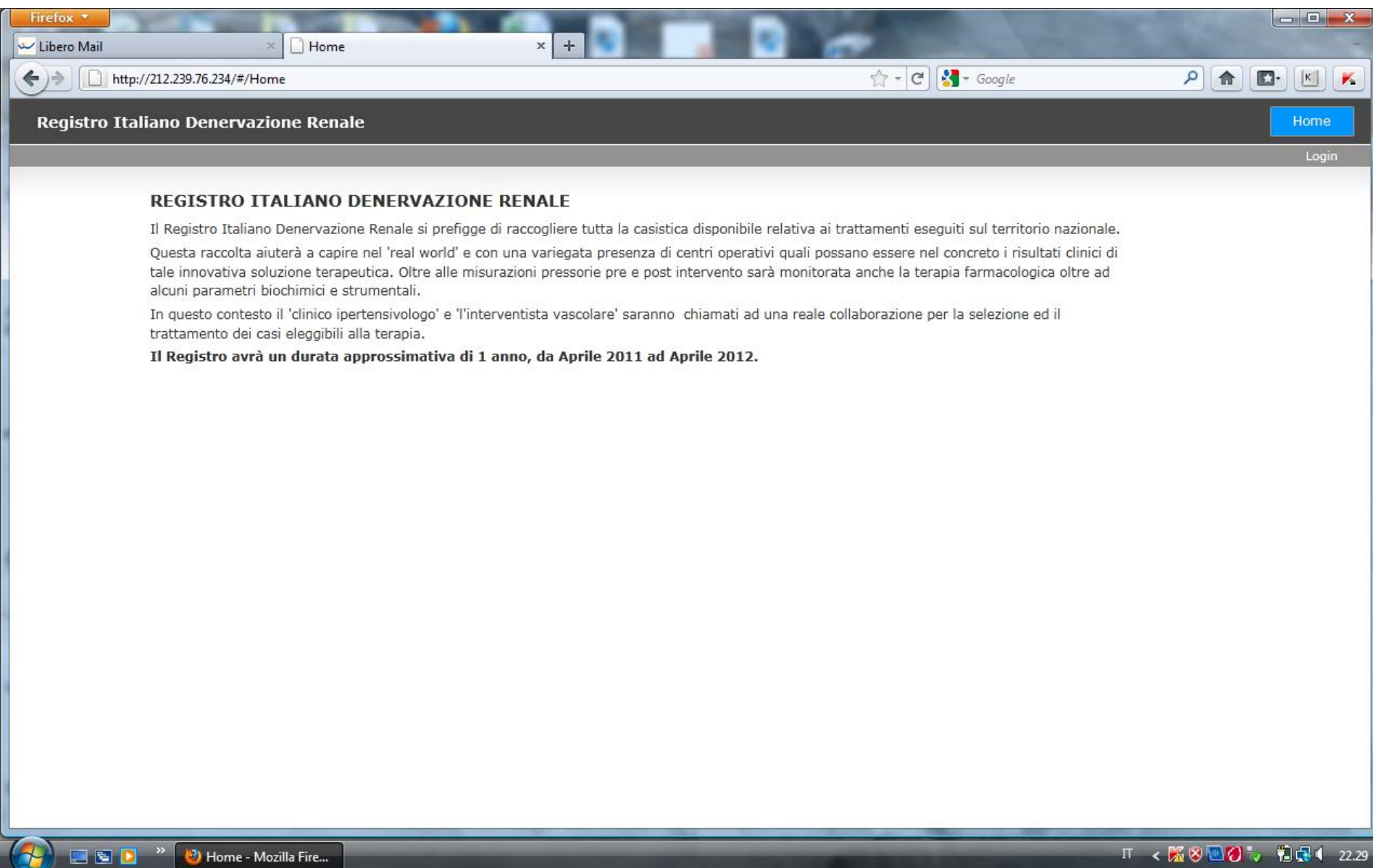
DRG 120 peso 3,1 concordato con Direz. Sanitaria

Centri Attivi RDN

31 Centri Attivi

138 Casi effettuati







Grazie