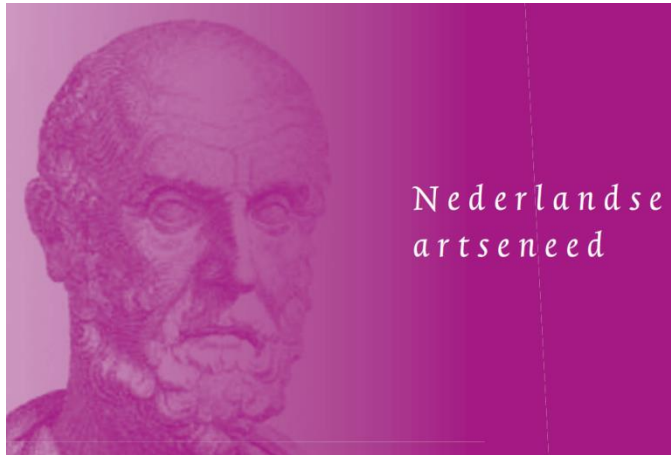


# *Devices hebben geen rol in de reguliere behandeling van hypertensie*

Prof. dr. Niels P. Riksen, internist



## Primum non nocere

### NEDERLANDSE ARTSENEED (2003)

Ik zweer/beloof dat ik de geneeskunst zo goed als ik kan zal uitoefenen ten dienste van mijn medemens. Ik zal zorgen voor zieken, gezondheid bevorderen en lijden verlichten.

Ik stel het belang van de patiënt voorop en eerbiedig zijn opvattingen. Ik zal aan de patiënt geen schade doen. Ik luister en zal hem goed inlichten. Ik zal geheim houden wat mij is toevertrouwd.

Ik zal de geneeskundige kennis van mijzelf en anderen bevorderen. Ik erken de grenzen van mijn mogelijkheden. Ik zal mij open en toetsbaar opstellen.

Ik ken mijn verantwoordelijkheid voor de samenleving en zal de beschikbaarheid en toegankelijkheid van de gezondheidszorg bevorderen. Ik maak geen misbruik van mijn medische kennis, ook niet onder druk.

Ik zal zo het beroep van arts in ere houden.

Dat beloof ik.

*of*

Zo waarlijk helpe mij God\* almachtig.

# Primum non nocere?

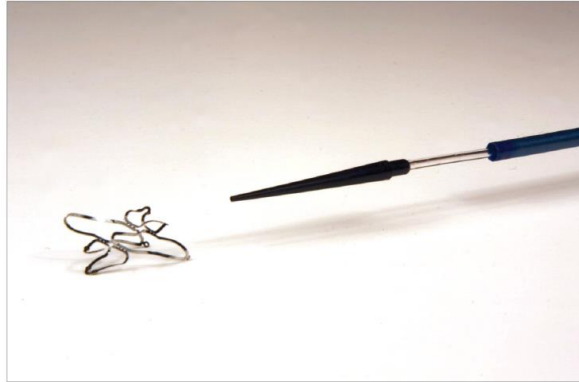
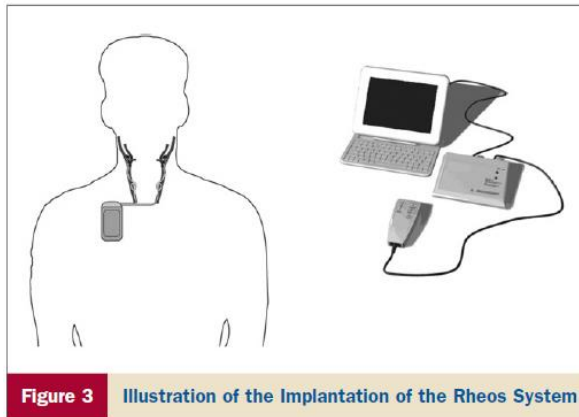


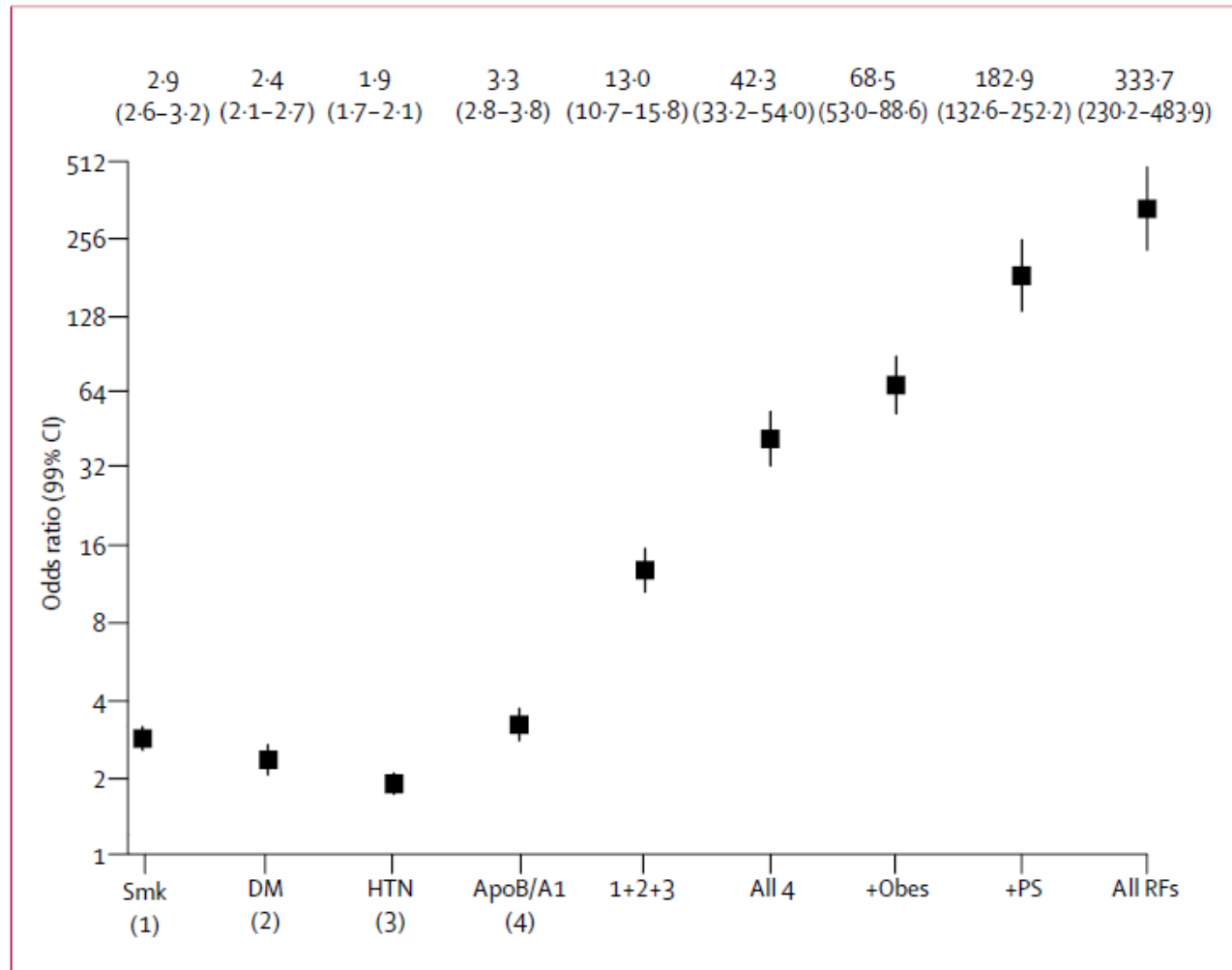
Figure 1: Arteriovenous ROX Coupler and deployment catheter



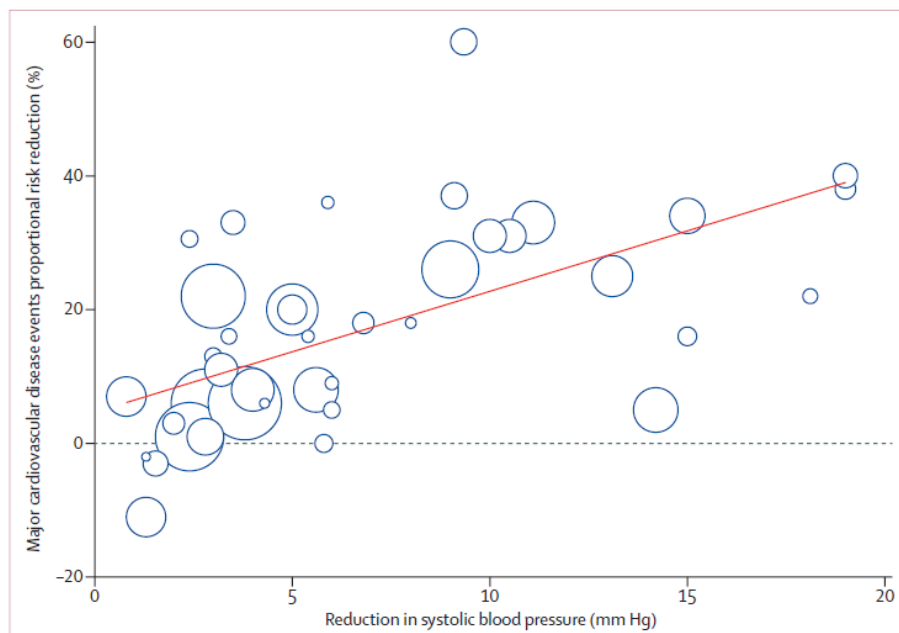
**Figure 3** Illustration of the Implantation of the Rheos System



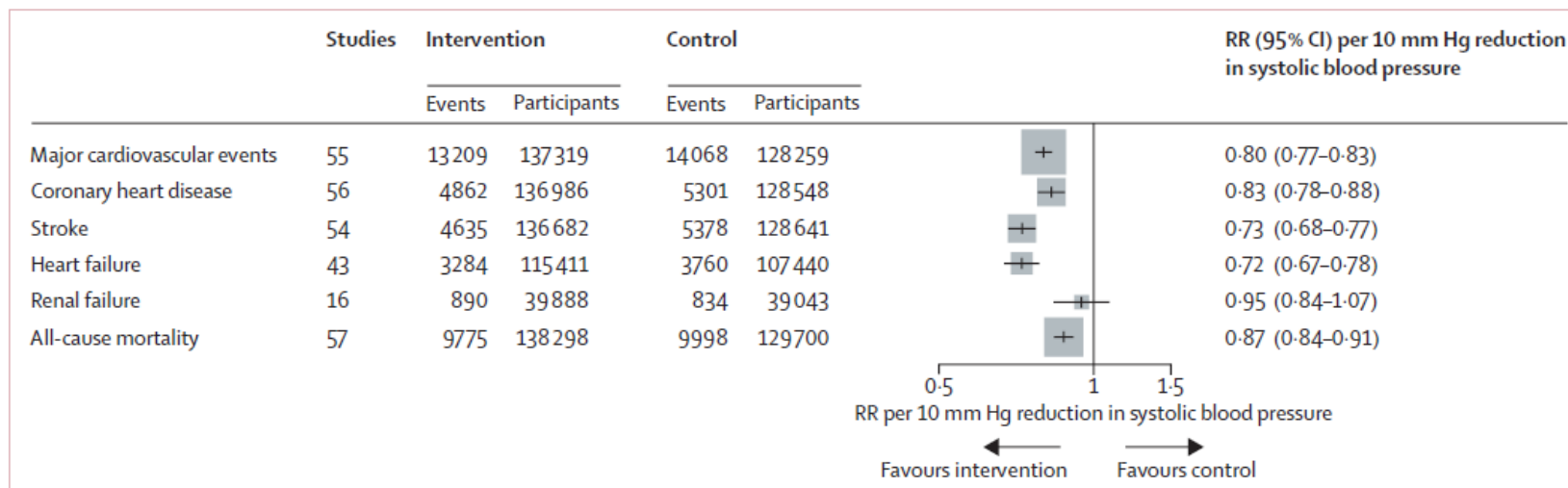
# Waarom behandelen we hypertensie?



# Hoe effectief is het verlagen van bloeddruk?



- RR 0.80
- hoogrisicopopulatie:  
MACE incidentie 15% in 3 jaar
- Dus NNT 33/3 jaar





## Therapieresistente hypertensie

- Therapietrouw
- Zout
- “chronotherapie”
- Nog meer pillen: spironolacton
- *Devices.....*

[Terug naar zoekresultaten](#)[Hypertensie in de tweede en derde lijn](#) > [Startpagina Hypertensie](#)

## Hypertensie in de tweede en derde lijn - startpagina

[Algemeen](#)[Verantwoording](#)

Behandeling therapieresistente hypertensie na het uitsluiten van therapie-ontrouw en secundaire hypertensie

### Uitgangsvraag

Hoe dient therapieresistente hypertensie te worden behandeld als therapie-ontrouw en secundaire hypertensie zijn uitgesloten?

### Aanbeveling

Voeg een aldosteronantagonist (in het bijzonder spironolacton) in lage eenmaal daagse dosering van 25 tot 50 mg toe bij therapieresistente hypertensie.

Doseer spironolacton bij voorkeur niet hoger dan 50 mg om bijwerkingen te voorkomen.

Overweeg bij therapieresistente hypertensie een van de drie medicamenten (bijvoorbeeld een calciumantagonist) in te nemen voor het slapen gaan.

Overweeg vastedosiscombinatietabletten te geven voor het verbeteren van de adherentie en niet zozeer voor verlaging van de bloeddruk.

# Efficacy and Safety of Spironolactone in Patients with Resistant Hypertension: A Meta-analysis of Randomised Controlled Trials



Chunbin Wang, MD, Bo Xiong, MD, Jing Huang, MD\*

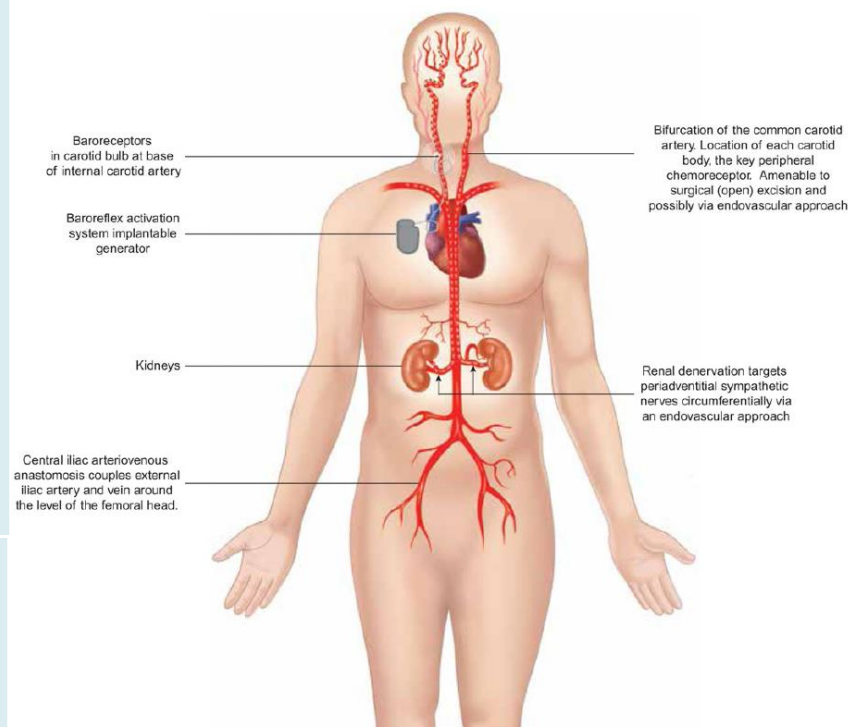
**Tabel 1 Gemiddelde verschillen in bloeddruk, gemeten met verschillende methoden, bij het gebruik van spironolacton ten opzichte van placebo/ramipril (gebaseerd op Wang, 2016)**

Meetmethode	Systolische bloeddruk in mmHg (95%BI)	Diastolische bloeddruk in mmHg (95%BI)
24-uurs ambulante bloeddruk	-10,50 (-12,30 tot -8,71)	-4,09 (-5,28 tot -2,91)
Dagbloeddruk	-10,20 (-12,41 tot -7,99)	-4,14 (-5,50 tot -2,78)
Nachtbloeddruk	-10,02 (-12,62 tot -7,41)	-3,21 (-4,84 tot -1,58)
Spreekkamerbloeddruk	-16,99 (-25,04 tot -8,95)	-6,18 (-9,30 tot -3,05)



**Table 1 Novel device technologies for treatment of hypertension**

Technology	Mode of action	Stage of development	Limitations
Renal sympathetic denervation Ablation catheters and generators available from several manufacturers including Medtronic, St Jude Medical, Boston Scientific, Terumo, and Verve Medical	Sympathomodulatory—results in destruction of renal afferent and efferent sympathetic nerves and BP reduction through mechanisms that remain unclear in human hypertension	CE Mark approval for hypertension for most catheters A variety of catheters/platforms now available includes: Radiofrequency ablation, ultrasound ablation, chemical ablation, and cryoablation using balloon/non-balloon and irrigated catheters	Lack of markers of procedural success Inability to screen for increased renal nerve signalling prevents identification of best responders Damage to renal artery from endovascular approach using thermal energy
Baroreflex activation therapy Barostim neo™ (CVRx Inc, Minneapolis, MN, USA)	Sympathomodulatory: unilateral electrical field stimulation of the carotid sinus stimulates the baroreflex and down-regulates sympathetic outflow while increasing parasympathetic tone	CE Mark approval for hypertension Pivotal study published with the first-generation device <sup>58</sup> Small proof of concept study with the second-generation device <sup>61</sup>	Open loop system lacks feedback mechanism Exceedingly high cost Implantable generator must be replaced at end of battery life (currently 3 years)
Baroreceptor amplification therapy Mobius HD™ (Vascular Dynamics, Mountain View, CA, USA)	Sympathomodulatory: dramatic increase in carotid bulb strain causes durable amplification of baroreceptor feedback and BP reduction	European and US studies now enrolling Case report and early report from first-in-man study published <sup>127,128</sup>	Concerns over instrumentation of the carotid artery, risks of distal embolization Open loop system with no feedback mechanism
Central iliac AV anastomosis ROX AV coupler™ (ROX Medical, San Clemente, CA, USA)	Targets mechanical aspects of the circulation Lowers BP through reduction in effective arterial volume and systemic vascular resistance	CE Mark approval for hypertension Small randomized controlled study in resistant hypertension published <sup>68</sup> and US IDE study with sham control is planned to start enrolling in 2016	30% incidence of ipsilateral venous stenosis Risk of high output cardiac states not known No long-term safety data
Carotid body ablation Cibiem Carotid Body Modulation System™ (Cibiem, Los Altos, CA, USA)	Sympathomodulatory: unilateral carotid body ablation reduces sympathetic vasomotor tone without affecting respiratory drive	Proof of concept study using unilateral surgical excision in resistant hypertension <sup>74</sup> Endovascular ablation planned using novel catheter-based system	Only appears effective in those with high carotid body tone. Screening for this will be essential Endovascular approach is complicated by the difficulty of accessing the target and risks to important adjacent structures
Deep brain stimulation Activa Neurostimulator, (Medtronic Inc, Minneapolis, MN, USA) Vercise™ DBS System (Boston Scientific, Marlborough, MA, USA)	Sympathomodulatory: electrical field stimulation of the dorsal and ventrolateral periaqueductal grey region within the midbrain reduces BP through mechanisms that are not clearly defined in human hypertension	The technology was primarily developed for management of movement disorders and chronic pain syndromes. <sup>129</sup> Isolated reports of BP-lowering independent of pain control <sup>130,131</sup>	Limited efficacy/safety data High costs of therapy Open loop system Frequent generator recharging required
Vagal nerve stimulation CardioFIT™ Systems (BioControl Medical, Yehud, Israel) Precision™ System, (GUIDANT Europe/Boston Scientific)	Sympathomodulatory—unilateral vagal nerve stimulation restores vagal tone and improves sympathovagal balance	Under investigation for use in heart failure and hypertension. Animal data only for hypertension indication <sup>132</sup>	Inability to selectively target nerve fibres to avoid bradycardia and bradypnoea
Median nerve stimulation Subcutaneous Neuromodulation System (Valencia Technologies, Valencia, CA, USA)	Sympathomodulatory—subcutaneous unilateral implantation of a coin-sized device (in a 20-min office procedure) causing electrical stimulation of the median nerve and subsequent down-regulation of sympathetic outflow	A double-blinded study in 29 patients has shown reduction in ambulatory BP at 3 (9.2 mmHg) and 6 (18.9 mmHg) months <a href="http://valenciatechnologies.com/clinicaltrial/">http://valenciatechnologies.com/clinicaltrial/</a>	No published randomized controlled data <sup>133</sup>



**Lobo, Eur Heart J 2017**

# Devices in therapieresistente hypertensie

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De volgende subvragen zijn apart uitgewerkt:

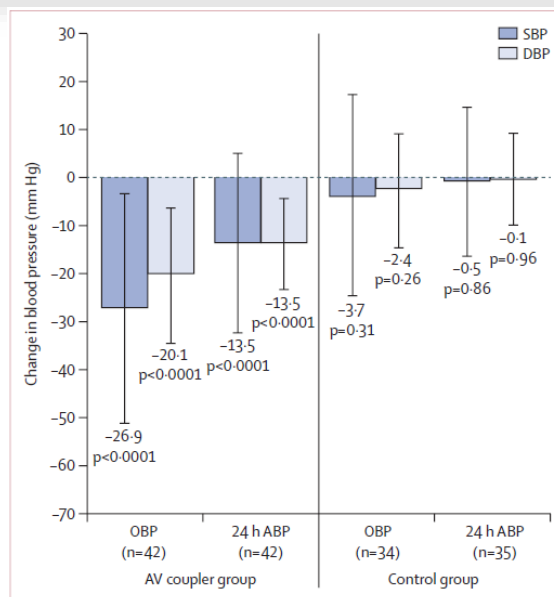
1. Wat is de toegevoegde waarde van een iliacale arterioveneuze shunt bij patiënten met therapieresistente hypertensie?
2. Wat is de toegevoegde waarde van baroreflexactivatietherapie bij patiënten met therapieresistente hypertensie?
3. Wat is de plaats van de carotisstent bij de behandeling van patiënten met therapieresistente hypertensie?
4. Wat is de plaats van renale denervatie bij de behandeling van patiënten met therapieresistente hypertensie?

# Iliacale arterioveneuze shunt

## Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial

Melvin D Lobo, Paul A Sobotka, Alice Stanton, John R Cockcroft, Neil Sulke, Eamon Dolan, Markus van der Giet, Joachim Hoyer, Stephen S Furniss, John P Foran, Adam Witkowski, Andrzej Januszewicz, Danny Schoors, Konstantinos Tsioufis, Benno J Rensing, Benjamin Scott, G André Ng, Christian Ott, Roland E Schmieder, for the ROX CONTROL HTN Investigators\*

N=83 TRH pts



BP na 6 maanden

	Number (%) of adverse events (n=42)
<strong>Procedural complication</strong>	
Arterial deployment*	3 (7.1%)
Intimal dissection iliac artery	1 (2.4%)
Transient bradycardia	1 (2.4%)
Contrast reaction	1 (2.4%)
Urinary retention	1 (2.4%)
Anaemia	1 (2.4%)
Transient or localised pain	2 (4.8%)
Nausea or lethargy	1 (2.4%)
Deep venous thrombosis	1 (2.4%)
Lower limb pain	1 (2.4%)
<strong>Device-related event</strong>	
Venous stenosis	12 (28.6%)

\* Coupler retrieved via arterial sheath and second coupler successfully deployed.

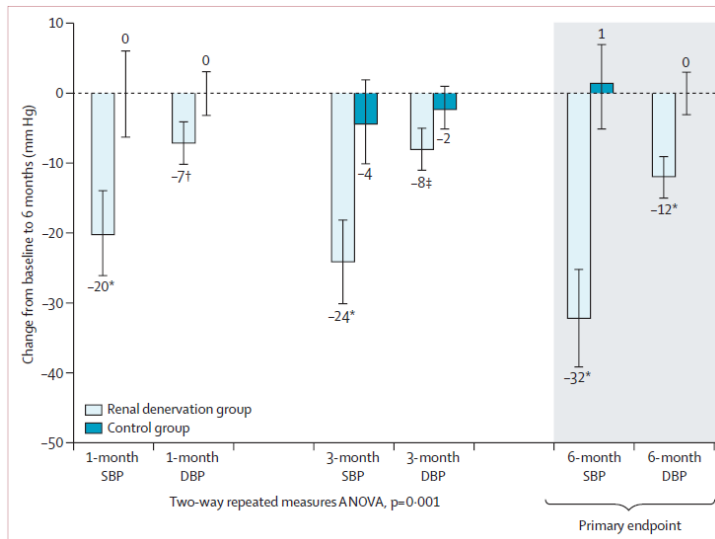
Table 3: Adverse events related to arteriovenous coupler placement or device

Aanbeveling

Behandel patiënten met therapieresistente hypertensie niet met een iliacale AV-anastomose.

Inleiding

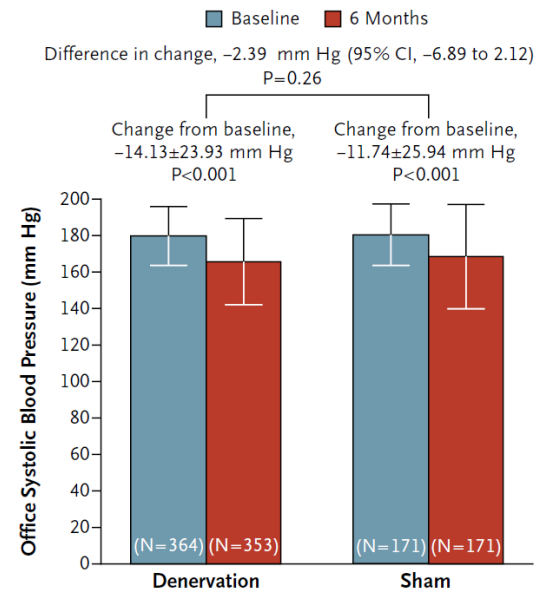
# Renale denervatie: een korte levenscyclus



**Esler, Lancet 2010, n=106, no sham control**

## Aanbeveling

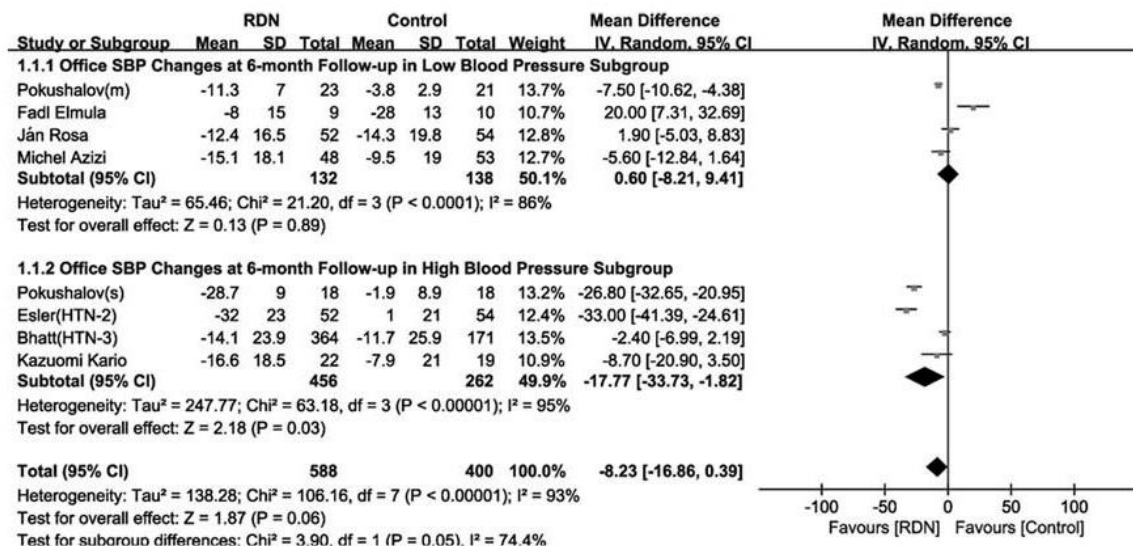
Verricht geen renale denervatie als behandeling bij patiënten met therapieresistente hypertensie.



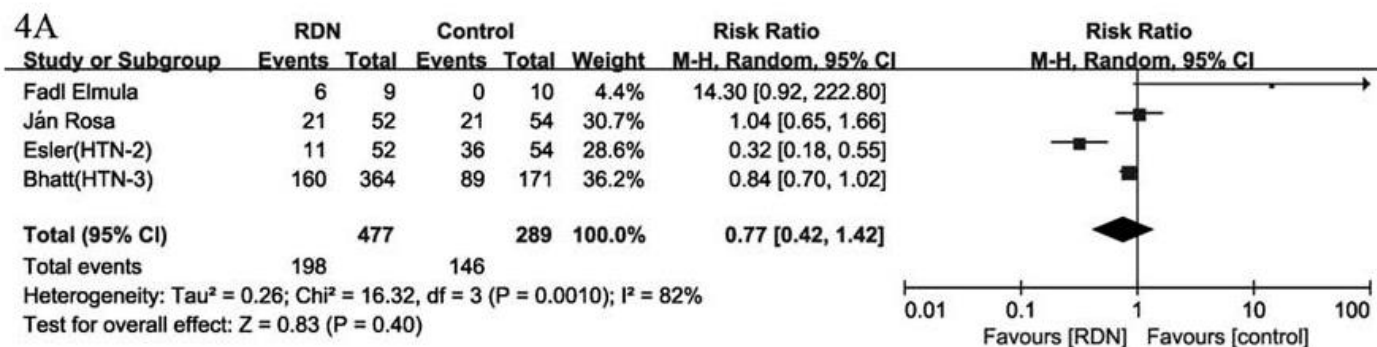
**Bhatt, NEJM 2014, n=535, sham controlled**

# Meta-analyse renale denervatie

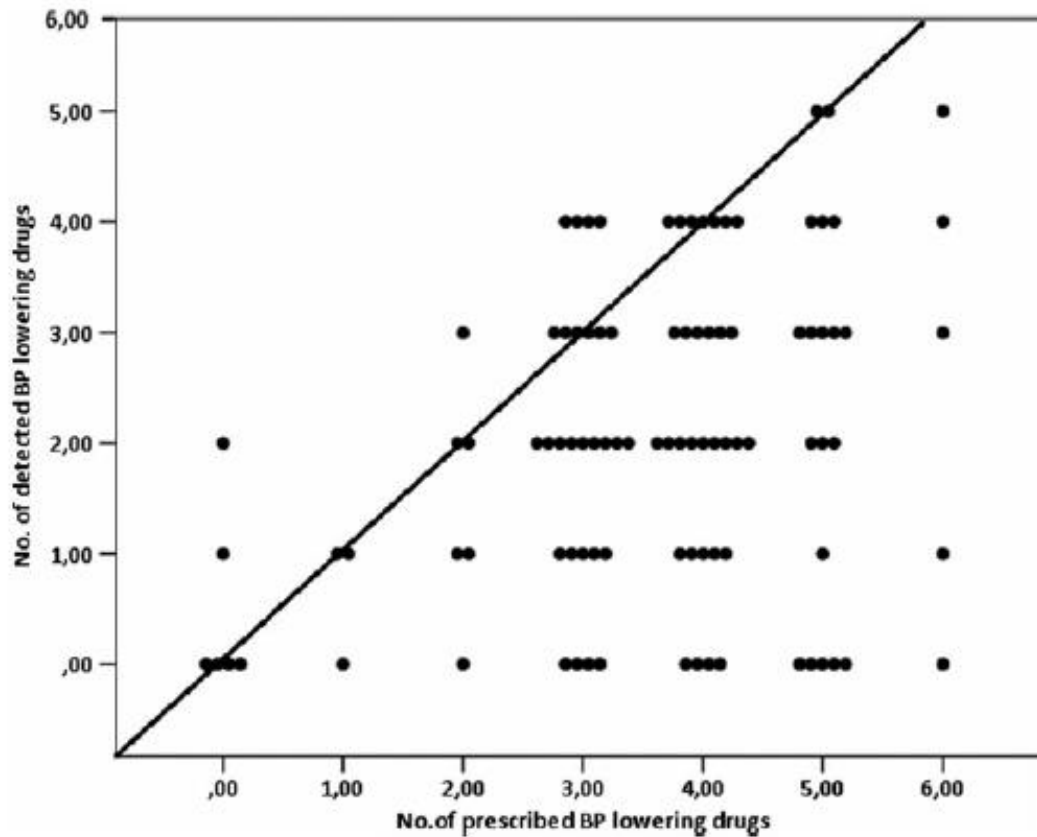
## Office SBP



## >10 mmHg decrease



# Therapietrouw.....

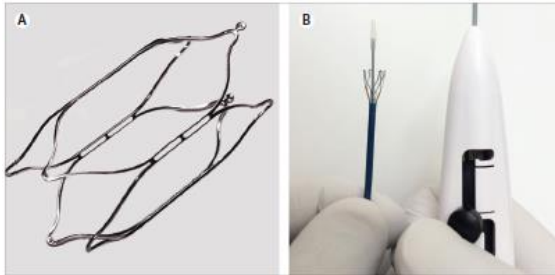


16% nonadherent

52% poorly adherent

32% adherent

# Carotisstent



## Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle clinical study



Wilko Spiering, Bryan Williams, Jan Van der Heyden, Monique van Kleef, Rob La, Jorie Versmissen, Adriaan Moelker, Abraham Kroon, Hannes Reuter, Gary Ansel, Gregg W Stone, Mark Bates, for the CALM-FIM\_EUR investigators\*

### Summary

**Background** Carotid baroreflex activation lowers blood pressure and might have potential application for the *Lancet* 2017; 390: 2655-61

N=106

Open label

Prim endpoint:

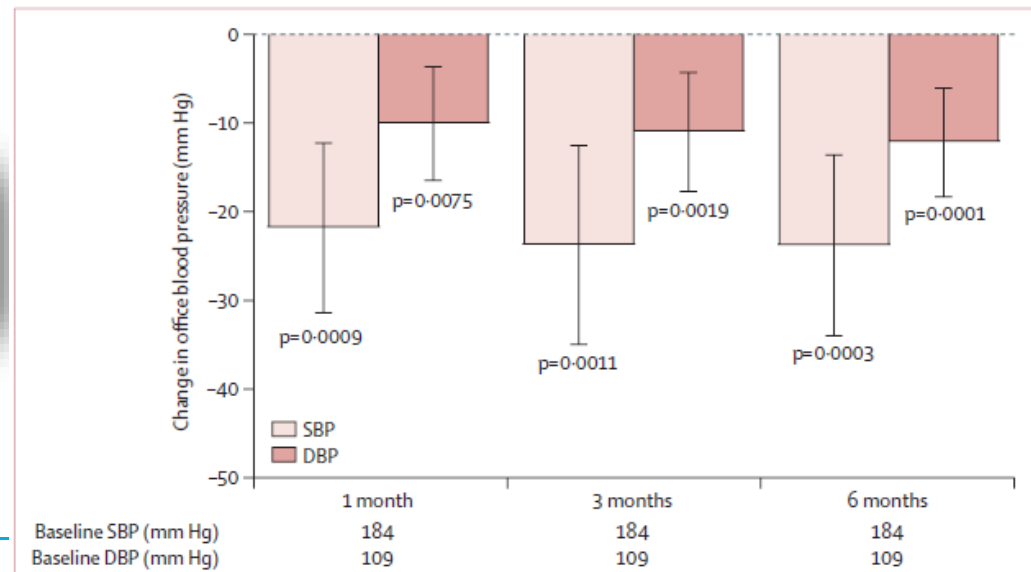
SAE at 6 months

Sec endpoint:BP

	Number of patients (%)	Intervention	Outcome
<b>Serious adverse events</b>			
Hypotension*	2 (7%)	Reduction in antihypertensive dose	Resolved without sequelae
Worsening of hypertension*	2 (7%)	Increase in antihypertensive dose	Resolved without sequelae
Claudication left leg	1 (3%)	Thromboendarterectomy	Resolved without sequelae
Wound infection	1 (3%)	Wound irrigation and antibiotic	Resolved without sequelae

### Aanbeveling

Plaats bij patiënten met therapieresistente hypertensie geen carotisstent (MobiusHD device) als routinezorg.



Spiering, Lancet 2017

Figure 3: Change from baseline in office blood pressure at 1, 3, and 6 months



## Uitgangsvraag

Wat is de toegevoegde waarde van baroreflexactivatietherapie bij patiënten met therapieresistente hypertensie?

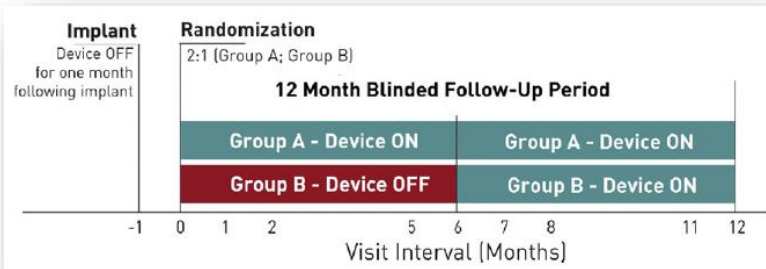
## Aanbeveling

Overweeg het plaatsen van baroreflexactivatietherapie bij patiënten met therapieresistente hypertensie onder volgende voorwaarden:

- jonger dan 75 jaar;
- bewezen medicatieadherentie (zie module [Vaststellen adherentie](#));
- gemiddelde dagwaarde van de ambulant gemeten bloeddruk boven 160/100 mmHg ondanks adequate doseringen van spironolacton en/of een diureticum, chronotherapie of combinatietabletten.

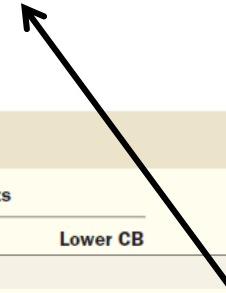


# Baroreflexactivatie



N=265 patienten, dubbelblinde sham RCT

54% vs 46% reached a SBP drop >10 mmHg



**Table 2** Summary of Coprimary Endpoints

	Endpoint Design			Endpoint Results			p Value
	Timing	Type	H <sub>A</sub>	n	Point Estimate	Lower CB	
Efficacy endpoints							
Acute responder	6 months	Super-superiority	$\pi_A > \pi_B + 20\%$	265	7.7	−5.1	0.97
Sustained responder	12 months	OPC	$\pi_{12\text{ Month}} \geq 65\%$	97	87.6	81.1	<0.001
Safety endpoints							
Procedure	30 days	OPC	$\pi_{30\text{ day}} > 82\%$	265	74.8	70.5	1.00
BAT	6 months	Noninferiority	$\pi_A > \pi_B - 15\%$	265	2.4	−4.1	<0.001
Device	12 months	OPC	$\pi_{12\text{ Month}} > 72\%$	265	87.2	83.8	<0.001

**Table 3** Summary of Adverse Events

Procedural	68 (25.5)
Surgical complication	13 (4.8)
Nerve injury with residual deficit	13 (4.8)
Transient nerve injury	12 (4.4)
Respiratory complication	7 (2.6)
Wound complication	7 (2.6)
<b>BAT</b>	
Hypertensive crisis (Group A)	9 (5.0)
Hypertensive crisis (Group B)	7 (8.3)
<b>Device</b>	
Hypertension-related stroke	34 (12.8)
	6 (2.3)

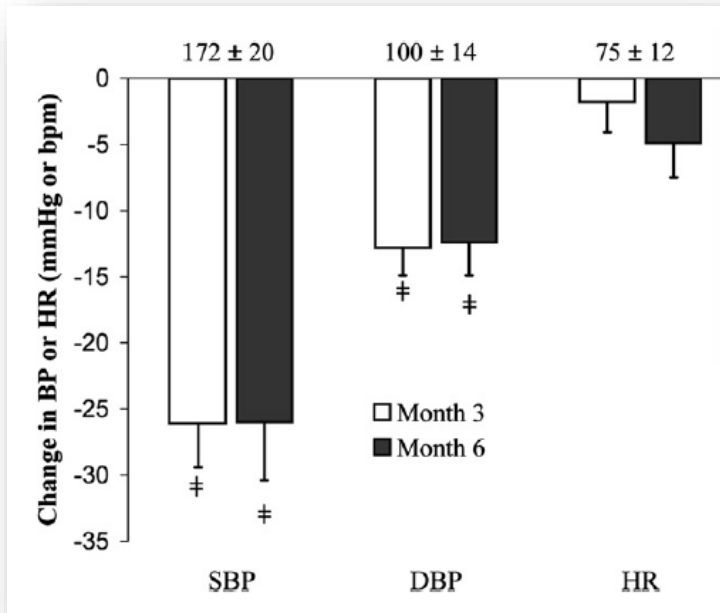
Secondary endpoint: mean change in SBP:  
16+/-29 mmHg vs 9+/-29 mmHg

NNT ongeveer 40 gedurende 3 jaar  
>> dus 4 zenuwlaesies

# Rheos >> Barostim neo

N=30

Open label



**Table 2**

System- or procedure-related complications

Event	Days From Implant	Procedure-related	System-related	Status	Patients Free From Events (%)
<b>Perioperative events</b>					<b>90 %</b>
Device pocket hematoma	3	Yes	No	Recovered, no residual effects	
Self-inflicted wound complication	7	Yes	No	Recovered, no residual effects	
Intermittent pain lateral of device system	30	Yes	No	Recovered, no residual effects	
<b>Long-term events</b>					<b>97 %</b>
Intermittent pain near the device system	44	Yes	No	Recovered, no residual effects	

Hoopgevend, maar eerst verder onderzoek nodig

# Conclusie

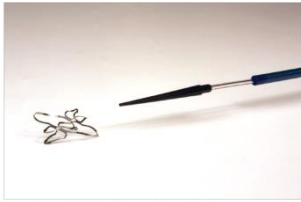
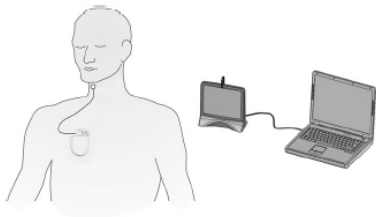
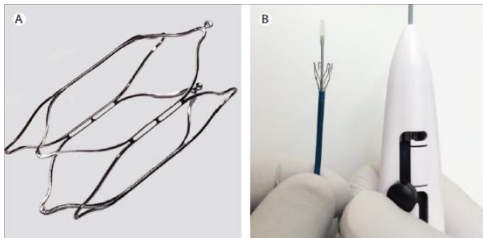
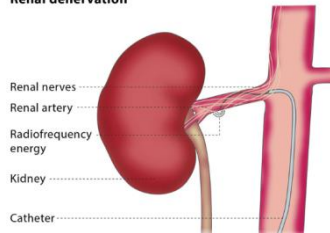


Figure 2: Aorticorenal BAX Coupler and deployment catheter

## Renal denervation



Just don't

Not effective

Promising, but  
needs further study

New device: Promising,  
but needs further study

In general:

- Against spironolactone
- compliance!
- long term consequences