

13^o Meeting
CardioLucca2019
 Cuore d'Autore Lucca, 7-9 febbraio 2019



Il futuro della denervazione renale nella terapia cardiovascolare




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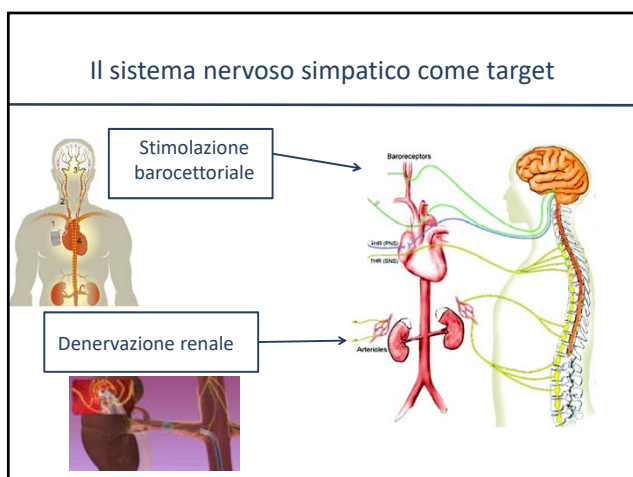
DISCLOSURE INFORMATION

Stefano Taddei

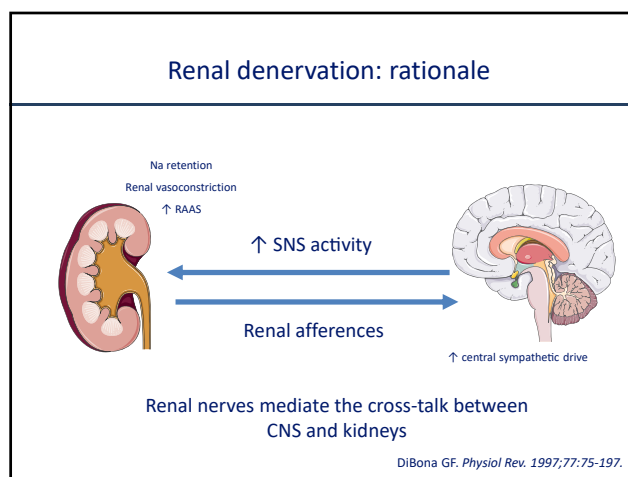
negli ultimi due anni ho avuto i seguenti rapporti anche di
 finanziamento con soggetti portatori di interessi commerciali in
 campo sanitario:

Servier, Pfizer, Boheringer Igelheim,
 Sanofi Aventis, Menarini

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Renal denervation: brief history of rise and fall ... and rise again?

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Denervazione renale: sperimentazione dei devices al momento dell'immissione in commercio

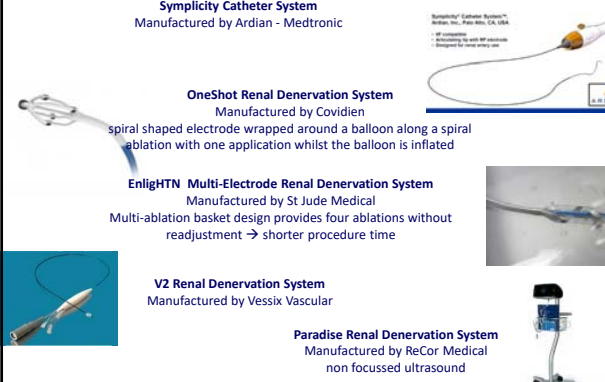
Symlicity Catheter System
Manufactured by Ardian - Medtronic

OneShot Renal Denervation System
Manufactured by Covidien
spiral shaped electrode wrapped around a balloon along a spiral ablation with one application whilst the balloon is inflated

EnligHTN Multi-Electrode Renal Denervation System
Manufactured by St Jude Medical
Multi-ablation basket design provides four ablations without readjustment → shorter procedure time

V2 Renal Denervation System
Manufactured by Vessix Vascular

Paradise Renal Denervation System
Manufactured by ReCor Medical
non focussed ultrasound



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Denervazione renale: sperimentazione dei devices al momento dell'immissione in commercio

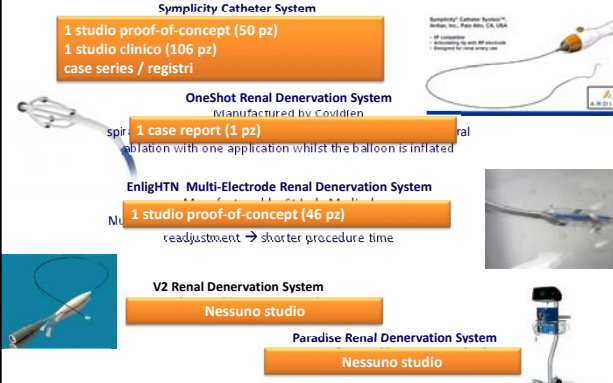
Symlicity Catheter System
1 studio proof-of-concept (50 pz)
1 studio clinico (106 pz)
case series / registri

OneShot Renal Denervation System
Manufactured by Covidien
1 case report (1 pz)

EnligHTN Multi-Electrode Renal Denervation System
Manufactured by St Jude Medical
1 studio proof-of-concept (46 pz)
readjustment → shorter procedure time

V2 Renal Denervation System
Nessuno studio

Paradise Renal Denervation System
Nessuno studio



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Perchè la denervazione renale è stata proposta per il trattamento dell'ipertensione resistente?

- La denervazione renale è una procedura la cui indicazione è la riduzione dei valori pressori.
- La logica vorrebbe che la sua applicazione clinica fosse stata preceduta da uno sviluppo analogo a quello al quale sono "obbligati" i farmaci antipertensivi.
- Pertanto per evitare uno sviluppo clinico pre-marketing lungo e costoso, la denervazione renale è stata proposta per pazienti affetti da ipertensione resistente/refrattaria per i quali le opzioni terapeutiche convenzionali sono inefficaci o non applicabili e quindi è possibile utilizzare metodologie ancora in fase sperimentale.

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Denervazione renale: evidenze cliniche

Clinical trials	Trial design	Study population	BP / drugs at baseline	BP reduction at the end	24-hours BP monitoring
Symplcity HTN-1 study	proof-of-concept efficacy and safety study	50 patients with severe RH (office systolic BP >160mmHg with 3+ medications, including a diuretic)	177/101 mmHg on BP-lowering 5.1 drugs	- 27/17 mmHg after 12 months	Not performed
Symplcity HTN-1 study - extended follow-up	efficacy and safety study	153 patients with severe RH	176/98 mmHg on 5.1 BP-lowering drugs	- 32/14 mmHg at 24 months	Not performed
Symplcity HTN-2 study	multicenter, prospective, randomized clinical trial	106 patients with RH and office systolic BP >160 mmHg (or >150 mmHg for patients with type 2 diabetes)	178/96 mmHg	-32/12 mmHg at 6 months	Performed in a subgroup: BP reduction -11/-7mmHg (p<0.05)

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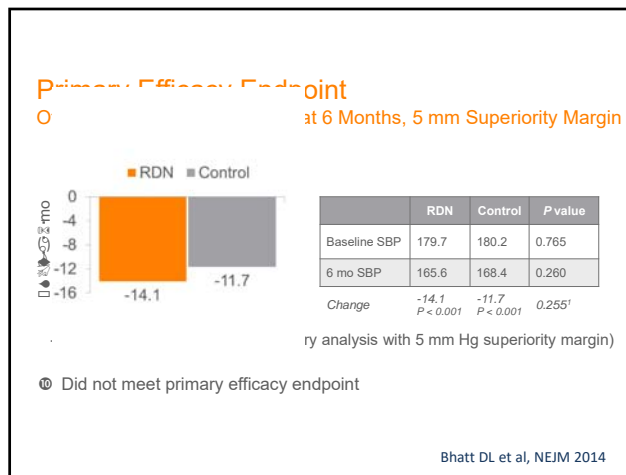
Studi negativi!!

- Brinkmann J et al *Hypertension* 2012;60:1485
- Fadl Elmula FE et al *Hypertension* 2013;62:526
- Ezzahti M et al *J Hypertens* 2014; 32:135

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La doccia fredda!!

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Simplicity HTN III - Reasons for failure

- 31% of operators performed only 1 procedure, only 12% performed >5 procedures
- 37% patients treated with only 1-2 applications of RF
- Patients in the sham actively titrated with diuretics and anti-hypertensives
- Most patients did not have resistant HTN

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In un mondo normale Simplicity HTN-3, a causa dei suoi vari problemi metodologici, non sarebbe mai stato pubblicato sul New England Journal of Medicine!

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La follia!!

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Cardiovascular Daily
Latest Breaking Cardiology News from
The American Heart Association and MedPage Today

American Heart Association | American Stroke Association | medpage TODAY

April 01, 2014

SYMPPLICITY: Is This the End of Renal Denervation?
As has been known since January, renal denervation with Medtronic's Symplivity catheter was safe, but it was no better than a sham procedure for reducing office blood pressure in the SYMPPLICITY HTN-3 trial, full results showed.
[Read more](#)

- In UK, dove la denervazione era stata utilizzata in modo estensivo e i grossi ospedali si erano attrezzati per essere centri hub, ora la metodica è stata proibita per l'utilizzo clinico, a meno che non sia eseguita all'interno di studi clinici controllati.

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2018 ESC/ESH Hypertension Guidelines

Device-based therapies for hypertension		
Recommendation	Class ^a	Level ^b
Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available. ^{3,67,368}	III	B

RCT = randomized controlled trial.
^aClass of recommendation.
^bLevel of evidence.

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Esaminiamo ora le cause di questo fallimento.

Esaminiamo ora le cause di questo **apparente** fallimento.

Problemi metodologici
 Tipologia di pazienti

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Problemi metodologici

- Tecnica "troppo" operatore dipendente
- Difficoltà di ottenere una denervazione completa

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Tipologia di pazienti:
 l'ipertensione resistente è l'indicazione appropriata per la denervazione renale?

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In realtà l'ipertensione veramente resistente, non è la condizione clinica ideale perché la denervazione renale mostri la sua efficacia.

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Il paziente iperteso realmente resistente è in genere caratterizzato da alterazioni strutturali che difficilmente possono regredire con qualsiasi tipo di terapia.

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Inoltre questi pazienti sono solitamente trattati con 4-5 classi di farmaci che includono beta-bloccanti e alfa-litici.

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Infine, l'ipertensione veramente resistente è una realtà clinica molto difficile da identificare.

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Possible future indications for RDN
Taddei S. 2014

- RDN use restriction to resistant hypertensive patients only might have stopped research on more promising target populations
- Young patients, with short disease duration
- Patients with high BP variability
- Patients with low compliance to conventional drug treatment
- Patients with multiple drug-related side effects

Which company will ever test these indications after Symplicity HTN-III publication?

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Un nuovo interesse per la
denervazione renale

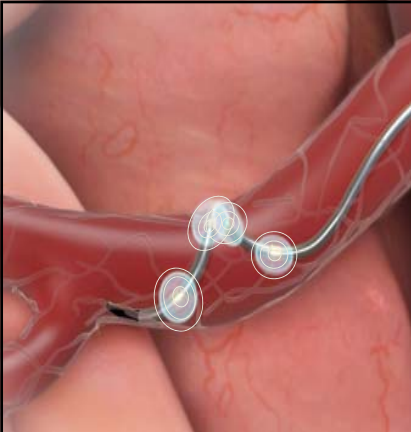
26

Un nuovo catetere



**SYMPPLICITY
SPYRAL™
Catheter**

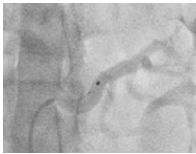

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The RDN procedure
itself is approximately
an hour long

The Lancet, 2017


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HTN-3	SPYRAL HTN
<ul style="list-style-type: none"> •Simplicity™ Flex catheter •Treated renal artery diameters 4 mm or greater •Treated main renal artery only •6 Fr 	<ul style="list-style-type: none"> •Simplicity Spyral™ catheter •Treat renal artery diameters 3 – 8 mm •Treat main renal artery, branches, and accessories •6 Fr
	

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Una diversa tipologia di pazienti

Spyral HTN global clinical trial program

<p>SPYRAL HTN-OFF MED</p> <p>100 patients Sham RCT (1:1)</p> <p>Patients consent to stop taking meds, or drug naive Compare ABPM change at 3 months At 3 months, drug added if uncontrolled</p>		<p>Second Phase</p> <p>SPYRAL HTN Pivotal Design and indication will be based on OFF/ON trial results</p>
<p>SPYRAL HTN-ON MED</p> <p>100 patients Sham RCT (1:1)</p> <p>1, 2, or 3 medications of specified classes Compare ABPM change at 3-6 months</p>		

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Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial

*Raymond R Townsend, Felix Mahfoud, David E Kandzari, Kazuomi Kario, Stuart Pocock, Michael A Weber, Sebastian Ewen, Konstantinos Tsioufis, Dimitrios Tousoulis, Andrew S P Sharp, Anthony F Watkinson, Roland E Schmieder, Axel Schmid, James W Choi, Cara East, Anthony Walton, Ingrid Hopper, Debbie L Cohen, Robert Wilensky, David P Lee, Adrian Ma, Chandan M Devireddy, Janice P Lee, Philipp C Lurz, Karl Fengler, Justin Davies, Neil Chapman, Sidney A Cohen, Vanessa DeBruin, Martin Fahy, Denise E Jones, Martin Rothman, Michael Böhm, on behalf of the SPYRAL HTN-OFF MED trial investigators**

The Lancet, 2017

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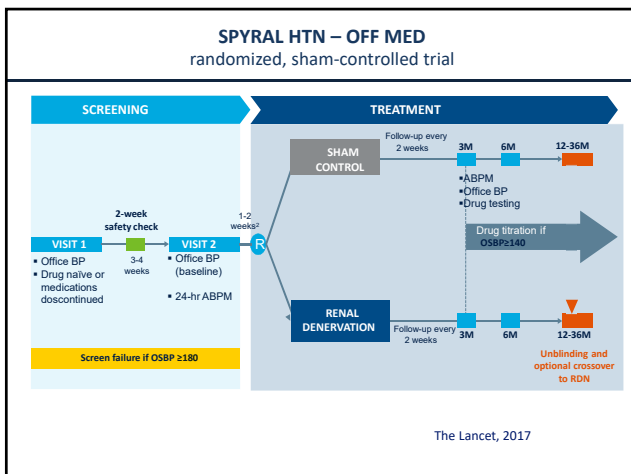
SPYRAL HTN-OFF MED

Key inclusion & exclusion criteria

<p>Inclusion</p>	<ol style="list-style-type: none"> 1. Patient is either: <ol style="list-style-type: none"> a. Not on antihypertensive medications, OR b. Permitting discontinuation of drug therapy 2. Office SBP ≥150 and <180 mm Hg 3. Office DBP ≥90 mm Hg 4. Systolic 24-hour mean ABPM ≥140 and <170 mm Hg 5. Low CV risk
<p>Exclusion</p>	<ol style="list-style-type: none"> 1. Ineligible renal artery anatomy (accessory arteries allowed) 2. eGFR <45 mL/min/1.73m² 3. Type 1 diabetes mellitus or type 2 diabetes mellitus with HbA1C >8.0% 4. Secondary causes of hypertension 5. Isolated systolic hypertension

The Lancet, 2017

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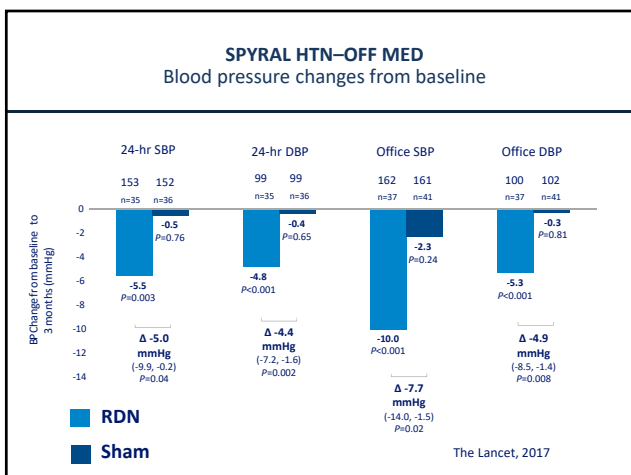


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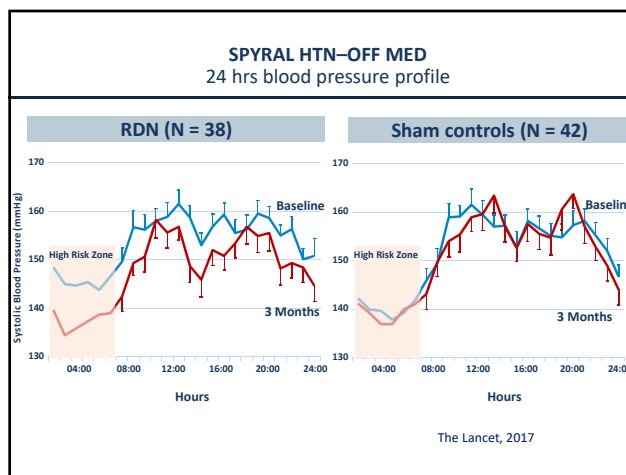
SPYRAL HTN–OFF MED Safety results at 3 months

Major Adverse Event (number of events)	RDN (n=38)	Sham Control (n=42)
Death	0	0
New myocardial infarction	0	0
Major bleeding	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
Vascular complications	0	0
Hospitalization for hypertensive crisis/emergency	0	0
New stroke	0	0

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Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial

*David E Kandzari, Michael Böhm, Felix Mahfoud, Raymond R Townsend, Michael A Weber, Stuart Pocock, Konstantinos Tsiofis, Dimitrios Tousoulis, James W Choi, Caro East, Sandeep Brar, Sidney A Cohen, Martin Fahy, Garrett Pilcher, Kazuomi Kario on behalf of the SPYRAL HTN-ON MED Trial Investigators**

The Lancet, 2018

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SPYRAL HTN-ON MED Key inclusion & exclusion criteria

Inclusion

1. Patient on 1-3 antihypertensive medications
2. Office SBP ≥ 150 and < 180 mm Hg
3. Office DBP ≥ 90 mm Hg
4. Systolic 24-hour mean ABPM ≥ 140 and < 170 mm Hg
5. Low CV risk

Exclusion

1. Ineligible renal artery anatomy (accessory arteries allowed)
2. eGFR < 45 mL/min/1.73m²
3. Type 1 diabetes mellitus or type 2 diabetes mellitus with HbA1C $> 8.0\%$
4. Secondary causes of hypertension
5. Isolated systolic hypertension

The Lancet, 2018

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SPYRAL HTN-ON MED Randomized, sham controlled trial

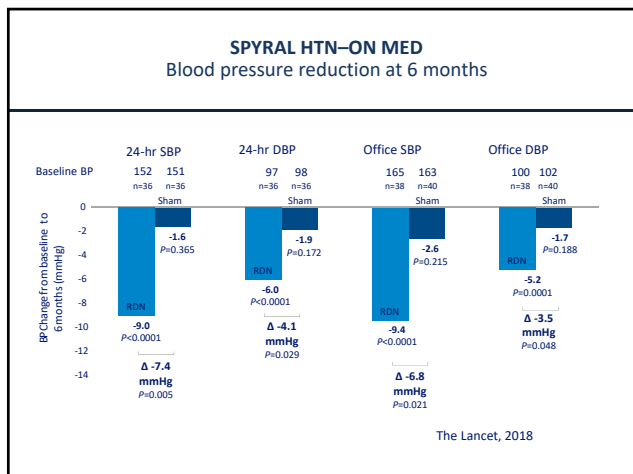
The Lancet, 2018

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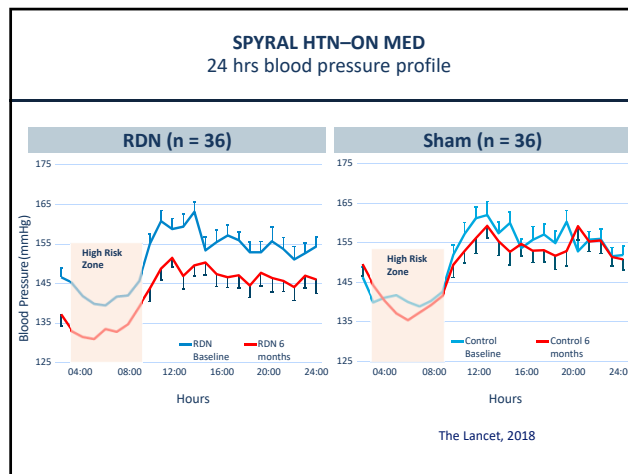
SPYRAL HTN-ON MED No major adverse events

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

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Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial

Michel Aziz, Roland E Schmieder, Felix Mahfoud, Michael A Weber, Joost Daemen, Justin Davies, Jan Bosile, Ajay J Kirtane, Yale Wang, Melvin D Lobo, Manish Saxena, Lida Foyz, Florian Rader, Philipp Lutz, Jeremy Soyer, Marc Sapoval, Terry Leay, Kintur Sanghvi, Josephine Abraham, Andrew S P Sharp, Naami D L Fisher, Michael J Bloch, Helen Reeve-Stoffer, Leslie Coleman, Christopher Mullin, Laura Mauri**, on behalf of the RADIANCE-HTN Investigators†

The Lancet, 2018

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	Renal denervation		Sham procedure		Mean between-group difference adjusted for baseline blood pressure (95% CI)	p value
	Randomisation	2 months	Randomisation	2 months		
Daytime ambulatory blood pressure (mm Hg)						
Patients with data	74	74	72	72	-	-
Systolic blood pressure	153 (7.8)	141.9 (11.9)	150.4 (9.8)	147.9 (13.3)	-2.2 (10.4)	0.0002
Diastolic blood pressure	93.1 (4.8)	87.9 (7.1)	93.5 (5.5)	90.9 (7.9)	-2.6 (-4.6 to -0.6)	0.01 (0.0007)
24-h ambulatory blood pressure (mm Hg)						
Patients with data	74	74	72	72	-	-
Systolic blood pressure	142.6 (8.1)	135.6 (11.4)	143.6 (10.4)	140.7 (11.8)	-3.1 (9.7)	0.006
Diastolic blood pressure	87.3 (5.0)	81.0 (6.8)	88.4 (5.7)	85.7 (7.1)	-3.0 (6.1)	0.07
Night time ambulatory blood pressure (mm Hg)						
Patients with data	74	74	71	71	-	-
Systolic blood pressure	130.3 (11.9)	125.6 (12.8)	130.5 (13.7)	129.4 (13.1)	-3.1 (11.5)	0.15
Diastolic blood pressure	78.2 (8.0)	74.8 (8.5)	80.0 (8.1)	77.3 (8.5)	-2.7 (7.3)	0.25
Office blood pressure (mm Hg)						
Patients with data	74	74	72	72	-	-
Systolic blood pressure	154.5 (12.4)	149.7 (15.1)	153.6 (15.7)	149.7 (17.4)	-3.9 (17.4)	0.007 (0.0007)
Diastolic blood pressure	99.7 (7.7)	94.7 (10.1)	99.1 (9.4)	98.0 (10.4)	-2.2 (10.4)	0.005
Home blood pressure (mm Hg)						
Patients with data	71	71	72	72	-	-
Systolic blood pressure	142.5 (8.8)	139.4 (11.7)	147.7 (12.3)	146.6 (15.4)	-1.1 (10.4)	<0.0001 (<0.0001)
Diastolic blood pressure	84.8 (6.3)	81.9 (7.8)	84.4 (7.0)	83.3 (8.1)	-1.3 (6.2)	0.0009

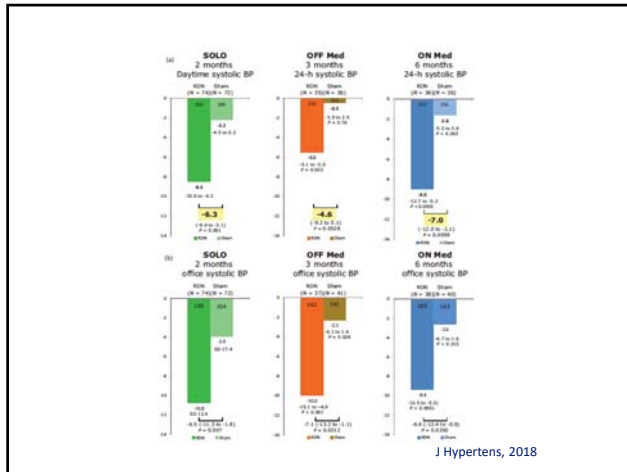
The Lancet, 2018

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European Society of Hypertension position paper on renal denervation 2018

Roland E. Schmieder^a, Felix Mahfoud^b, Michel Azizi^{c,d}, Atul Pathak^e, Kyriakos Dimitriadis^f, Abraham A. Kroon^g, Christian Ott^{h,i}, Filippo Scalise^j, Giuseppe Mancini^k, and Costas Tsioufis^k, on behalf of Members of the ESH Working Group on Interventional Treatment of Hypertension

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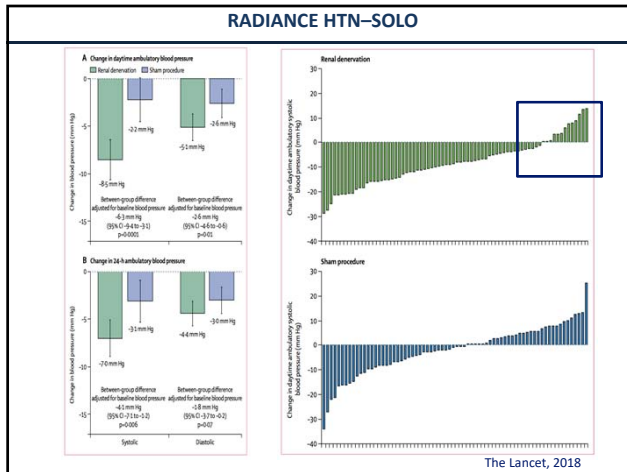


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Limitazioni

- Studi di tipo proof-of-concept
- Impossibilità di stabilire se la denervazione è stata efficace
- Variabilità nella risposta antipertensiva

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2018 ESC/ESH Hypertension Guidelines

Device-based therapies for hypertension

Recommendation	Class ^a	Level ^b
Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available. ^{3,67,368}	III	B

RCT = randomized controlled trial.
^aClass of recommendation.
^bLevel of evidence.

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Le nuove linee guida ESC/ESH sull' ipertensione

ESH and ESC Guidelines

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

2013 2014 2017 2018

HTN-3 SPYRAL HTN-OFF MED SPYRAL HTN-ON MED RADIANCE SOLO

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Prospettive future per la denervazione renale

Le nuove evidenze dimostrano che la denervazione renale ha tuttora forti potenzialità di sviluppo clinico.

Sulla base dei risultati dei recenti studi clinici, questa tecnica non è più "confinata" all'ipertensione resistente, ma è possibile proporla ad esempio a pazienti con scarsa compliance o che non tollerano la terapia farmacologica.

Tuttavia la selezione dei pazienti e l'esecuzione della procedura deve essere limitata a centri con un reale "expertise" di ipertensione arteriosa e di emodinamica interventistica

Nel futuro è quindi necessario un forte programma di sviluppo scientifico e clinico che ci porti a poter considerare la denervazione una delle opzioni terapeutiche nella pratica clinica quotidiana.

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