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Practical Question: How We Should Define "Responsiveness" to Renal Denervation – HTN and Beyond HTN Indications

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When I started working on this talk:

“Wooow,
how easy is that”

“Responder” is more or less clear!

- In the view of the renal denervation trials (Symplicity):
  - 10mmHg
- In the view of the National High Blood Pressure Education Program
  - 5mmHg
- If I would be the patient:
  - 2mmHg, because that reduces my stroke risk by 10%

When and how was “responder” used in the context of renal denervation?

It came from Symplicity HTN-1

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

www.thelancet.com Published online March 30, 2009 DOI:10.1016/S0140-6736(09)60566-3

Statistical analysis

We did univariate analysis of both patient demographic and procedural characteristics predicting response in office blood pressure greater than 10 mm Hg. We analysed estimated

Symplicity HTN-2 used different endpoints

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

*Symplicity HTN-2 Investigators**

www.thelancet.com Published online November 17, 2010 DOI:10.1016/S0140-6736(10)62039-9

Endpoints

The primary effectiveness endpoint was between-group change in average office-based measurements of systolic blood pressure from baseline to 6 months after randomisation. Secondary endpoints were acute

What was the endpoint in prior drug studies?

- Late 1960s:
  - the earliest studies showed a relationship between BP lowering and a reduction in cardiovascular events
  - they focused on the reduction of diastolic BP
- 2000: US FDA required an absolute mean reduction in diastolic and systolic BP
- 2000s and beyond: General definition of response started moving to:
  - Decrease in diastolic and/or systolic BP by 10mmHg
  - and/or achieving a target BP

Basile Ther Advc CV Disease 2009

Systolic or diastolic BP?

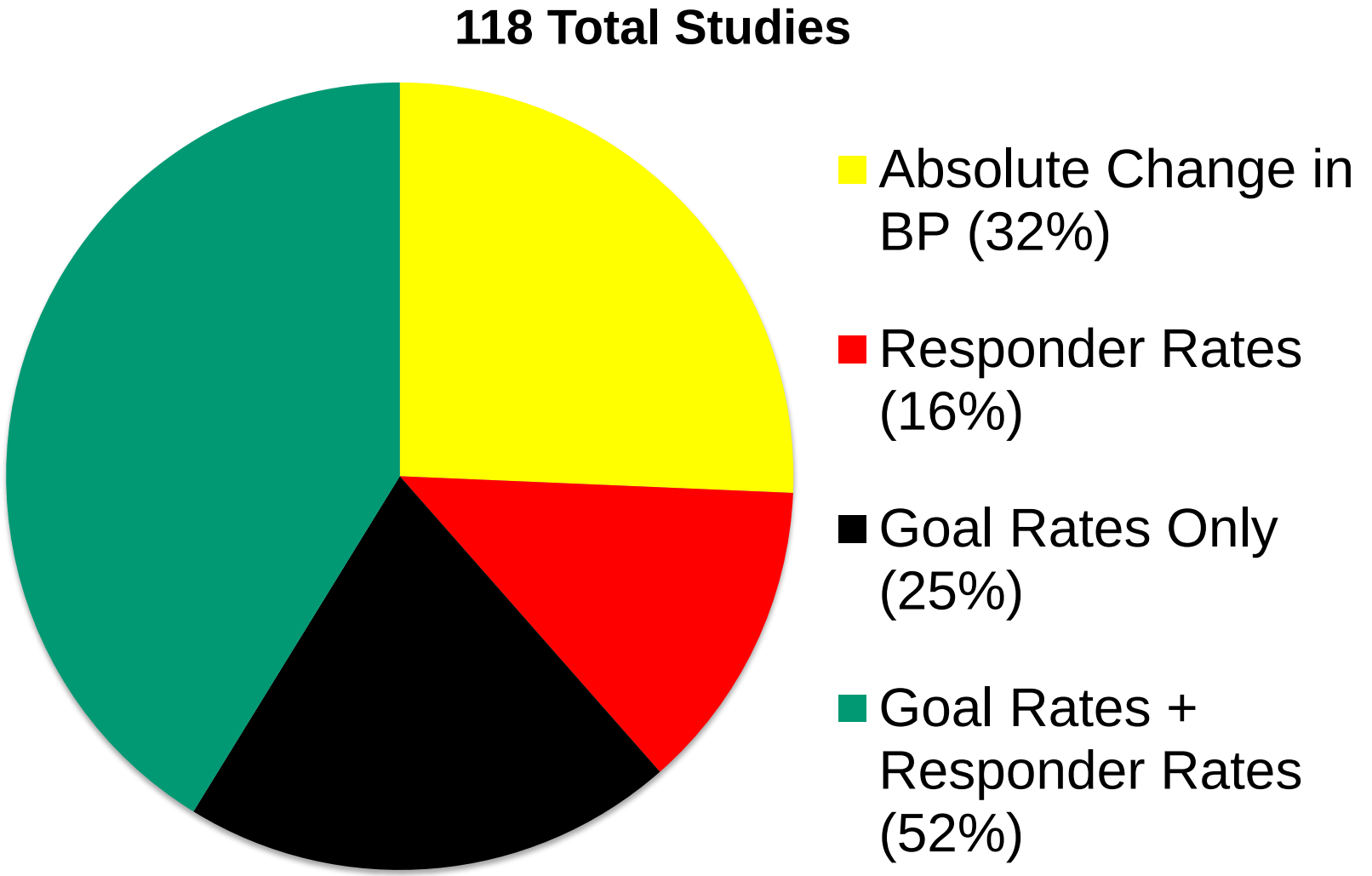
- The use of systolic BP responder rates is uncommon in the published literature due to the historical focus on diastolic BP
- However, over the age of 50 years, systolic BP is more important than diastolic BP
- Diastolic BP is more difficult to measure
- If the systolic BP goal is reached, the diastolic BP goal is also generally achieved

➢ For these reasons, today systolic BP is often preferred as primary endpoint

What other options are there?

- Goal rates
  - The percent of people that achieve a certain systolic or diastolic blood pressure goal
    - For example: % of people achieve diastolic BP < 90mmHg
  - Does not include decrease from baseline
- Combined goal rates
  - Percent of people that achieve a systolic and diastolic blood pressure goal
    - For example: % of people BP < 140/90
  - Does not include decrease from baseline

Overall studies between 2001-2007



Basile Ther Adv CV Disease 2009

Symplicity HTN 3 combined absolute change in BP and responder rate in one single endpoint:

Regarding the primary effectiveness end point, a reduction in office-based SBP of ≥5 mm Hg is considered a clinically meaningful improvement.[33]

This approach requires more than a significant decrease!
The decrease has to be significantly larger than 5mmHg

Different Goal Rate have been used

	Goal BP (mmHg)								
	DBP alone			SBP alone			SBP/DBP combined		
	<90[a]	<85	<80	<140[a]	<130	<140/90[a]	<130/85[a]	<130/80	Other
ACE inhibitor ± diuretic	5	1	1	2	1	7	3		1
ARB ± diuretic	15	4		6	3	20	8	6	2
CCB ± diuretic	9	1		4	2	9	1	1	4
β-blocker ± diuretic	1			1		12		1	1
Renin inhibitor ± diuretic						3			
Renin inhibitor ± ARB						1			
Diuretic	5		1	3	2	4			
α_1- or α_2-blocker	3			2		1			
ACE inhibitor + CCB	1	1			1	1	3	1	
ARB + CCB							1		

[a]Specific goal included < or ≤ the listed value (e.g. <90 mmHg or ≤90 mmHg).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; DBP, diastolic BP; SBP, systolic BP.

Table 1. Frequency with which different BP goal rates were assessed in randomized, controlled clinical trials of antihypertensive drugs in adults with essential hypertension during the last 6 years (61 studies); some studies evaluated more than one goal rate and more than one drug regimen.

Basile Ther Adv CV Disease 2009

Goal Rates and Response Rates have different results – the LIFE study

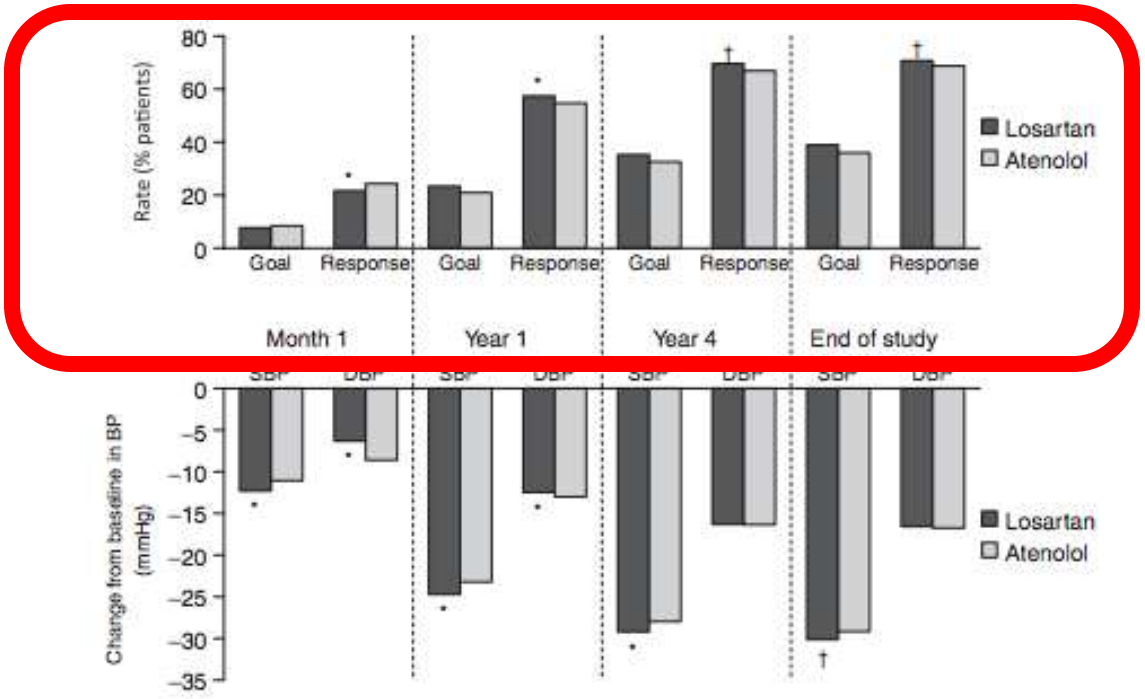


Figure 3. Rates of BP goal achievement [<140/90 mmHg] or response (SBP<140 mmHg, or ≥140 mmHg and ≥20 mmHg decrease from baseline or DBP <90 mmHg, or ≥90 mmHg and ≥10 mmHg decrease from baseline) and mean BP reductions at 1 month, 1 year, 4 years and at the end of the study in the LIFE study [Devereux *et al.* 2007]. *$p \leq 0.007$ *versus* atenolol at same timepoint; †$p < 0.05$ *versus* atenolol at same timepoint. At month 1, both groups were receiving monotherapy; at other timepoints depicted, patients had hydrochlorothiazide ± other agents added to try and achieve a BP goal of <140/90 mmHg. Use of additional medications was comparable in the two treatment groups throughout the study. BP, blood pressure; DBP, diastolic BP; LIFE, Losartan Intervention For Endpoint reduction; SBP, systolic BP.

LIFE study: Losartan vs. Atenolol 2007

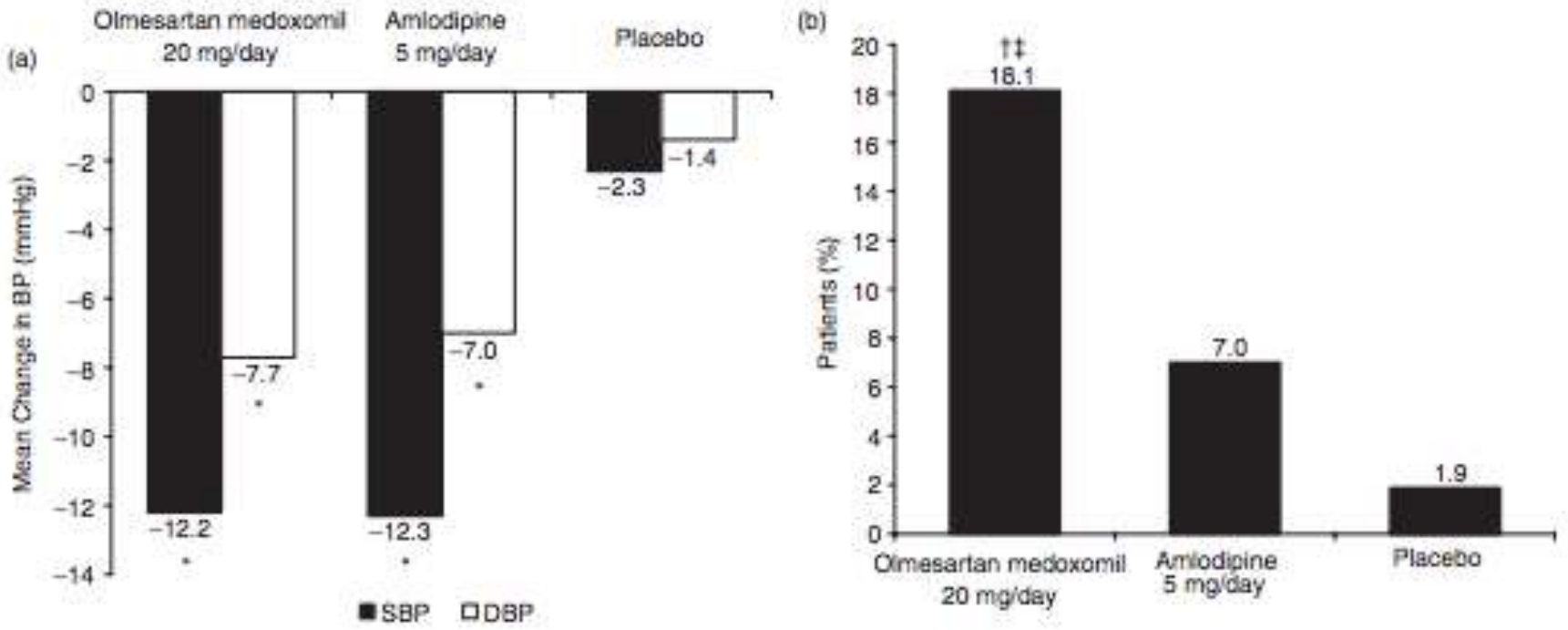
Goal: < 140/90

Response: SBP < 140 **or** decrease by 10 mmHg

Response Rates are much higher than Goal Rates!

Bang Blood Pressure 2007

Absolute difference can be the same and BP goal rate can be different



Absolute difference in 24h Ambulatory BP was the same…

… but percent achieving goal ambulatory BP rate was different (18.1% vs. 7.0%)

Chrysant J Hum HTN 2003
Chrysant BP Monitoring 2006

What are our current "goal" definitions by societies?

Table 6. Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

Guideline	Population	Goal BP, mm Hg	Initial Drug Treatment Options
2014 Hypertension guideline	General ≥60 y	<150/90	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB
	General <60 y	<140/90	Black: thiazide-type diuretic or CCB
	Diabetes	<140/90	Thiazide-type diuretic, ACEI, ARB, or CCB
	CKD	<140/90	ACEI or ARB
ESH/ESC 2013[37]	General nonelderly	<140/90	β-Blocker, diuretic, CCB, ACEI, or ARB
	General elderly <80 y	<150/90	
	General ≥80 y	<150/90	
	Diabetes	<140/85	ACEI or ARB
	CKD no proteinuria	<140/90	ACEI or ARB
	CKD + proteinuria	<130/90	
CHEP 2013[38]	General <80 y	<140/90	Thiazide, β-blocker (age <60y), ACEI (nonblack), or ARB
	General ≥80 y	<150/90	
	Diabetes	<130/80	ACEI or ARB with additional CVD risk ACEI, ARB, thiazide, or DHPCCB without additional CVD risk
	CKD	<140/90	ACEI or ARB
ADA 2013[39]	Diabetes	<140/80	ACEI or ARB
KDIGO 2012[40]	CKD no proteinuria	≤140/90	ACEI or ARB
	CKD + proteinuria	≤130/80	
NICE 2011[41]	General <80 y	<140/90	<55 y: ACEI or ARB
	General ≥80 y	<150/90	≥55 y or black: CCB
ISHIB 2010[42]	Black, lower risk	<135/85	Diuretic or CCB
	Target organ damage or CVD risk	<130/80	

Abbreviations: ADA, American Diabetes Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CHEP, Canadian Hypertension Education Program; CKD, chronic kidney disease; CVD, cardiovascular disease; DHPCCB, dihydropyridine calcium channel blocker; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISHIB, International Society for Hypertension in Blacks; JNC, Joint National Committee; KDIGO, Kidney Disease: Improving Global Outcome; NICE, National Institute for Health and Clinical Excellence.

What is a meaningful decrease in BP?

- MEDLINE, Cochrane Collaboration, Web of Science, Office of National Statistics:
  - lowering BP by 5 mm diastolic BP reduces stroke by 34% and ischemic heart disease by 21%

Law, Health Tech Assessment 2003

What is a meaningful decrease in BP?

- MEDLINE 1966-2007 meta-analysis

- Decrease of 10 mm SBP or 5 mm DBP means
  - Coronary heart disease risk down from 27% to 17%
  - Stroke reduces down from 48% to 33%

Law, BMJ 2009

So how should we define “responder” in the context of renal denervation?

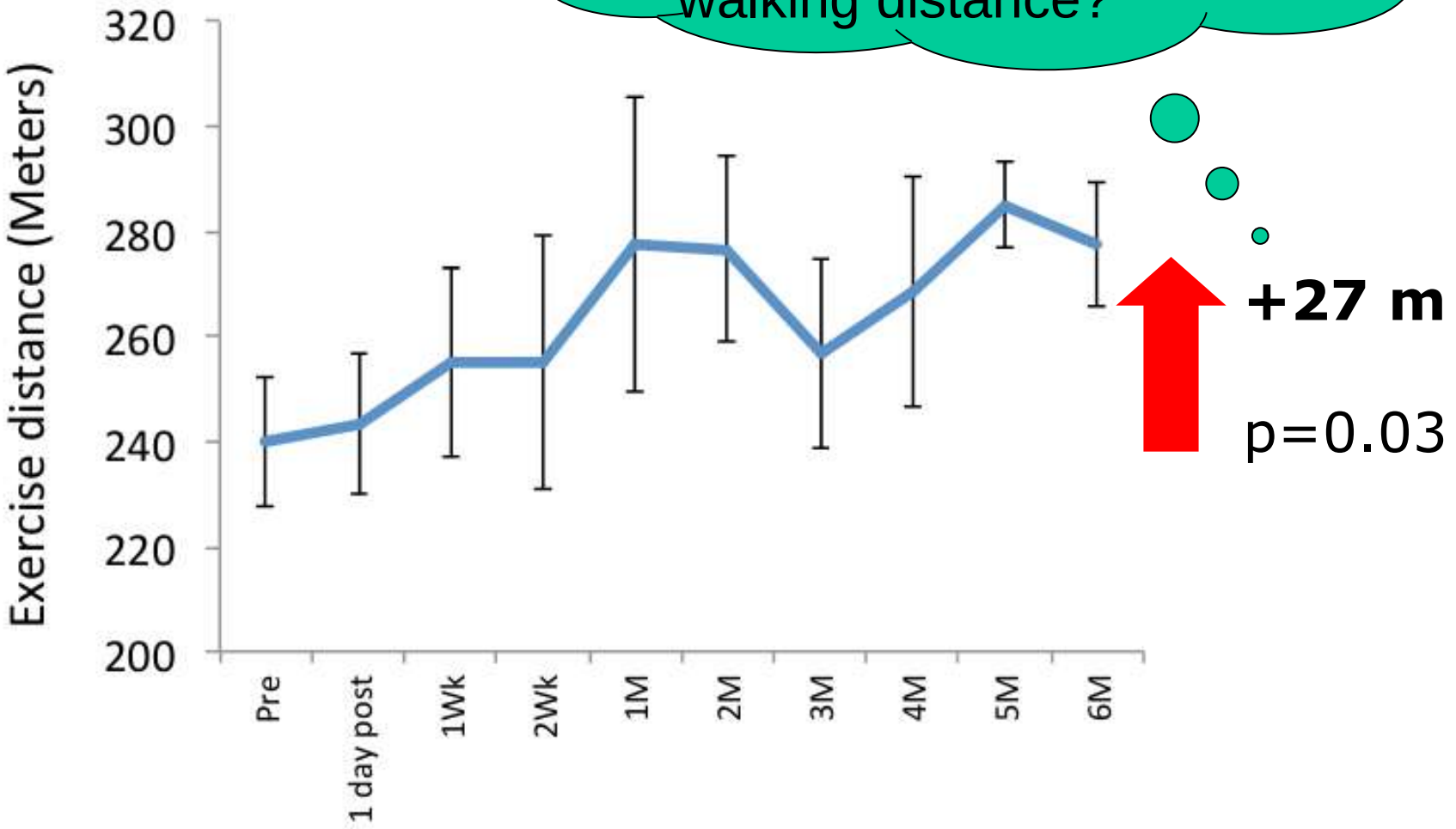
- This is an ongoing debate
  - Decrease by a certain number?
  - Reach a certain goal?
- The answer also depends upon the purpose of the study!
- At the current stage we will have to prove (again) that renal denervation does work at all
  - So we should go for a sensitive parameter, i.e. any decrease
  - Neither a “clinically meaningful improvement” nor “responder rate” should be part of the primary endpoint definition

Endpoint (and responder) definitions for interventional treatment modalities for hypertension are much more difficult than we expected ….

… but it will be even more difficult with other diseases

Renal denervation in chronic heart failure

What is a clinically meaningful increase in walking distance?



Davies, Int J Cardiol 2013

… and this questi
for all othe

We do not really know what the best parameter is

- Mortality
- Hospital re-admission
- Changes in medication
- BNP
- EF
- LVEDP, PA pressu
- Quality of live sco

And we are lost when it comes to the question what we should call a responder

Obstructive Sleep Apnea

Effects of Renal Sympathetic Denervation on Blood Pressure, Sleep Apnea Course, and Glycemic Control in Patients With Resistant Hypertension and Sleep Apnea

Adam Witkowski, Aleksander Prejbisz, Elżbieta Florczak, Jacek Kądziela, Paweł Śliwiński, Przemysław Bieleń, Ilona Michałowska, Marek Kabat, Ewa Warchoł, Magdalena Januszewicz, Krzysztof Narkiewicz, Virend K. Somers, Paul A. Sobotka, Andrzej Januszewicz

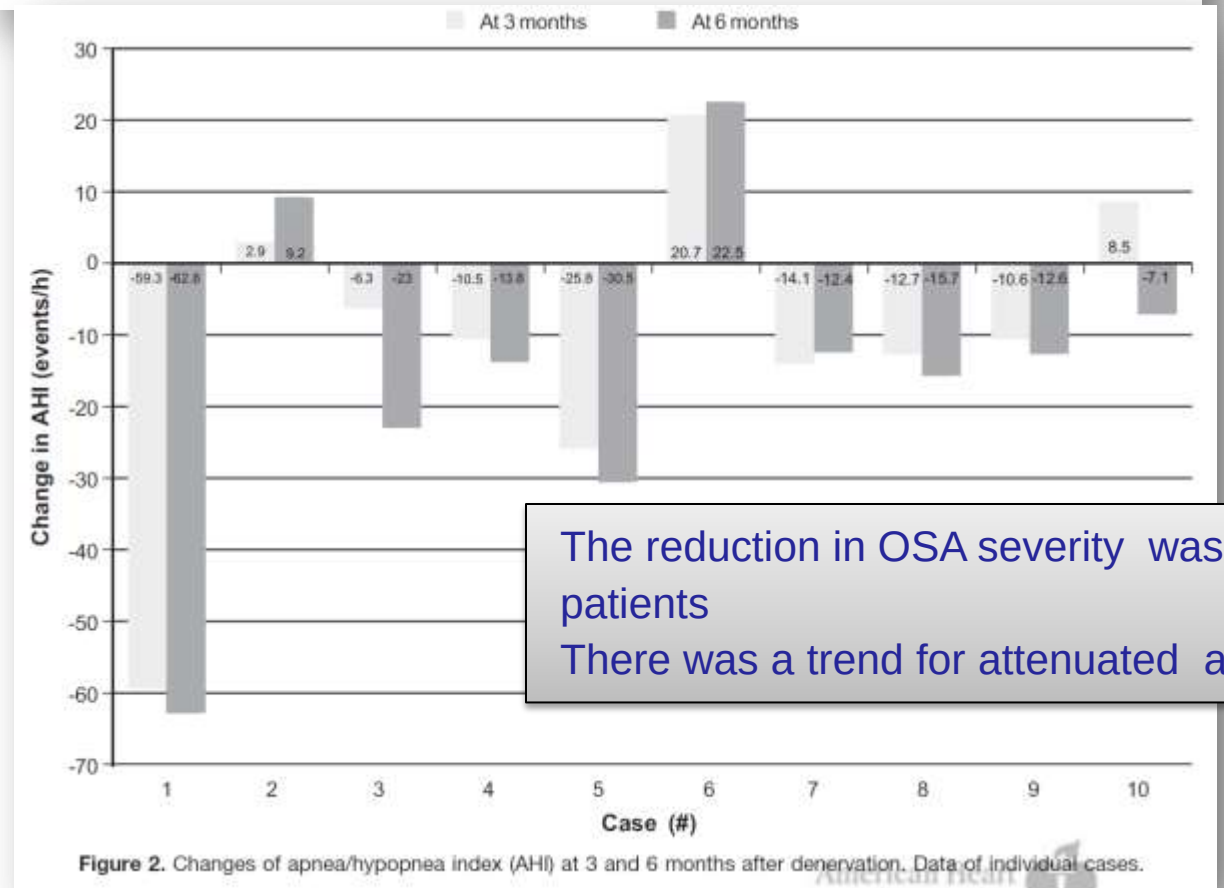


Figure 2. Changes of apnea/hypopnea index (AHI) at 3 and 6 months after denervation. Data of individual cases.

The reduction in OSA severity was observed in 8 out of 10 patients

There was a trend for attenuated apnea/hypopnea index

Obstructive Sleep Apnea

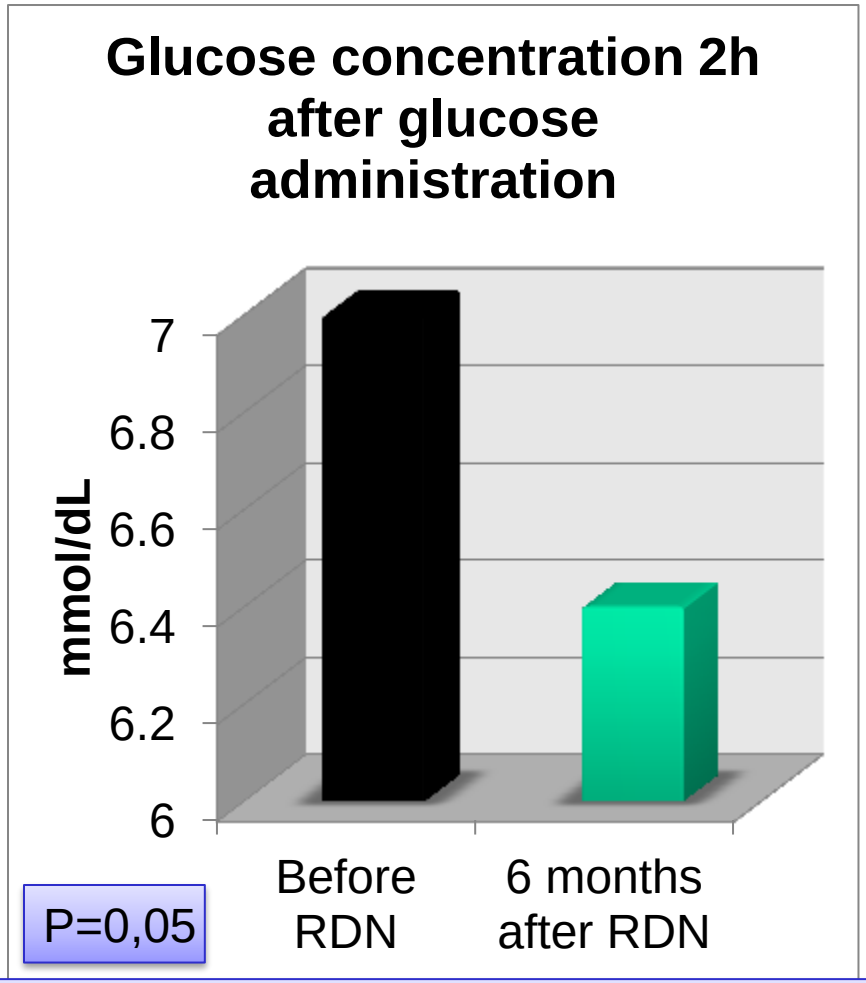
- Parameters
  - Apnea-Hypopnea Index
    - CPAP reduces 8 events/hour
  - Subjective sleepiness (median Epworth Sleepiness score) decrease
    - CPAP reduces 4 events / hour
- So we know how to measure
- But the decision what a clinical meaningful response means is obviously subjective
  - It will determine the outcome of your trial!

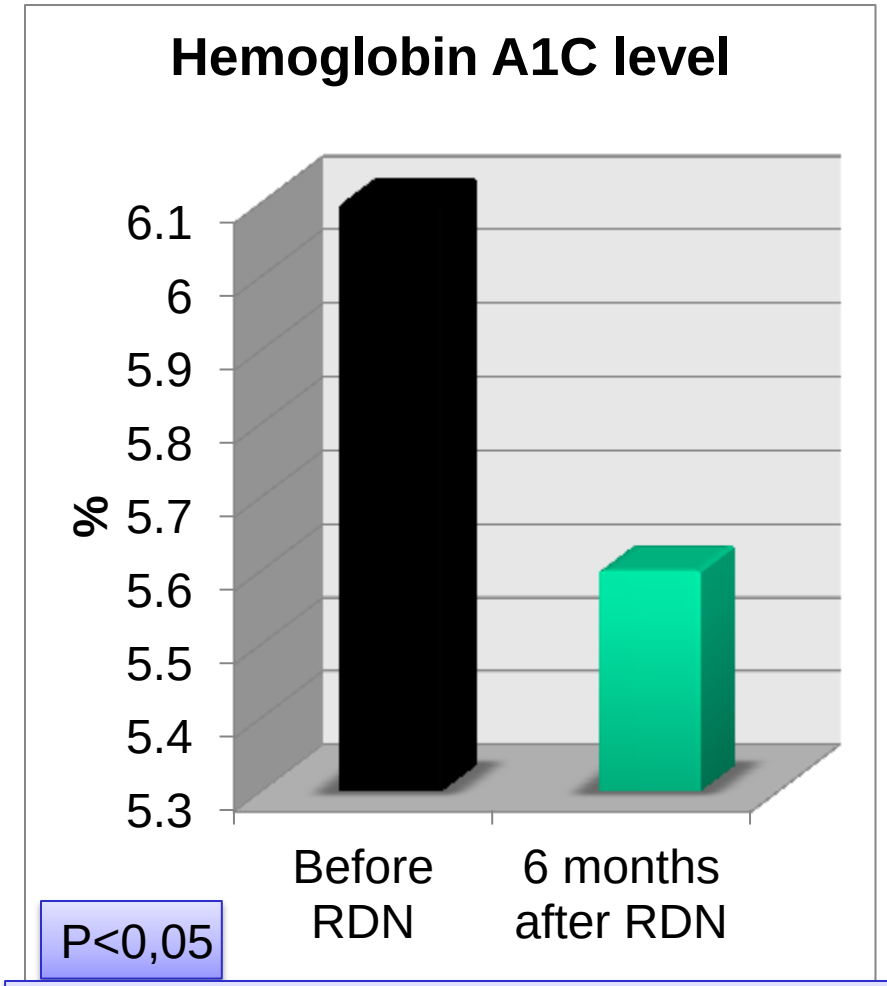
Witkowski HTN 2011, Drager JACC 2013, Zhao ZYXZZ 2013

Arrhythmias?

- Planned arrhythmia outcomes in RDN Afib studies
  - AF recurrence/burden
  - Relapse of atrial tachyarrhythmia >30s
  - Drug free recurrence
  - AF Freedom
  - Symptoms
- Planned arrhythmia outcomes in RDN VT studies
  - Time to first ICD event or incessant VT (RESCUE-VT, RESET-VT trials)

Renal denervation may be beneficial in diabetes





At 6 months significant decrease in plasma glucose concentration 2 hours after glucose challenge was observed

At 6 months significant decrease in HgbA1C level was observed

Witkowski HTN 2011

Glucose Intolerance

- What is the ideal outcome definition?
  - Glucose concentration?
  - Hgb A1C
- Absolute difference?
- Decrease of a certain amount?
- Meeting goal?
- And so the question begins again…

When I finished working on this talk:

“Wooow,
how difficult is that”

Take home message (re-) learned:

Whether a trial ends up being positive or negative does only partially depend upon whether the treatment is effective or not

It much more depends upon how endpoints have been selected and how responders have been defined

Thank You!