Les incontournables de 2017 HTA essentielle

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Inserm
Institut national
de la santé et de la recherche médicale

PARIS
DESCARTES

DISCLOSURE

Stéphane LAURENT, MD, PhD

Potential conflict of interest

Research grant, advisory board, honorarium as speaker or chairman

Last 10 years

Drug companies

ASTRA-ZENECA
BAYER-SCHERING
BOEHRINGER-INGELHEIM
CHIESI
DAICHII-SANKYO
ESTEVE
MENARINI
MSD
NEGMA
NOVARTIS
PFIZER
RECORDATI
SERVIER

Manufacturers

ALAM MEDICAL
ATCOR-HOGIMED
AXELIFE
ESAOTE-PIE MEDICAL
FUKUDA-DENSHI
HEMO SAPIENS
OMRON
TENSIOMED

Les incontournables de 2017

HTA essentielle

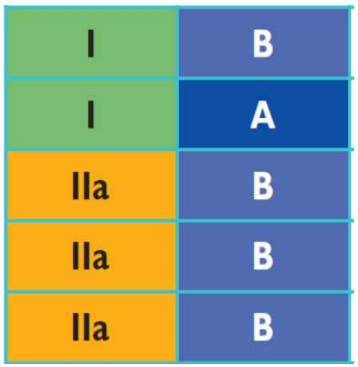
1. **PA cible au cours du traitement**

2013 ESH-ESC Guidelines

2013 ESH-ESC

Target SBP < 140 mmHg

- Low-moderate CV risk
- Diabetes
- Previous stroke or TIA
- CHD
- Diabetic or non-diabetic CKD



Primary prevention

Secondary prevention

less than 140 for all!

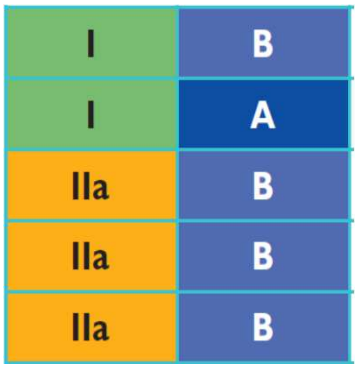
In practice: # 130-135 mmHg

2007 and 2013 ESH-ESC Guidelines

2013 ESH-ESC

Target SBP < 140 mmHg

- Low-moderate CV risk
- Diabetes
- Previous stroke or TIA
- CHD
- Diabetic or non-diabetic CKD



Primary prevention

Secondary prevention

2007 ESH-ESC

Target BP **< 140 / 90** if low and moderate CV risk

Target BP **< 130 / 80** if High CV risk

Previous stroke
Diabetes
Renal dysfunction
Coronary Heart Disease (CHD)

2017 Meta-analyses

Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 – Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials

Costas Thomopoulos[a], Gianfranco Parati[b,c], and Alberto Zanchetti[d,e]

Diabetes

J Hypertens 2017, May

Effects of blood-pressure-lowering treatment on outcome incidence in hypertension. 11. Effects of total cardiovascular risk and achieved blood pressure: overview and meta-analyses of randomized trials

Costas Thomopoulos[a], Gianfranco Parati[b,c], and Alberto Zanchetti[d,e]

CV risk and achieved BP

J Hypertens 2017, Nov

Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials

Costas Thomopoulos[a], Gianfranco Parati[b,c], and Alberto Zanchetti[d,e]

High normal and normal BP

J Hypertens 2017, Nov

2017 Meta-analyse n° 10

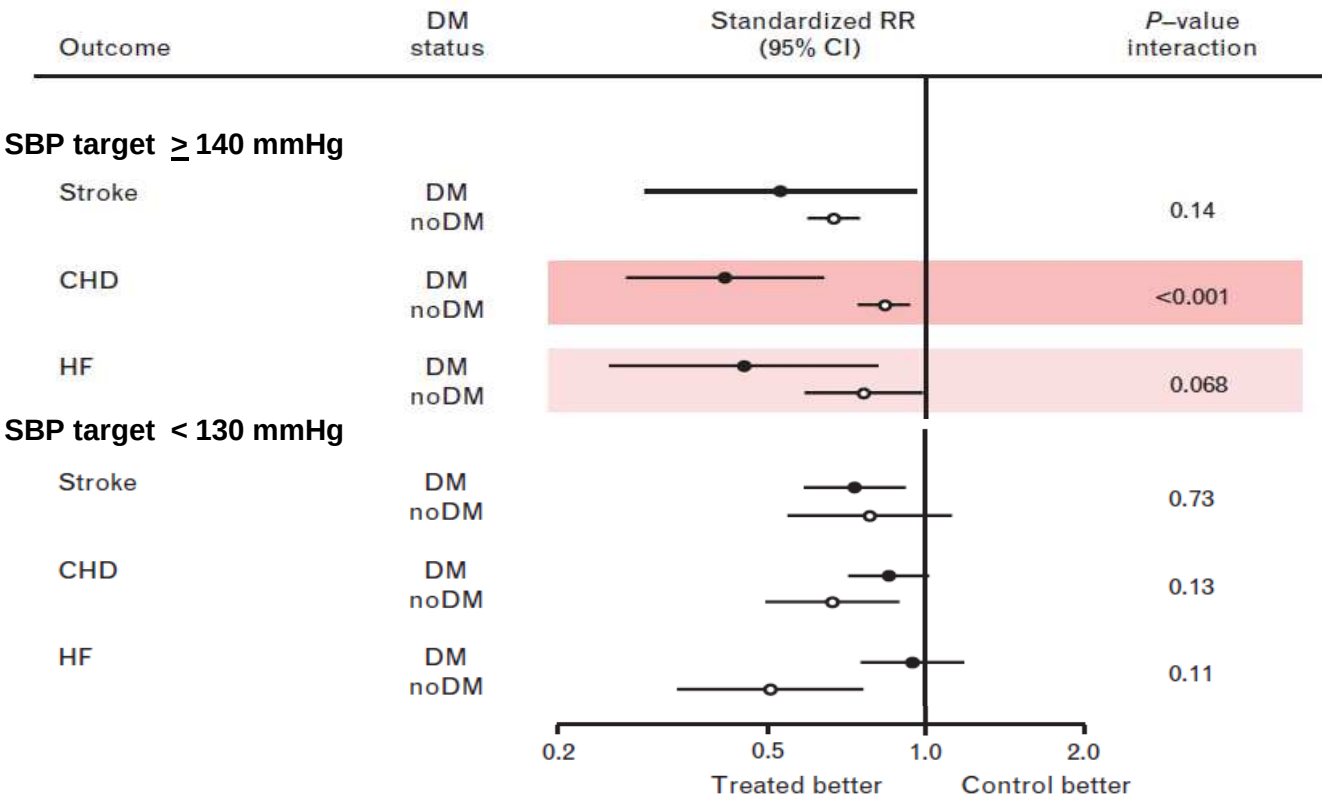
Diabetes

Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 – Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials

Costas Thomopoulos[a], Gianfranco Parati[b,c], and Alberto Zanchetti[d,e]

41 RCTs on 61 772 DM and 191 353 without

Conclusion: Contrary to past recommendations, in diabetes mellitus there is little or no further benefit in lowering SBP below 130 mmHg, whereas continuing benefit is seen in no diabetes mellitus also at SBP below 130 mmHg.



2017 Meta-analyse n° 11

CV risk and achieved BP in non DM

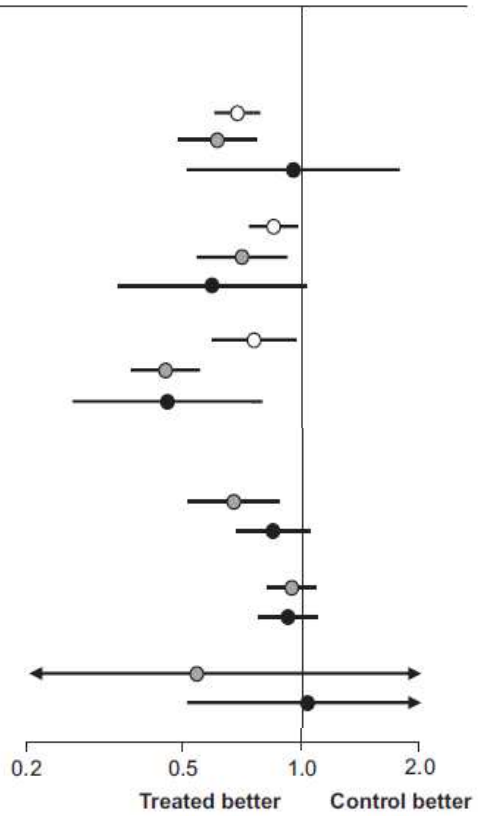
Effects of blood-pressure-lowering treatment on outcome incidence in hypertension. 11. Effects of total cardiovascular risk and achieved blood pressure: overview and meta-analyses of randomized trials

Costas Thomopoulos[a], Gianfranco Parati[b,c], and Alberto Zanchetti[d,e]

Conclusion: A high level of cardiovascular risk is not in itself a restraint to target at SBP values less than 130 mmHg, if treatment is well tolerated.

72 RCTs on 260 210 patients without DM

Outcome	Achieved SBP (mmHg)	Trials (n)	Standardized RR (95% CI)	P-value trend	P-value between targets
Patients at high-very high CV risk					
Stroke	≥140	9	0.68 (0.60-0.78)	0.51	0.39
	130-139	6	0.60 (0.48-0.76)		0.031
	<130	2	0.96 (0.51-1.78)		
CHD	≥140	6	0.85 (0.74-0.98)	0.20	0.24
	130-139	5	0.71 (0.54-0.91)		0.43
	<130	2	0.59 (0.34-1.02)		
HF	≥140	3	0.76 (0.59-0.97)	0.26	0.17
	130-139	4	0.54 (0.44-0.68)		0.49
	<130	3	0.46 (0.26-0.79)		
Patients at low-moderate CV risk					
Stroke	130-139	7	0.67 (0.51-0.88)		0.33
	<130	4	0.85 (0.68-1.05)		
CHD	130-139	8	0.94 (0.82-1.09)		0.88
	<130	4	0.92 (0.78-1.09)		
HF	130-139	5	0.54 (0.11-2.80)		0.39
	<130	2	1.03 (0.51-2.11)		



2017 Meta-analyse n° 12

Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials

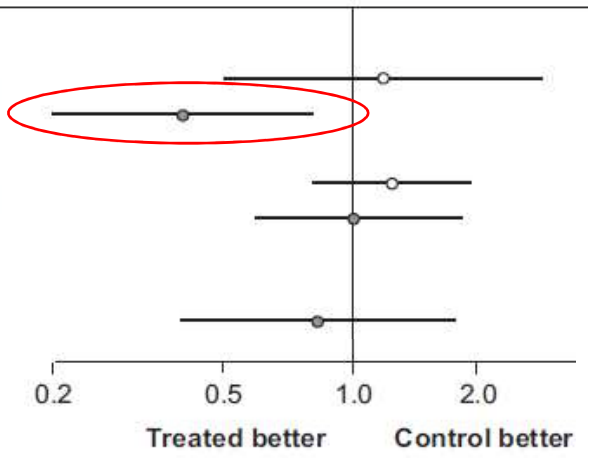
Costas Thomopoulos[a], Gianfranco Parati[b,c], and Alberto Zanchetti[d,e]

High normal and normal BP (120-139/80-89 mmHg)

Conclusion: Individuals with very high cardiovascular risk due to symptomatic cardiovascular disease should consider BP-lowering treatment even when their BP is in the high-normal and normal range.

24 RCTs on 47 991 individuals

Outcome	CV risk	Trials (n)	Standardized RR (95% CI)	P-value homogeneity
Stroke	L-M	4	1.20 (0.51-2.78)	0.006
	H-VH	8	0.40 (0.20-0.81)	
CHD	L-M	4	1.25 (0.82-1.92)	0.089
	H-VH	6	1.00 (0.60-1.84)	
HF	L-M	1	-	-
	H-VH	5	0.82 (0.38-1.81)	



RR for Δ SBP/DBP 10/5 mmHg

Target blood pressure for primary prevention in the upcoming Guidelines ?

2018 ESH / ESC Guidelines

June 2018

August 2018

Target blood pressure for primary prevention in the upcoming Guidelines ?

AHA / ACC 2017

Hypertension, Nov 13, 2017

Whelton PK, et al.

2017 High Blood Pressure Clinical Practice Guideline: Executive Summary

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

8.1.5. BP Goal for Patients With Hypertension

Recommendations for BP Goal for Patients With Hypertension References that support recommendations are summarized in Online Data Supplement 26 and Systematic Review Report.		
COR	**LOE**	**Recommendations**
I	SBP: B-R[SR] DBP: C-EO	1. For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher (see Section 8.1.2), a BP target of less than 130/80 mm Hg is recommended (1-5).

Target BP ≤ 130 / 80 if 10 year CV risk ≥ 10%

Target blood pressure for primary prevention in the upcoming Guidelines ?

AHA / ACC 2017

Whelton PK, et al.

2017 High Blood Pressure Clinical Practice Guideline: Executive Summary

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Hypertension, Nov 13, 2017

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IIb	SBP: B-NR DBP: C-EO	2. For adults with confirmed hypertension, without additional markers of increased CVD risk, a BP target of less than 130/80 mm Hg may be reasonable (6-9).

Target BP ≤ 130 / 80 if no additional markers of increased CV risk

Recommandations AHA/ACC 2017

Nouveaux seuils de définition de l'HTA

Table 6. Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

2013 ESH-ESC
2014 JNC8
2014 AHA/ACC

Optimal
Normal

High normal
Grade I HT

Recommandations AHA/ACC 2017

Nouveaux seuils de définition de l'HTA

et d'initiation du TT

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2014 JNC8
2014 AHA/ACC

Optimal
Normal

High normal
Grade I HT

≥ 130/80 mmHg: Initiation du TT antiHT
- En prévention secondaire
- En prévention primaire seulement si le risque CV à 10 ans est ≥ 10%

Recommandations AHA/ACC 2017

Nouveaux seuils de définition de l'HTA

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2013 ESH-ESC
2014 JNC8
2014 AHA/ACC

Optimal
Normal

High normal
Grade I HT

≥ 140/90 mmHg: Initiation du TT antiHT en prévention primaire
… même si le risque CV à 10 ans est ≤ 10%

SPRINT study

ORIGINAL ARTICLE

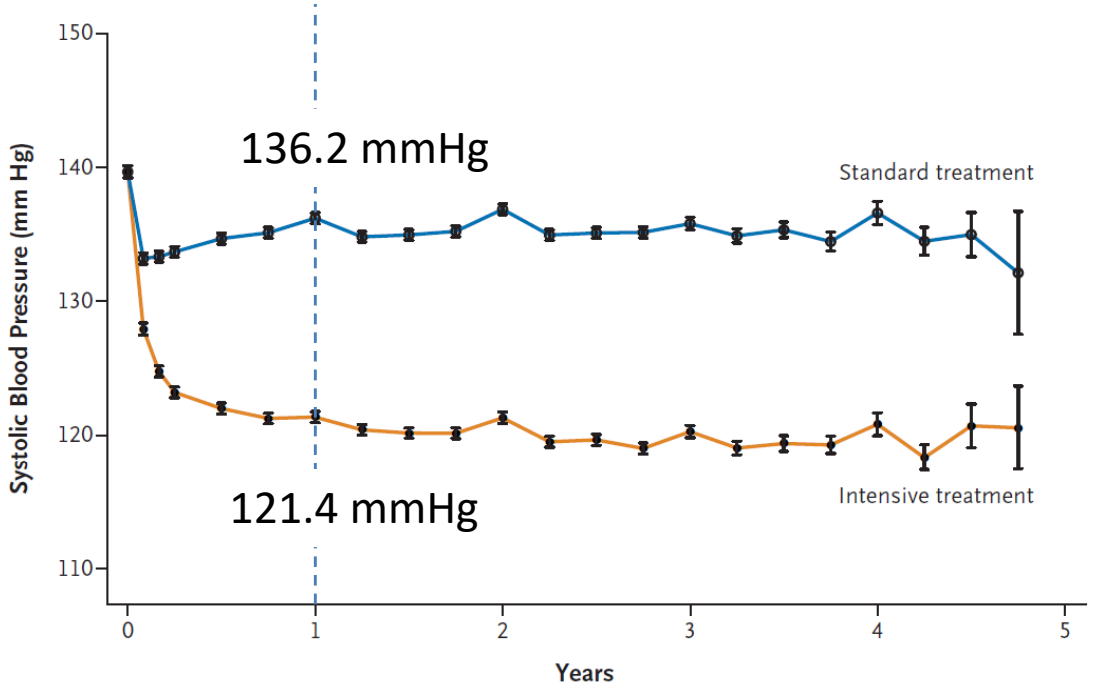
A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

NEJM 2015

n=9360

Target SBP
< 140 mmHg
vs
< 120 mmHg



No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286
Mean No. of Medications										
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0

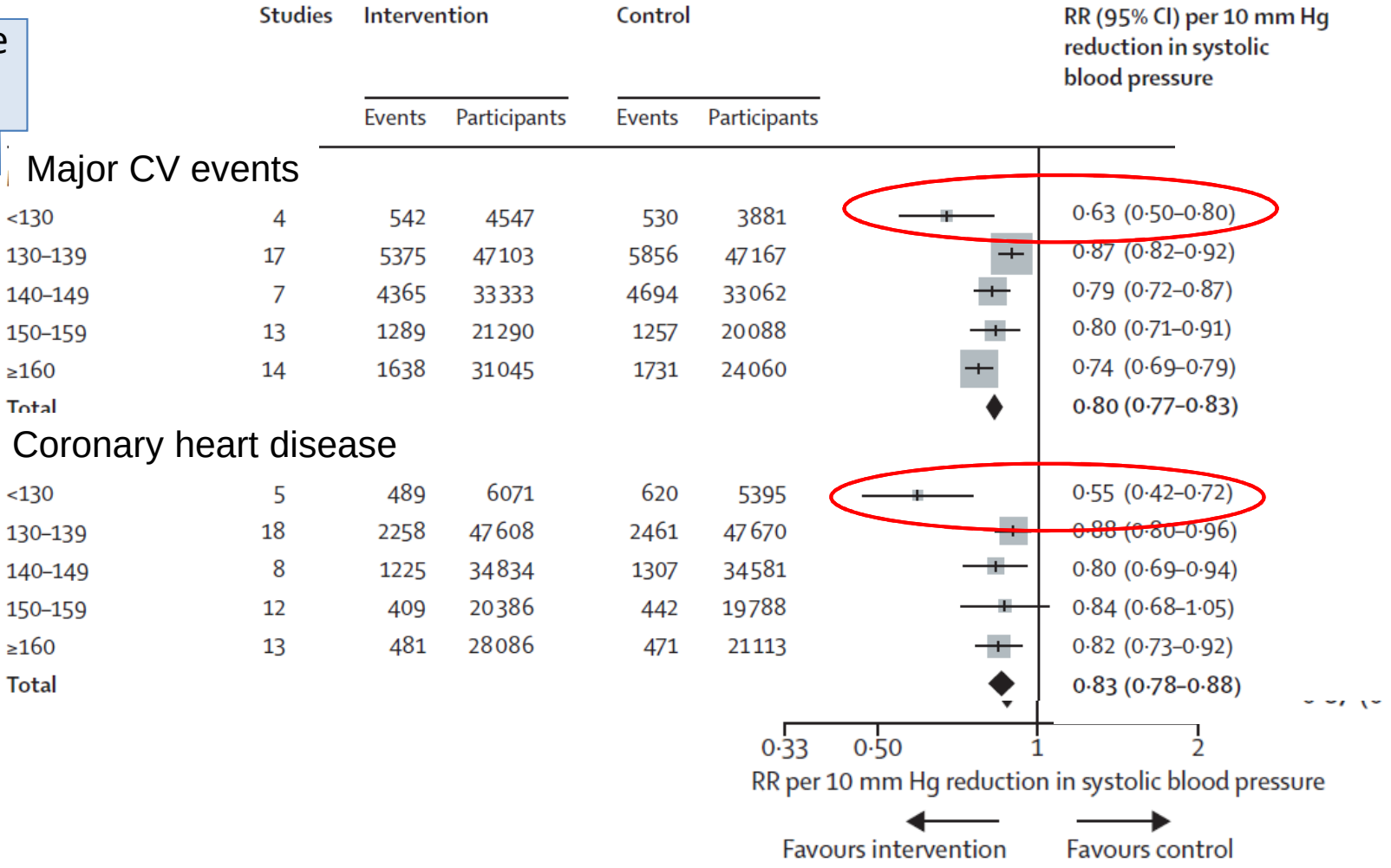
Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis

Dena Ettehad, Connor A Emdin, Amit Kiran, Simon G Anderson, Thomas Callender, Jonathan Emberson, John Chalmers, Anthony Rodgers, Kazem Rahimi

Ettehad D et al. Lancet 2015

Yes, it is safe to lower SBP below 130 mmHg

Baseline SBP



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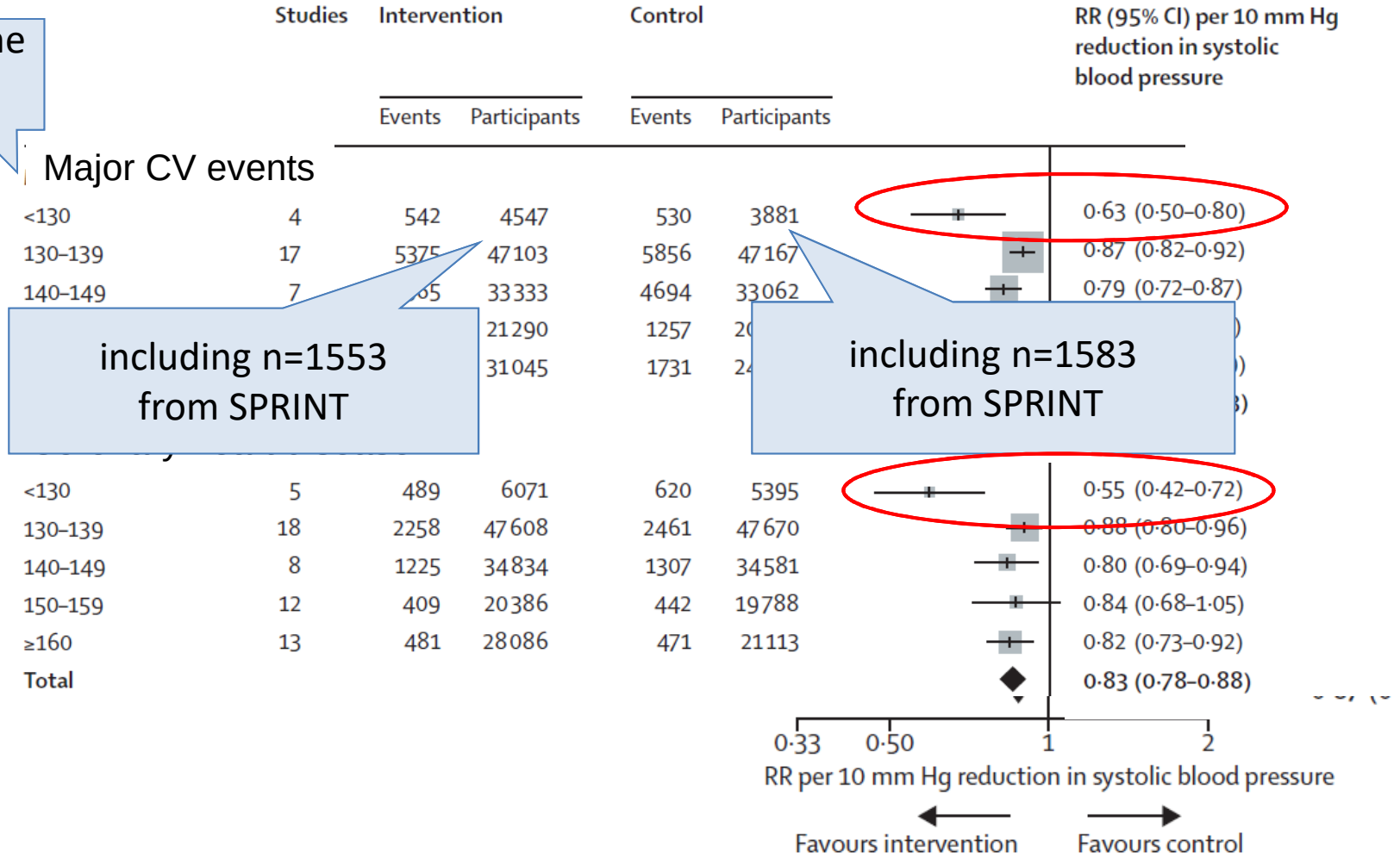


SPRINT study

ORIGINAL ARTICLE

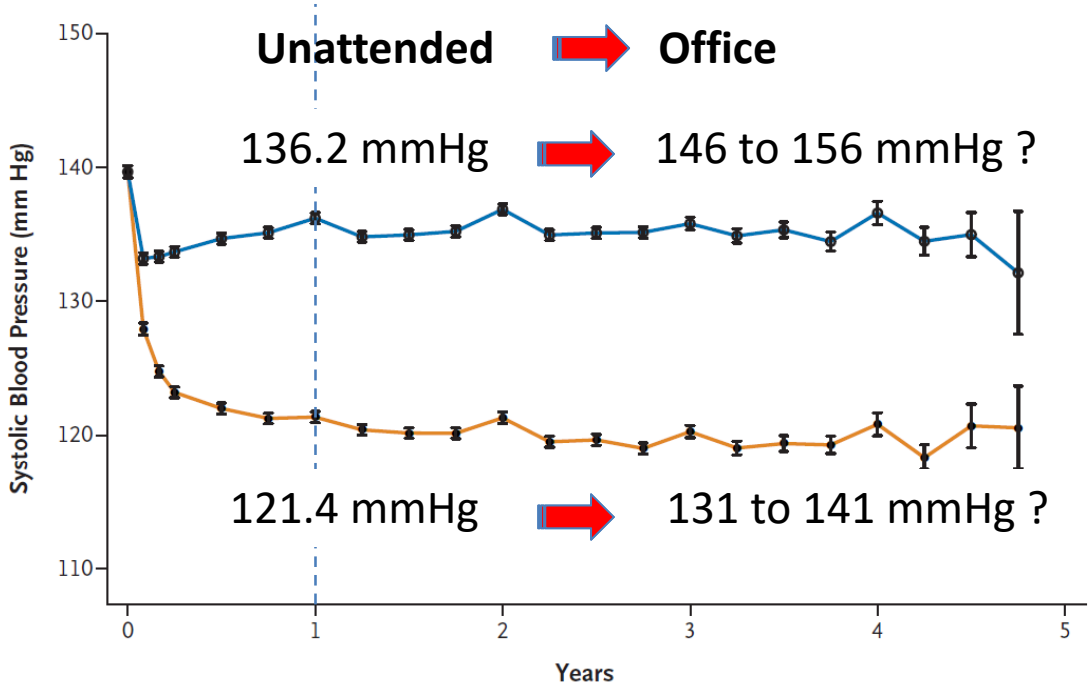
A Randomized Trial of Intensive versus Standard Blood-Pressure Control

Underestimation of the true « office » achieved SBP

NEJM 2015

n=9360

Target SBP
< 140 mmHg
vs
< 120 mmHg



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2017 AHA/ACC Guidelines: Target BP

There have been 8 recent meta-analyses addressing the issues of BP reduction and target BP levels for the treatment of hypertension (37-39, 43-47). Although treatment of hypertension was associated with improved outcomes in all 8 meta-analyses, the optimal target BP remains unclear. In the current systematic review and meta-analysis, we sought to determine the optimal targets for BP lowering during antihypertensive therapy in adults.

An electronic literature search was performed by Doctor Evidence, a global medical evidence software and services company, across PubMed and EMBASE from 1966 to April 13, 2015, using key words and relevant subject headings for "hypertension" combined with terms for the interventions of interest (see Online Data Supplement Part 2, Table 2.1). An additional PubMed search was performed through May 6, 2015. SPRINT (Systolic Blood Pressure Intervention Trial) was included in November 2015, and SPS3 (Secondary Prevention of Small Subcortical Strokes Trial) was included in April 2016 at the request of the ERC (48, 49). The ERC also searched bibliographies of recent, relevant meta analyses (37-39, 50).

All analyses were performed using an online platform (Doctor Evidence. 2016. DOC Data, Version 2.0. Santa Monica, CA: Doctor Evidence, LLC) that incorporated R statistical software using Metafor (55).

2017 AHA/ACC Guidelines: Target BP

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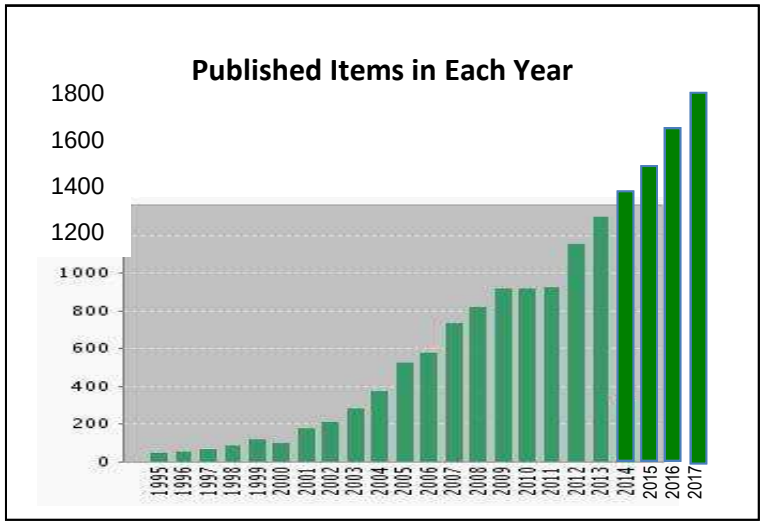
Les incontournables de 2017

HTA essentielle

1. PA cible au cours du traitement

2. **Organes cibles: rigidité artérielle et vieillissement artériel accéléré**

Web of Science
(December 2017)
TS=arterial stiffness
Selection: all documents,
n = 15,575



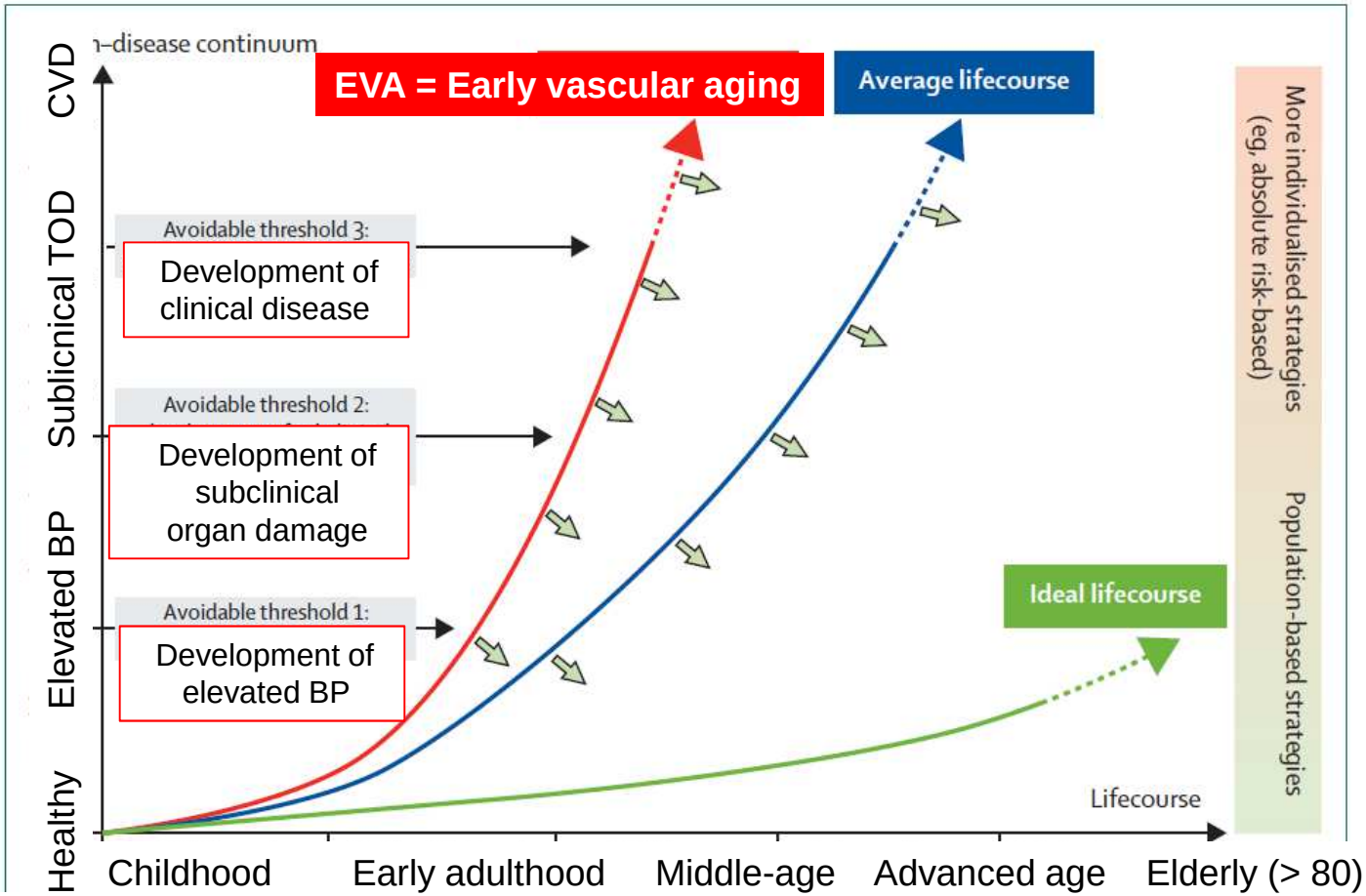
A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the *Lancet* Commission on hypertension

THE LANCET

Olsen M et al. Lancet, September 2016

Michael H Olsen, Sonia Y Angell, Samira Asma, Pierre Boutouyrie, Dylan Burger, Julio A Chirinos, Albertino Damasceno, Christian Delles, Anne-Paule Gimenez-Roqueplo, Dagmara Hering, Patricio López-Jaramillo, Fernando Martinez, Vlado Perkovic, Ernst R Rietzschel, Giuseppe Schillaci, Aletta E Schutte, Angelo Scuteri, James E Sharman, Kristian Wachtell, Ji Guang Wang*

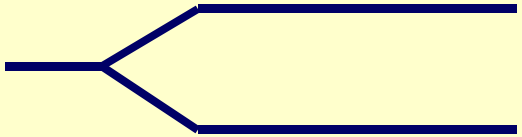
A lifecourse approach



La rigidité artérielle est-elle un critère de substitution?

Etude interventionnelle SPARTE: la réduction de la rigidité artérielle se traduit-elle par moins de complications CV et rénales?

Stratégie thérapeutique basée sur les recommandations



Stratégie thérapeutique basée sur la mesure de la rigidité artérielle (VOP)

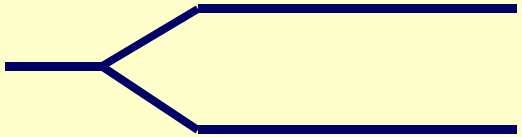
24 centres d'investigation en France

Paris HEGP	Grenoble
Lille	Paris Hotel Dieu
Paris La Pitié	Rouen CN
Bordeaux	Créteil
Montpellier	Strasbourg
Bobigny	Fleury-Merogis
Amiens	Lyon Croix Rousse
Rennes	Toulon
Tours	Lyon Montbrison
Rouen BG	Lyon Bron
Poitiers	Nimes
Marseille	
Bondy	

La rigidité artérielle est-elle un critère de substitution?

Etude interventionnelle SPARTE: la réduction de la rigidité artérielle se traduit-elle par moins de complications CV et rénales?

Stratégie thérapeutique basée sur les recommandations



Stratégie thérapeutique basée sur la mesure de la rigidité artérielle (VOP)

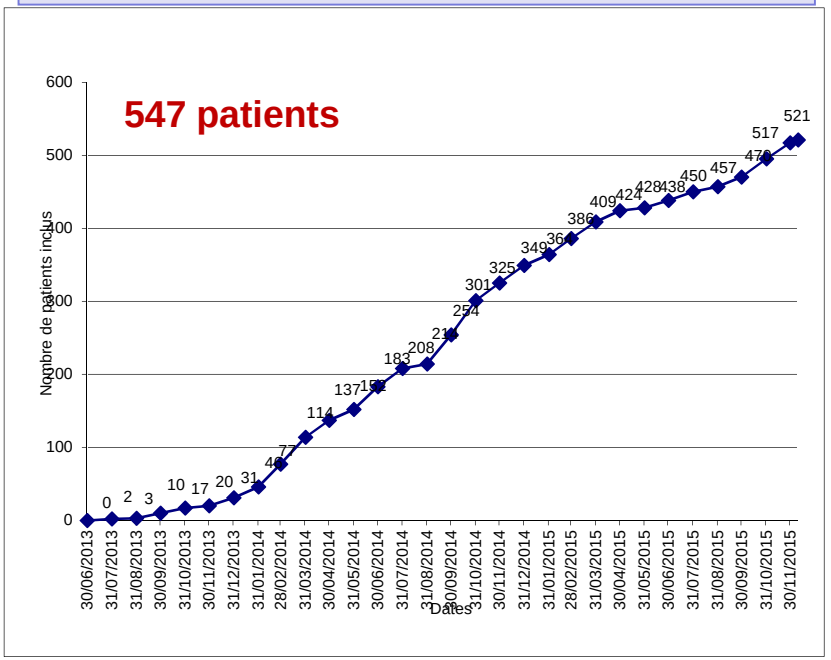
October 21, 2017

100 % of patients at the 12 month visit

87% 24 month visit

47% 36 month visit

Last visit, last patient: January 26, 2020

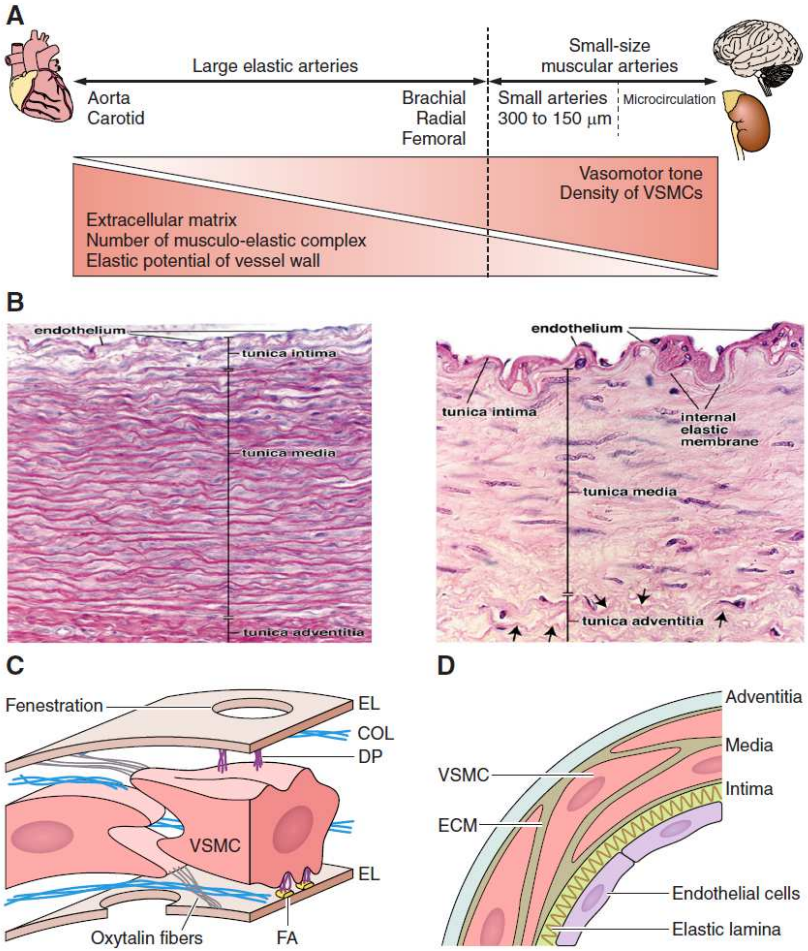


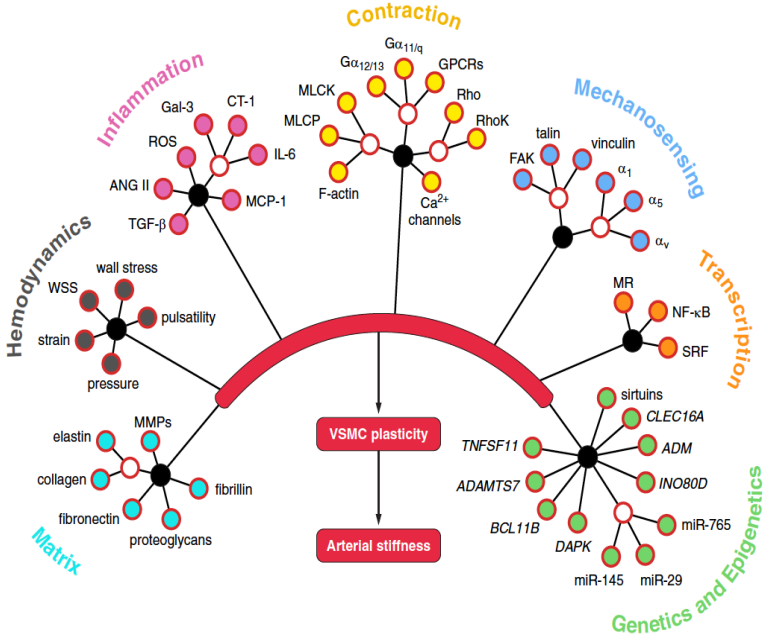
Déterminants cellulaires et moléculaires de la rigidité artérielle

VASCULAR SMOOTH MUSCLE CELLS AND ARTERIAL STIFFENING: RELEVANCE IN DEVELOPMENT, AGING, AND DISEASE

Patrick Lacolley, Véronique Regnault, Patrick Segers, and Stéphane Laurent

Lacolley et al. Phys Rev 2017,97:1555-1617





Les incontournables de 2017

HTA essentielle

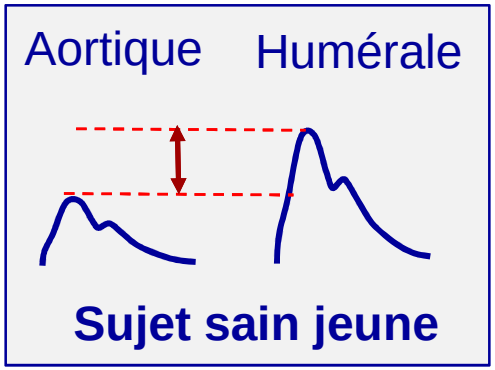
1. PA cible au cours du traitement

2. Organes cibles: rigidité artérielle – déterminants cellulaires et moléculaires

3. **Organes cibles: pression artérielle centrale**

La PA humérale ne reflète pas toujours la PA aortique

Amplification =
Humérale *moins* Aortique



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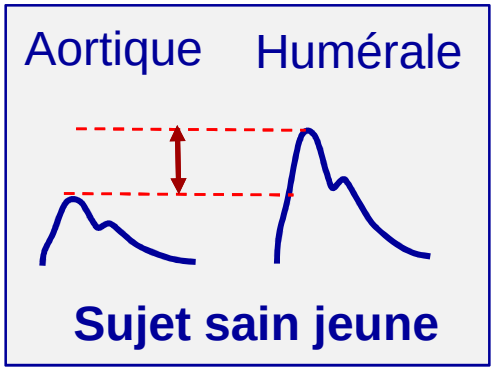

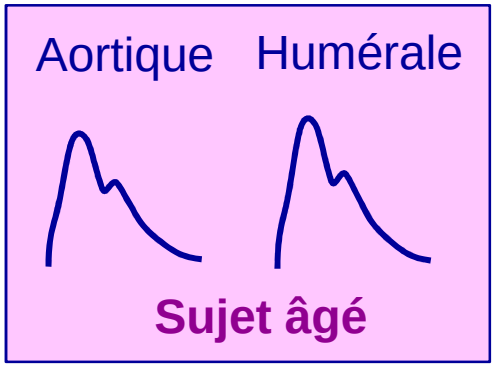

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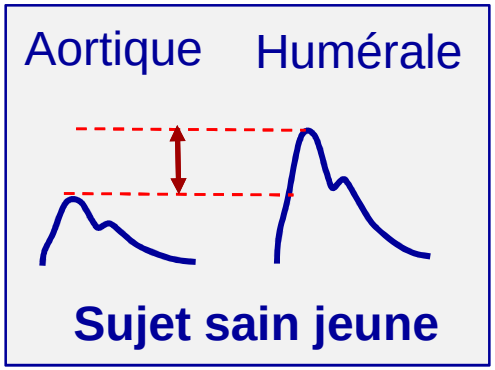
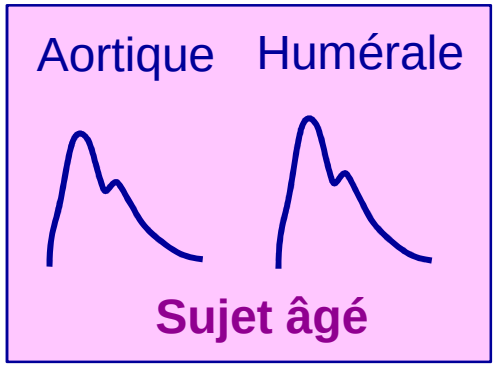




↗ SBP and PP aortique

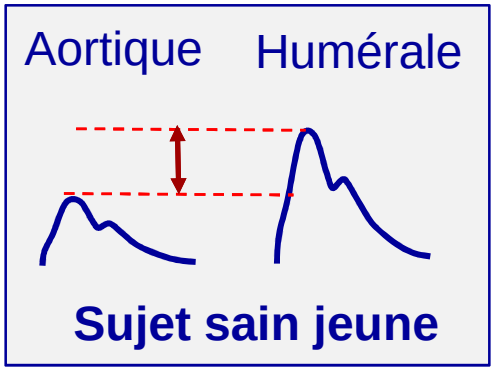
↗ Atteinte des organes cibles

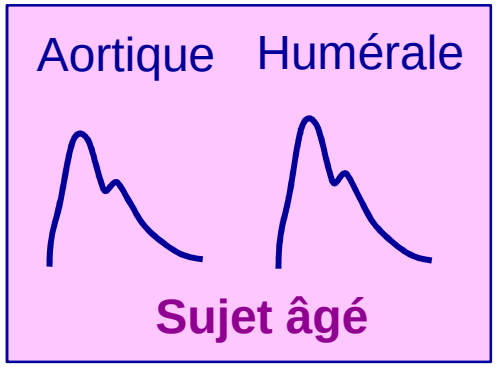
Meilleure corrélation
PP Ao > PP hum

↗ Complications CV et rénales

La PA humérale ne reflète pas toujours la PA aortique

Amplification =
Humérale *moins* Aortique





Meilleure valeur prédictive
PP Ao > PP hum?

non

↗ SBP and PP aortique

↗ Atteinte des organes cibles

↗ Complications CV et rénales

Meilleure corrélation
PP Ao > PP hum

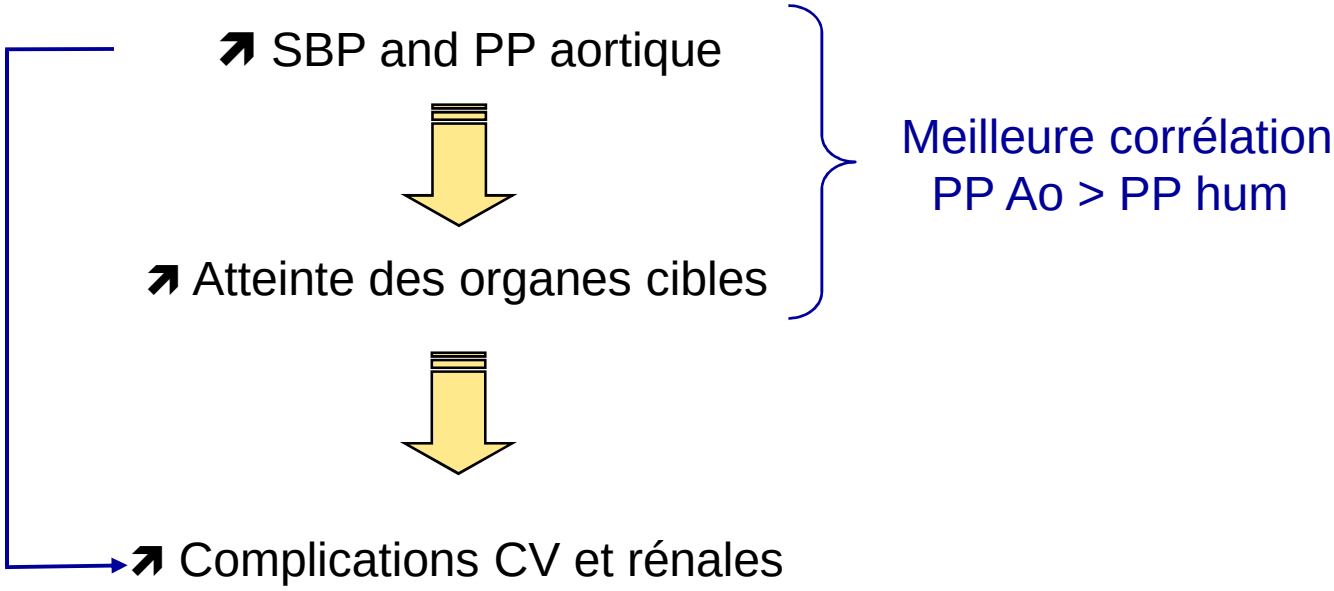
La PA humérale ne reflète pas toujours la PA aortique

Les valeurs absolues de PAS et PP aortique ne sont pas adéquates

- ❑ Indices de réflexion d'ondes de pression (Reflection magnitude, AIx, amplification)
- ❑ Mesure de la PAS aortique sur les 24h
- ❑ **Meilleure calibration de PAS et PP aortique**

Meilleure valeur prédictive PP Ao > PP hum?

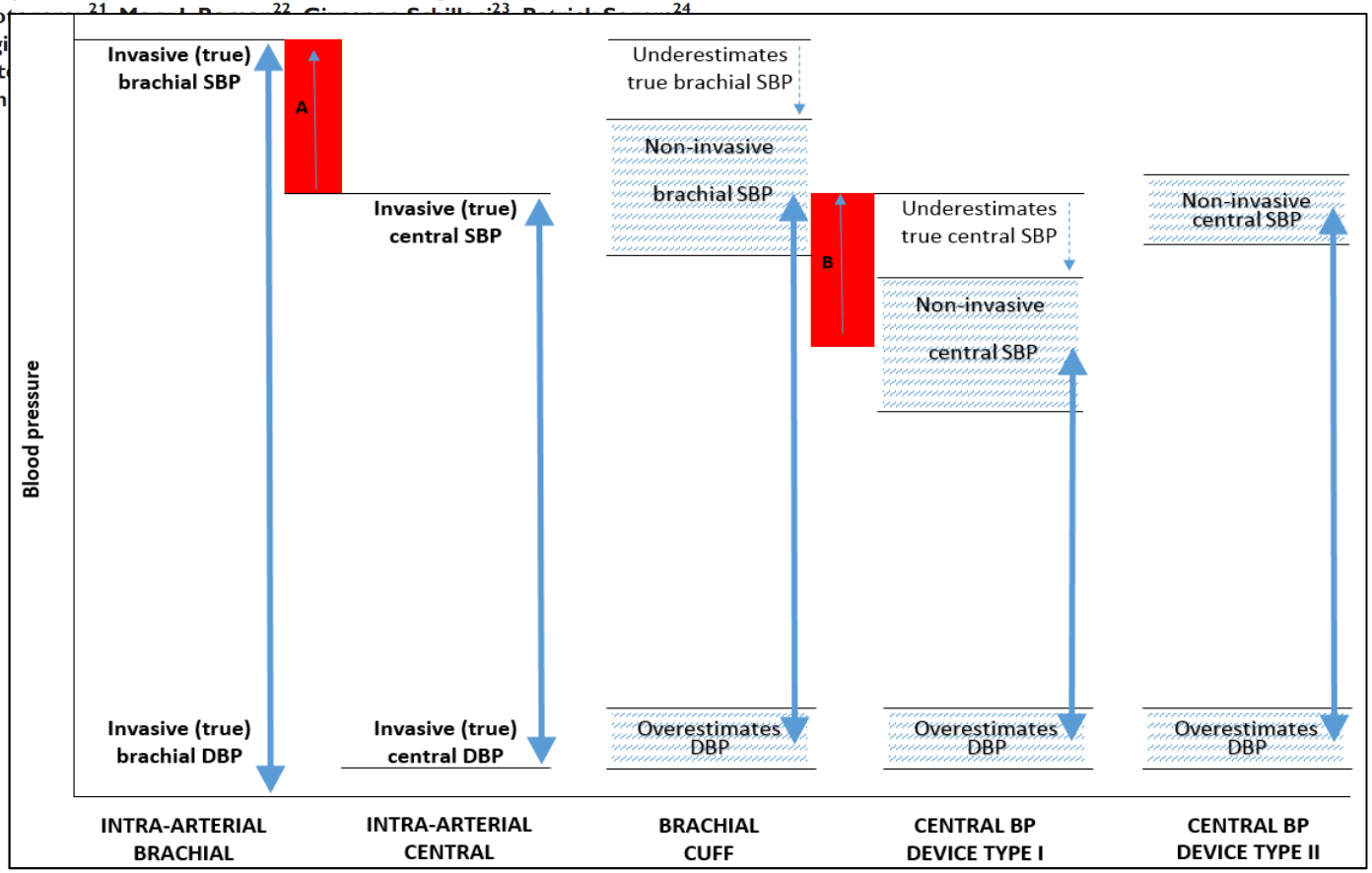
non



Validation of non-invasive central blood pressure devices: ARTERY Society task force consensus statement on protocol standardization

James E. Sharman[1]*, Alberto P. Avolio[2], Johannes Baulmann[3], Athanase Benetos[4], Jacques Blacher[5], C. Leigh Blizzard[1], Pierre Boutouyrie[6], Chen-Huan Chen[7], Phil Chowienczyk[8], John R. Cockcroft[9], J. Kennedy Cruickshank[10], Isabel Ferreira[11], Lorenzo Ghiadoni[12], Alun Hughes[13], Piotr Jankowski[14], Stephane Laurent[6], Barry J. McDonnell[9], Carmel McEniery[15], Sandrine C. Millasseau[16], Theodoros G. Papaioannou[17], Gianfranco Parati[18,19], Jeong Bae Park[20], Athanase D. Pro[21], [22], [23], [24], George S. Stergi, Luc M. Van Bort, Ian B. Wilkinson

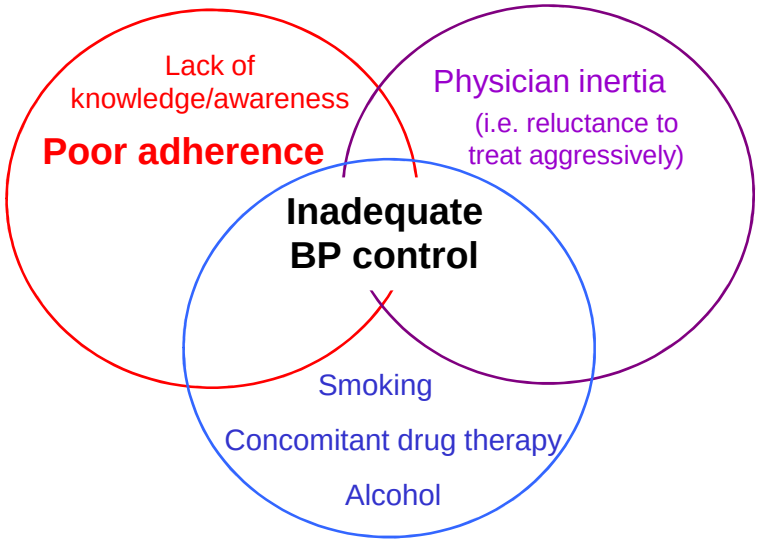
Sharman J et al. Eur Heart J 2017;38:2805-2812.



Les incontournables de 2017
HTA essentielle

1. PA cible au cours du traitement
2. Organes cibles: rigidité artérielle – déterminants cellulaires et moléculaires
3. Organes cibles: pression artérielle centrale

4. Observance médicamenteuse



Drug adherence in hypertension: from methodological issues to cardiovascular outcomes

Idir Hamdidouche[a,c,d], Vincent Jullien[a,c,d], Pierre Boutouyrie[a,c,d], Eliane Billaud[a,c], Michel Azizi[b,c,d,e], and Stéphane Laurent[a,c,d]

Hamdidouche et al. J Hypertens 2017;35:1133-1144
Hamdidouche et al. J Hypertens 2017;35:1891-1898

Methods	Indirect			
	Clinician estimation	Questionnaires	Pill count	Prescription refill
Type of data	Qualitative	Qualitative	Quantitative	Quantitative
Device mostly used	Interview	MMAS-4, 8	–	MPR/PDC
Reliability	–	–	+	+
Validity	+	+	+	+
Objectivity	–	–	–	–
Simplicity	+++	+++	++	–
Cost	–	–	–	+
Availability	+++	+++	++	–
Clinical use	+++	+++	+	–

MPR, Medication Possession Ratio
PDC, Proportion of Days Covered by treatment

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Hamdidouche et al. J Hypertens 2017;35:1133-1144
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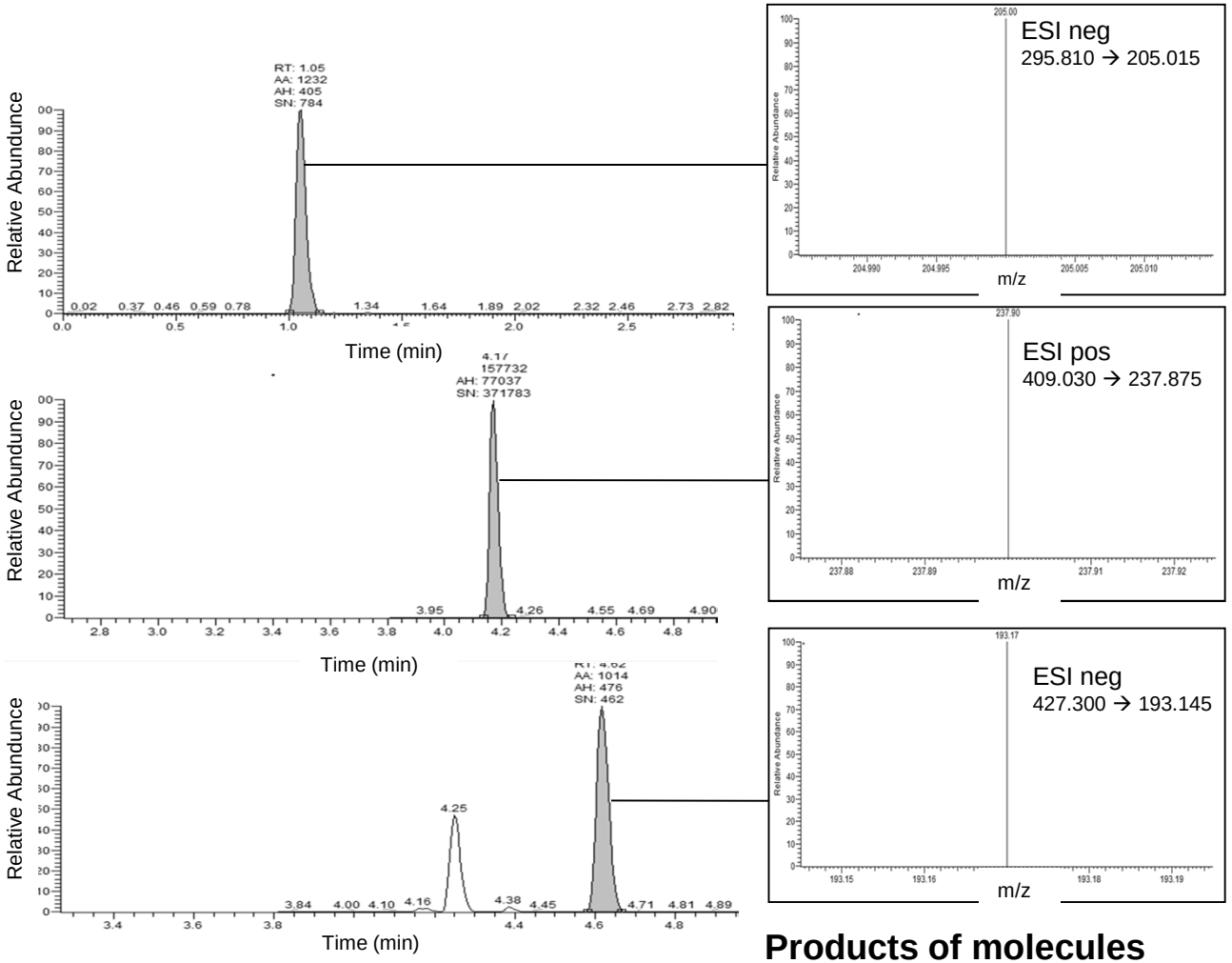
Methods	Direct		
	DOT	Electronic monitoring	Drug assay
Type of data	Quantitative	Quantitative	Qualitative
Device mostly used	–	MEMS	LC–MS/MS
Reliability	+++	++	+++
Validity	+++	++	++
Objectivity	+++	+	++
Simplicity	–	+	+/–
Cost	+	+++	++
Availability	–	–	+/–
Clinical use	–	–	+

DOT Directly Observed Therapy

Any of 24 antiHT drugs
Amiloride
Amlodipine
Atenolol
Bisoprolol
Candesartan
Carvedilol
Celiprolol
Chlortalidone
Clonidine
Furosemide
Hydrochlorothiazide
Indapamide
Irbesartan
Labetalol
Metoprolol
Moxonidine
Nicardipine
Olmesartan
Prazosine
Rilmenidine
Spironolactone (canrenone)
Urapidil
Valsartan
Verapamil

Urinary drug detection by LCMS/MS in a fully adherent patient



Hydrochlorothiazide

Amlodipine

Irbesartan

Chromatograms

Products of molecules fragmentation

Urinary drug detection by LCMS/MS in a fully NON-adherent patient

Treatment prescribed:

Irbesartan 150mg, once/day

Nebivolol, 5mg, once/day

Spironolactone 25mg, once/day

Hydrochlorothiazide (HTCZ) 12.5mg, once/day

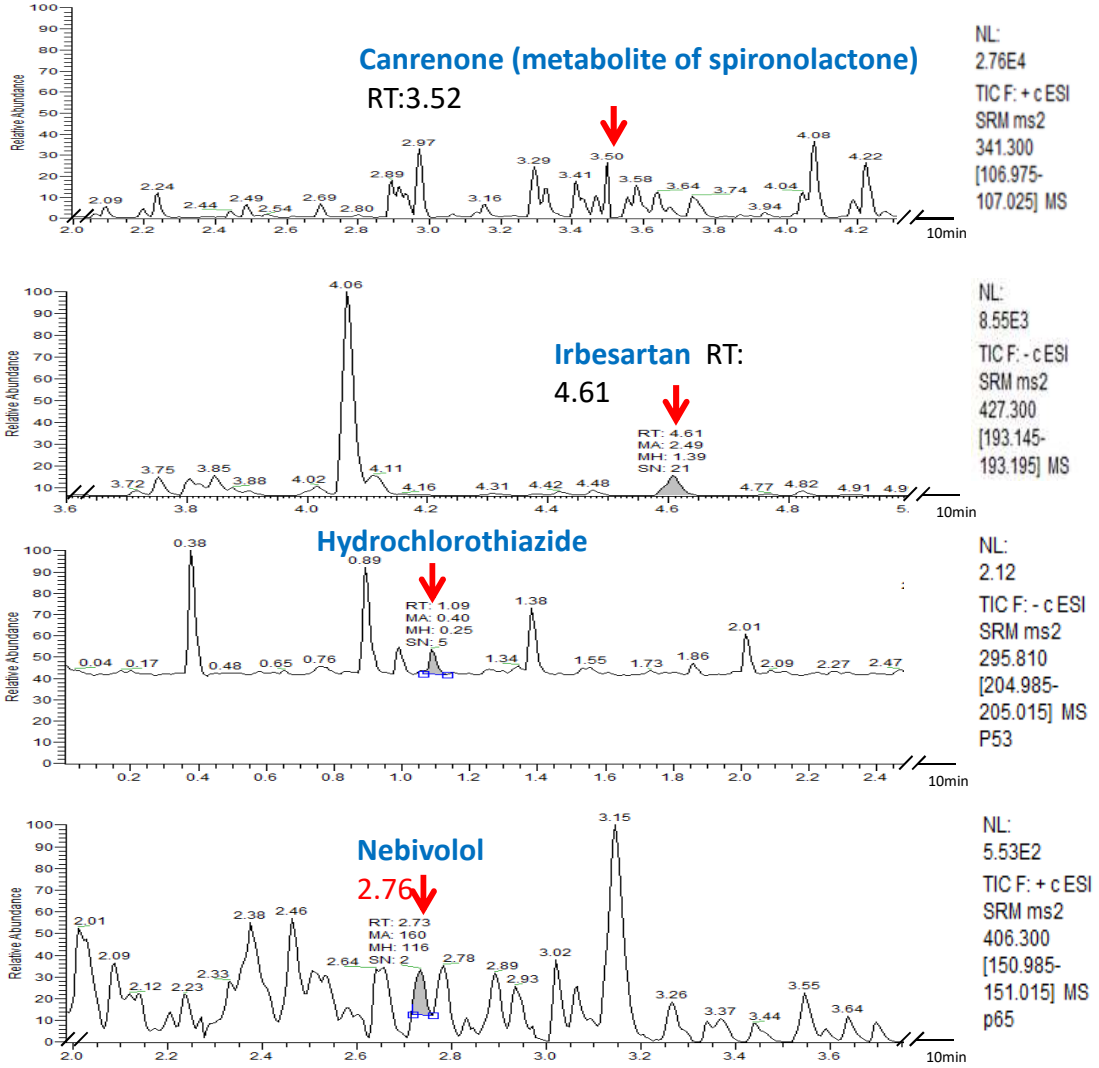
Result of LC-MS/MS analysis:

Irbesartan: not detected

Nebivolol: not detected

Spironolactone: not detected

HTCZ: not detected

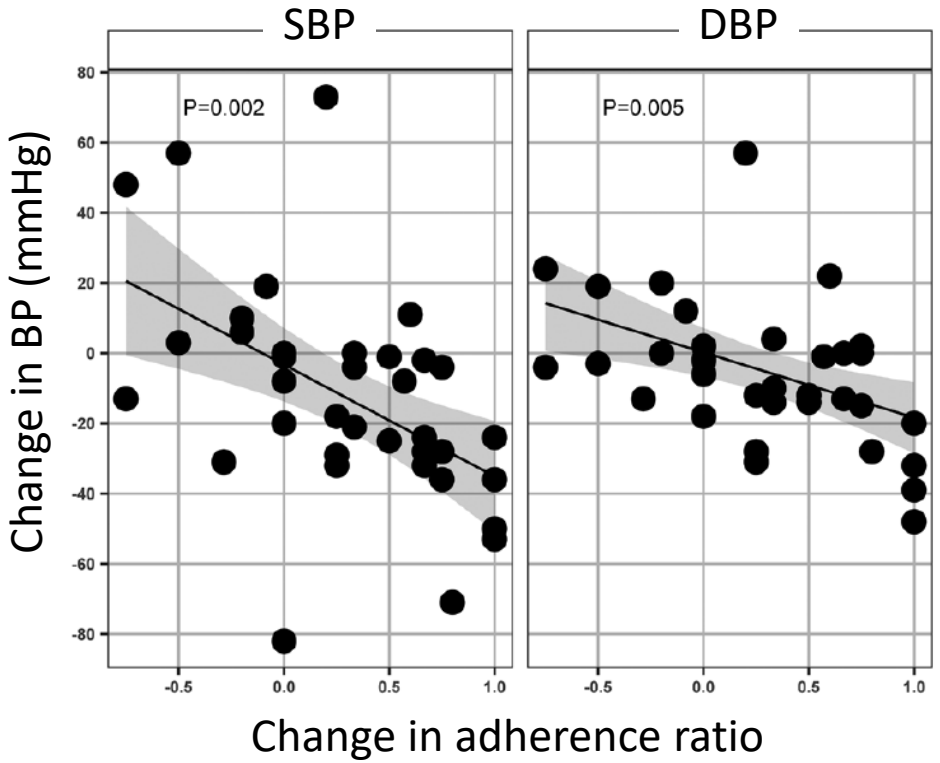


Biochemical Screening for Nonadherence Is Associated With Blood Pressure Reduction and Improvement in Adherence

Pankaj Gupta, Prashanth Patel, Branislav Štrauch, Florence Y. Lai, Artur Akbarov, Gaurav S. Gulsin, Alison Beech, Věra Marešová, Peter S. Topham, Adrian Stanley, Herbert Thurston, Paul R. Smith, Robert Horne, Jiří Widimský, Bernard Keavney, Anthony Heagerty, Nilesh J. Samani, Bryan Williams, Maciej Tomaszewski

Gupta P et al. Hypertension 2017

Repeated urinary drug detection by LC-MS/MS in non adherent patients



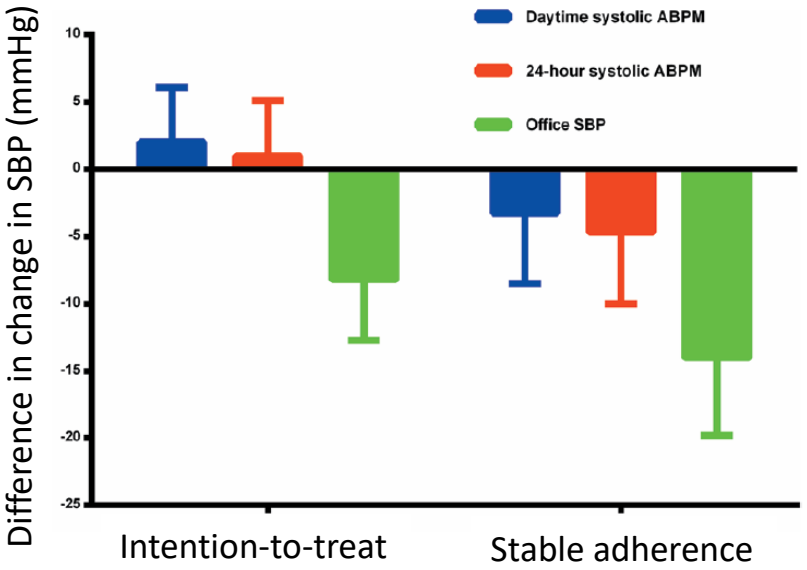
Drug adherence (LC-MS/MS) and renal denervation

Impact of Medication Adherence on the Effect of Renal Denervation

The SYMPATHY Trial

Rosa L. de Jager, Esther de Beus, Martine M.A. Beeftink, Margreet F. Sanders, Evert-Jan Vonken, Michiel Voskuil, Erik M. van Maarseveen, Michiel L. Bots, Peter J. Blankestijn; on behalf of the SYMPATHY Investigators

De Jager et al. Hypertension 2017



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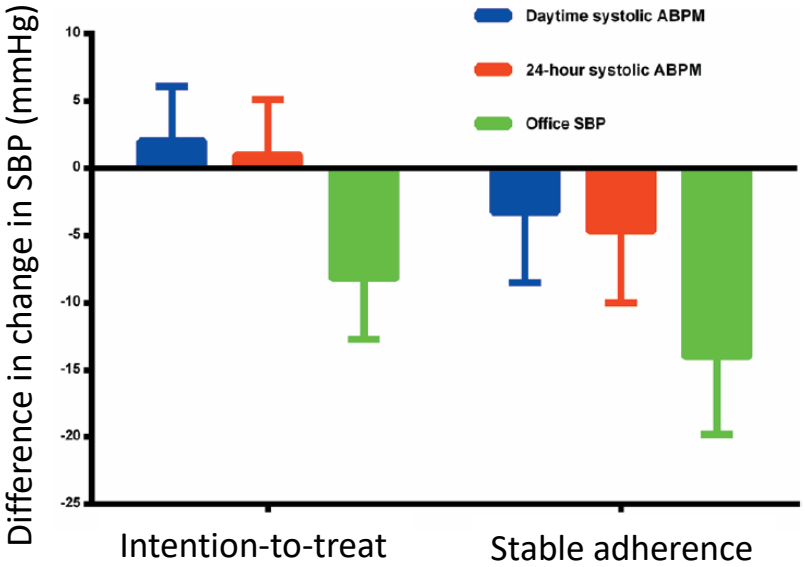
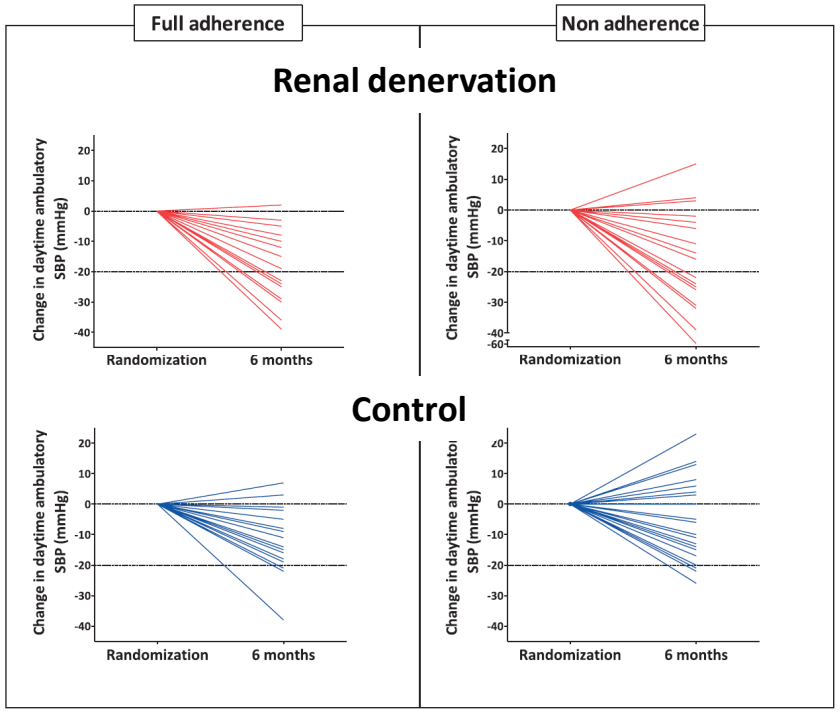


Adherence to Antihypertensive Treatment and the Blood Pressure–Lowering Effects of Renal Denervation in the Renal Denervation for Hypertension (DENERHTN) Trial

Azizi M et al. Circulation 2016



Les incontournables de 2017

Ce que j'aurais pu aussi vous présenter…

- HTA et grossesse (SFHTA)
- HTA et dysfonction érectile (SFHTA)
- HTA du sujet noir (SFHTA)
- …

Les incontournables de 2017

Ce que j'aurais pu aussi vous présenter…

- HTA et grossesse (SFHTA)
- HTA et dysfonction érectile (SFHTA)
- HTA du sujet noir (SFHTA)
- Microbiote et HTA (rapport du NIH)
- Nouveaux gènes impliqués dans le contrôle de la PA (GWAS)
- Réduction des apports sodés et PA
- Accumulation cutanée du sodium
- Remodelage des artères rétiniennes
- …

Merci!