



COLUMBIA UNIVERSITY
MEDICAL CENTER

 **NewYork-Presbyterian**



Vascular
Research
Clinic

Management of Resistant Hypertension

Professor John Cockcroft
Visting Professor
Dept Advanced Cardiology
Columbia Presbyterian Hospital
Columbia University
New York



The Wellcome Trust



British Heart Foundation



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Wales Cardiac
Network

Declaration of Interests

Scientific Advisor Cardiex

Scientific Advisor Nuralogix

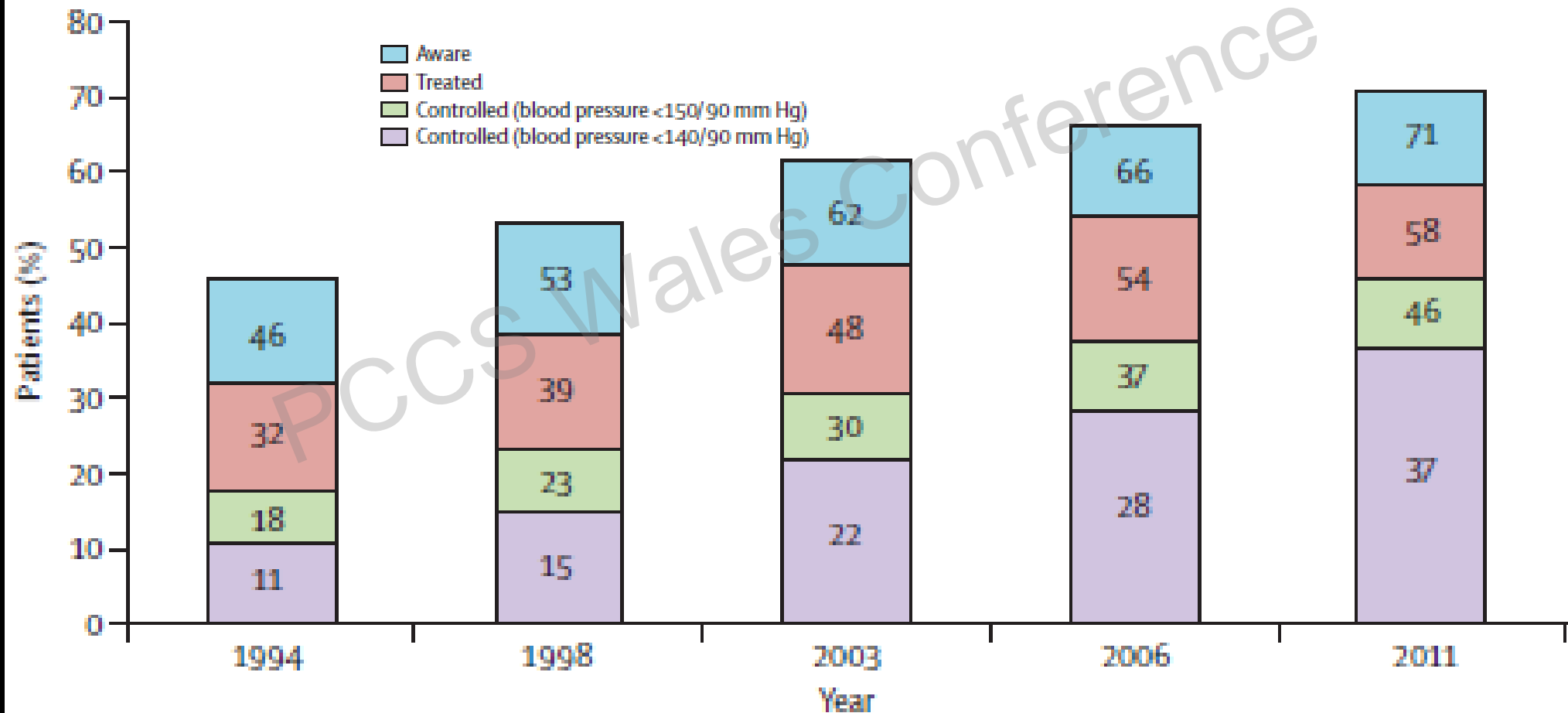
Effective Drug Therapy for Hypertension

- 1940s Sympathetic blockers
- 1950s Thiazide diuretics
- 1960s β -blockers
- 1970s Calcium channel blockers
- 1980s ACE inhibitors
- 1990s AT₁ blockers
- 2000s Direct renin inhibitors



Hypertension management in England: a serial cross-sectional study from 1994 to 2011

Emanuela Falaschetti, Jennifer Mindell, Craig Knott, Neil Poulter



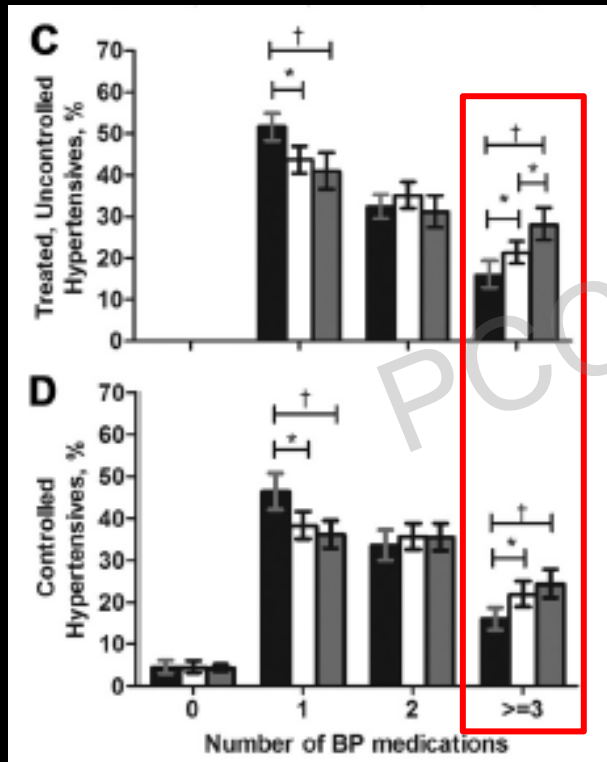
RESISTANT HYPERTENSION.....

PCCS Wales Conference

Hypertension

Uncontrolled and Apparent Treatment Resistant Hypertension in the United States, 1988 to 2008

Brent M. Egan, MD; Yumin Zhao, PhD; R. Neal Axon, MD;
Walter A. Brzezinski, MD; Keith C. Ferdinand, MD



Uncontrolled RH: BP above goal on a rational pharmacologic regimen consisting of **three or more drugs** with complimentary mechanisms of action at optimal doses and preferably including a diuretic.

<140/90 mmHg and <130/80 for diabetes & CKD

Controlled RH: BP controlled by **four or more drugs** at optimal doses, preferably including a diuretic.

RH, resistant hypertension; BP, blood pressure; CKD, chronic kidney disease
Egan et al *Circulation* 2008; 124: 1046-1058

Latest NICE/BHS UK Guidelines for Management of Resistant Hypertension

Step 4 treatment

- 1.4.46 If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. [2019]
- 1.4.47 Before considering further treatment for a person with resistant hypertension:
- Confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings.
 - Assess for postural hypotension.
 - Discuss adherence (see [recommendation 1.4.40](#)). [2019]
- 1.4.48 For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step 4 treatment or seeking specialist advice. [2019]

Latest NICE/BHS UK Guidelines for Management of Resistant Hypertension

1.4.48 For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step 4 treatment or seeking specialist advice. **[2019]**

Follow the [MHRA safety advice on ACE inhibitors and angiotensin II receptor antagonists: not for use in pregnancy, how to use for breastfeeding and clarification on breastfeeding](#).

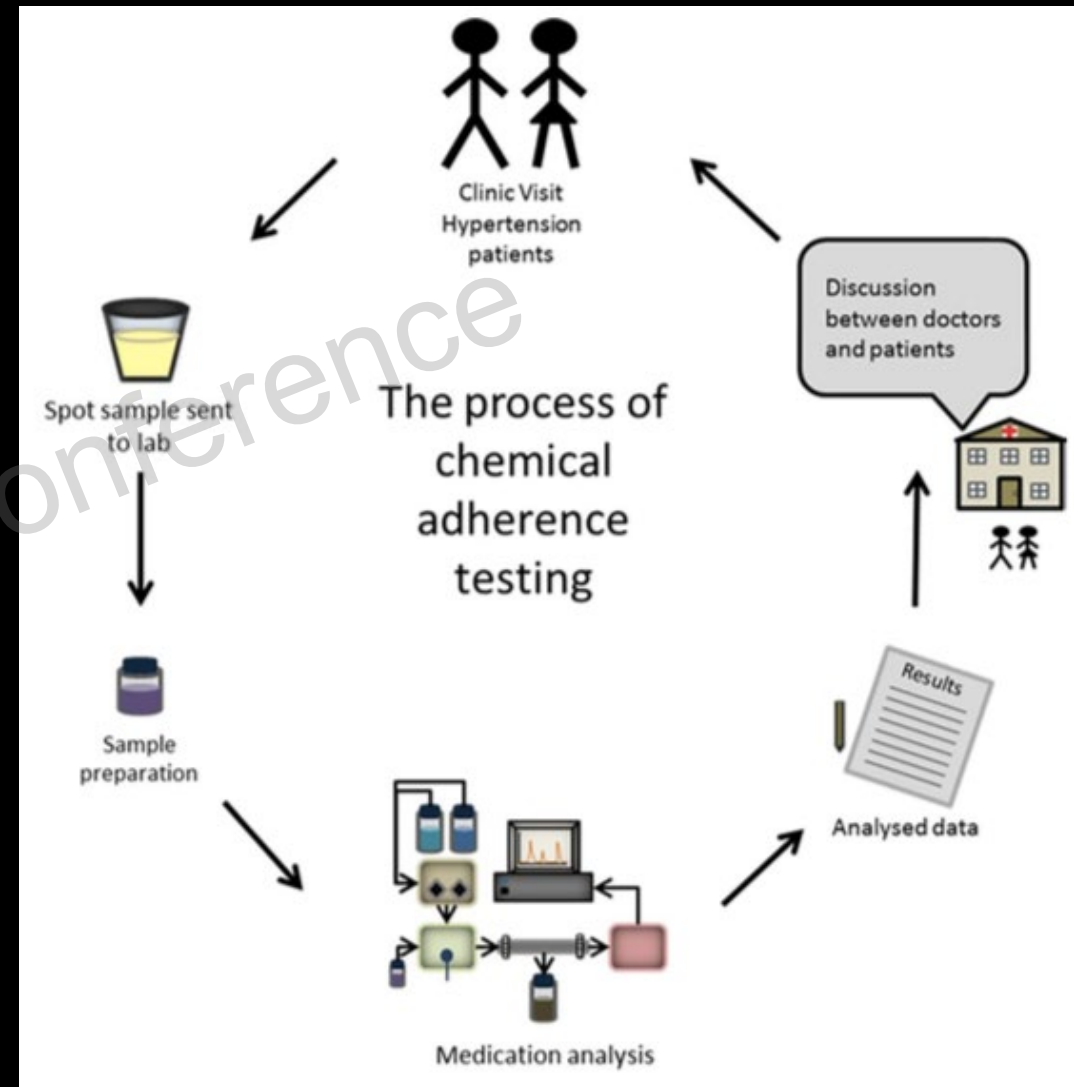
1.4.49 Consider further diuretic therapy with low-dose spironolactone for adults with resistant hypertension starting step 4 treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalaemia. **[2019]**

In March 2019, this was an off-label use of some preparations of spironolactone. See [NICE's information on prescribing medicines](#).

REVIEW

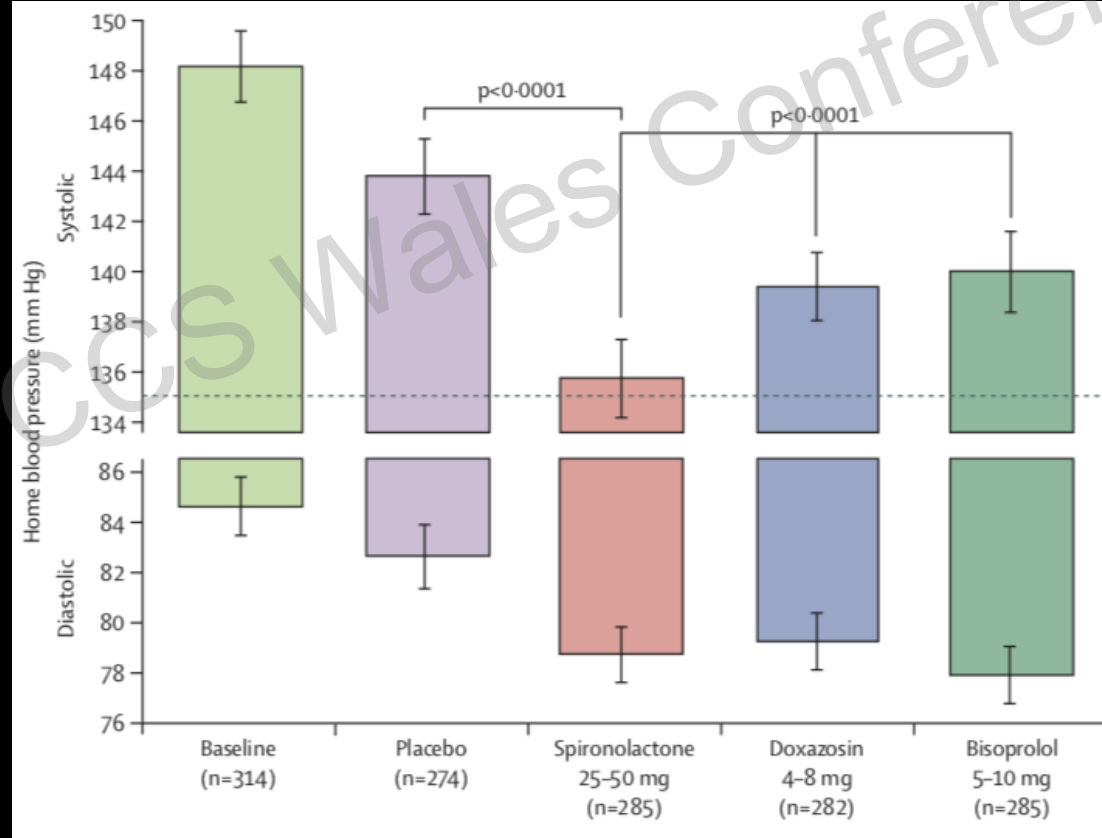
Nonadherence in Hypertension: How to Develop and Implement Chemical Adherence Testing

Dan Lane¹, Alexander Lawson, Angela Burns, Michel Azizi, Michel Burnier², Donald J.L. Jones³, Benjamin Kably, Kamlesh Khunti, Reinhold Kreutz⁴, Prashanth Patel, Alexandre Persu⁵, Wilko Spiering⁶, Stefan W. Toennes⁷, Maciej Tomaszewski⁸, Bryan Williams⁹, Pankaj Gupta¹⁰, Indranil Dasgupta¹¹; Endorsed by the European Society of Hypertension (ESH) Working Group on Cardiovascular Pharmacotherapy and Adherence



Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

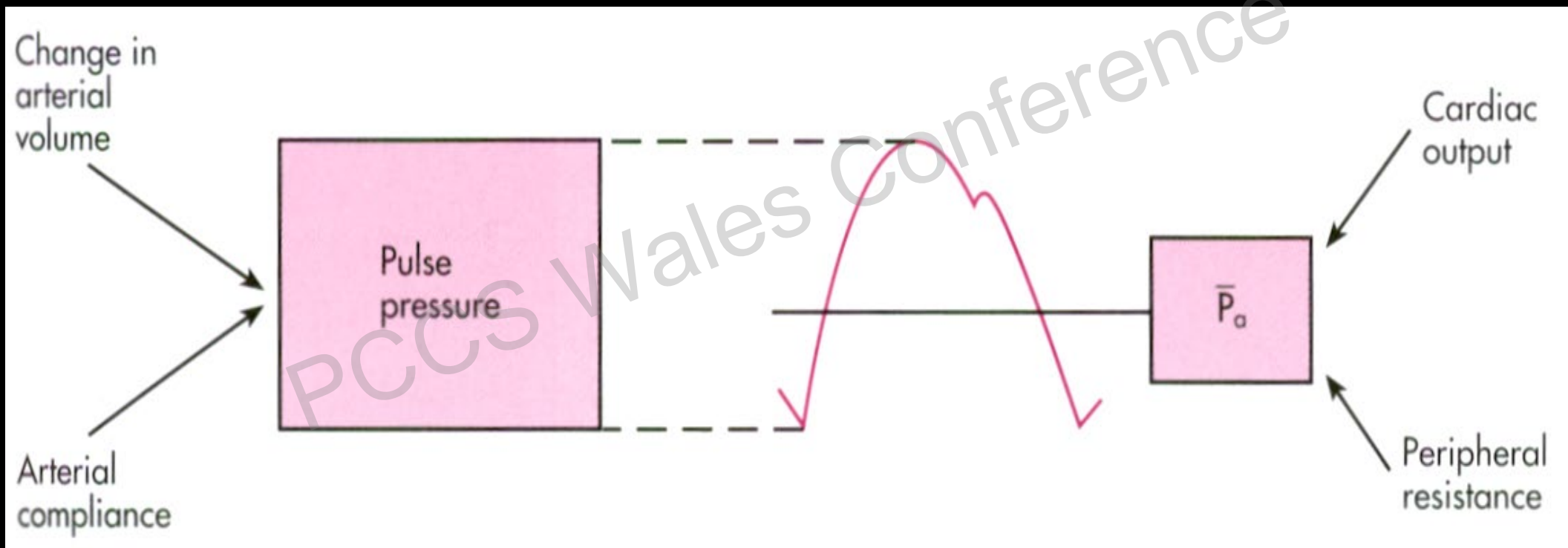
Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group*



Why is BP resistant to treatment.....

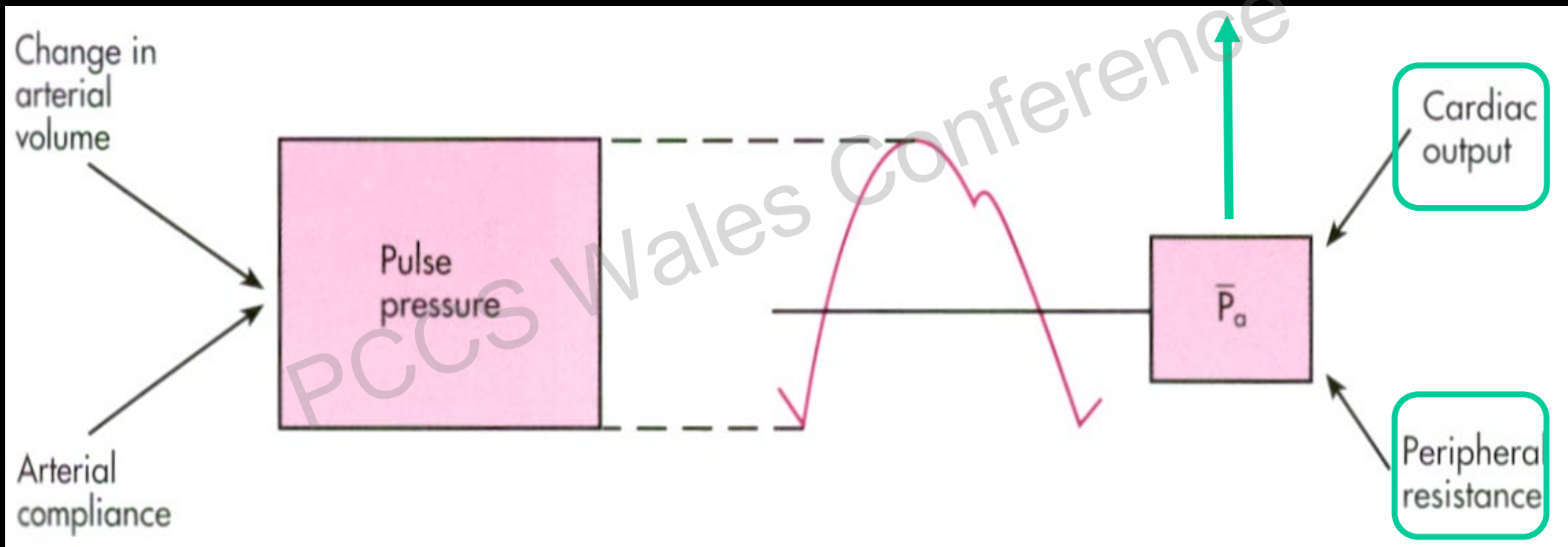
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The Physiology of Blood Pressure



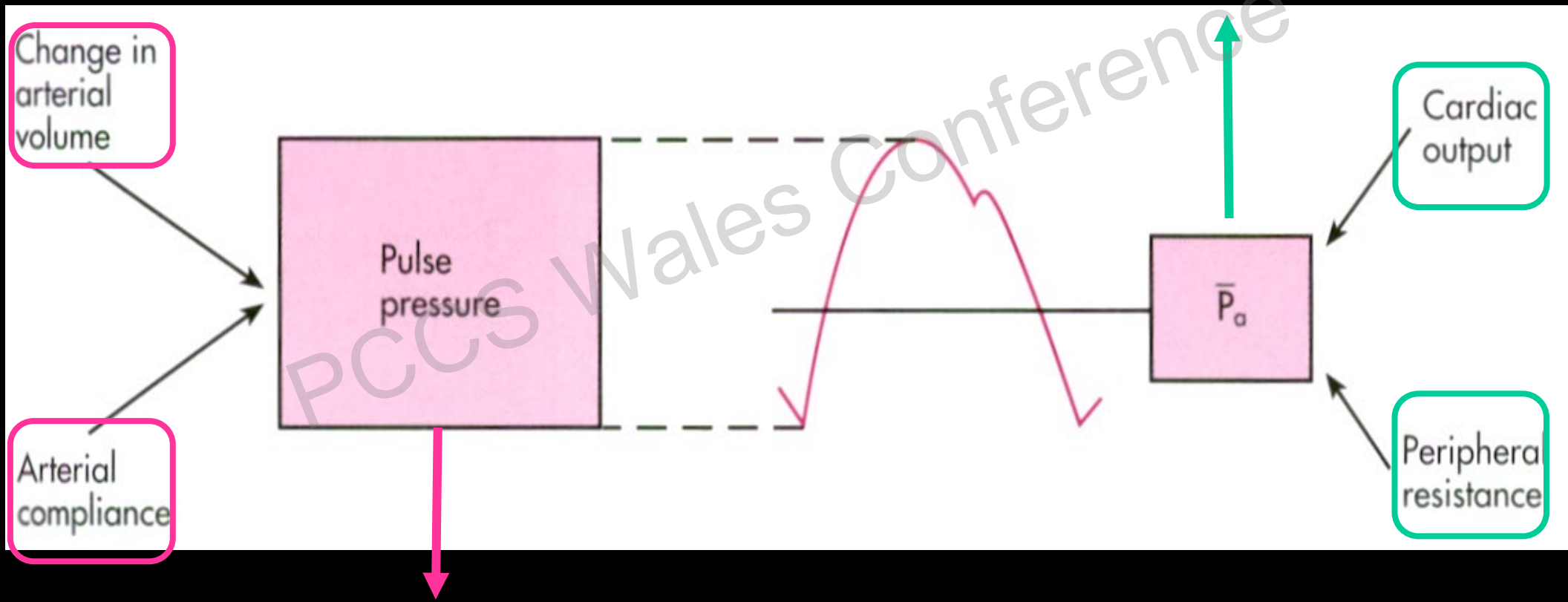
The Physiology of Blood Pressure

Essential Hypertension



The Physiology of Blood Pressure

Essential Hypertension



Isolated Systolic Hypertension

Arterial Stiffness as a Cause of Resistant Hypertension?

Thomas G. Pickering, MD, DPhil

Table. Characteristics Associated With Resistant Hypertension and Corresponding Changes in Arterial Stiffness

CHARACTERISTIC	RESISTANT HYPERTENSION	INCREASED ARTERIAL STIFFNESS
Old age	Yes	Yes
Female sex	Yes (older, not younger)	Yes (older, not younger)
Black race	Yes	Yes
Obesity/sleep apnea	Yes	Yes
Diabetes	Yes	Yes
Chronic kidney disease	Yes	Yes
Left ventricular hypertrophy	Yes	Yes

Adapted from Epstein.¹

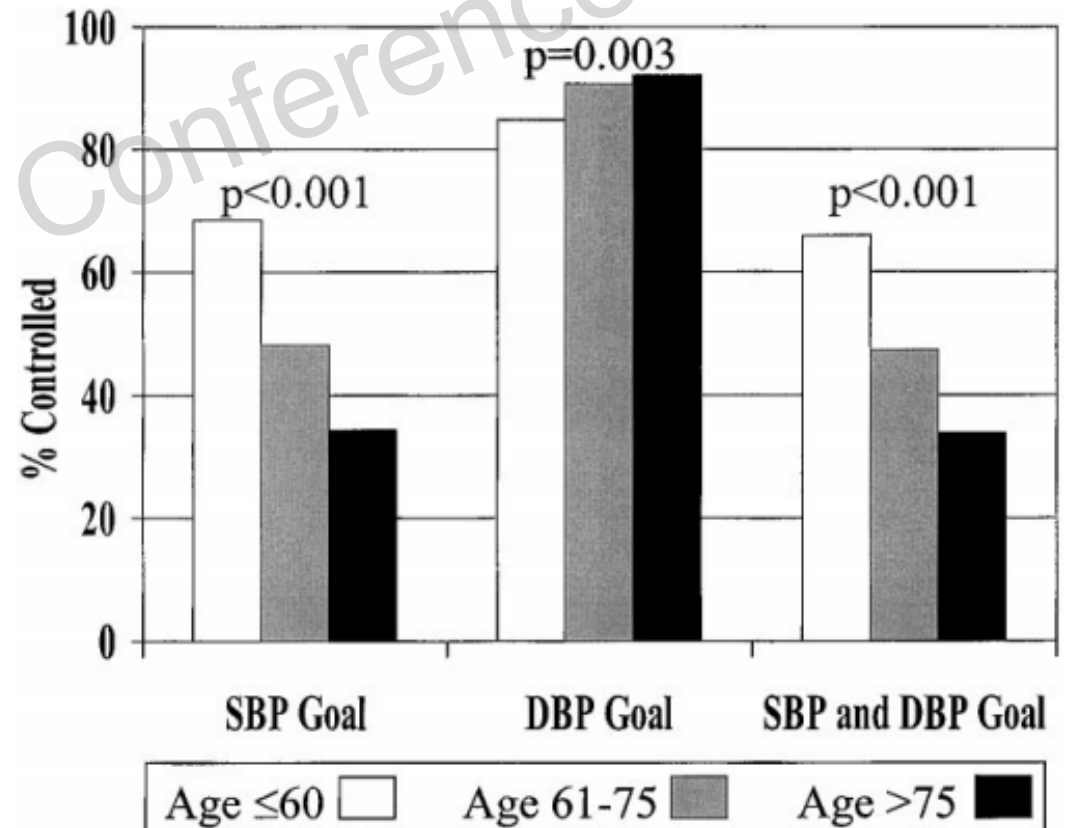
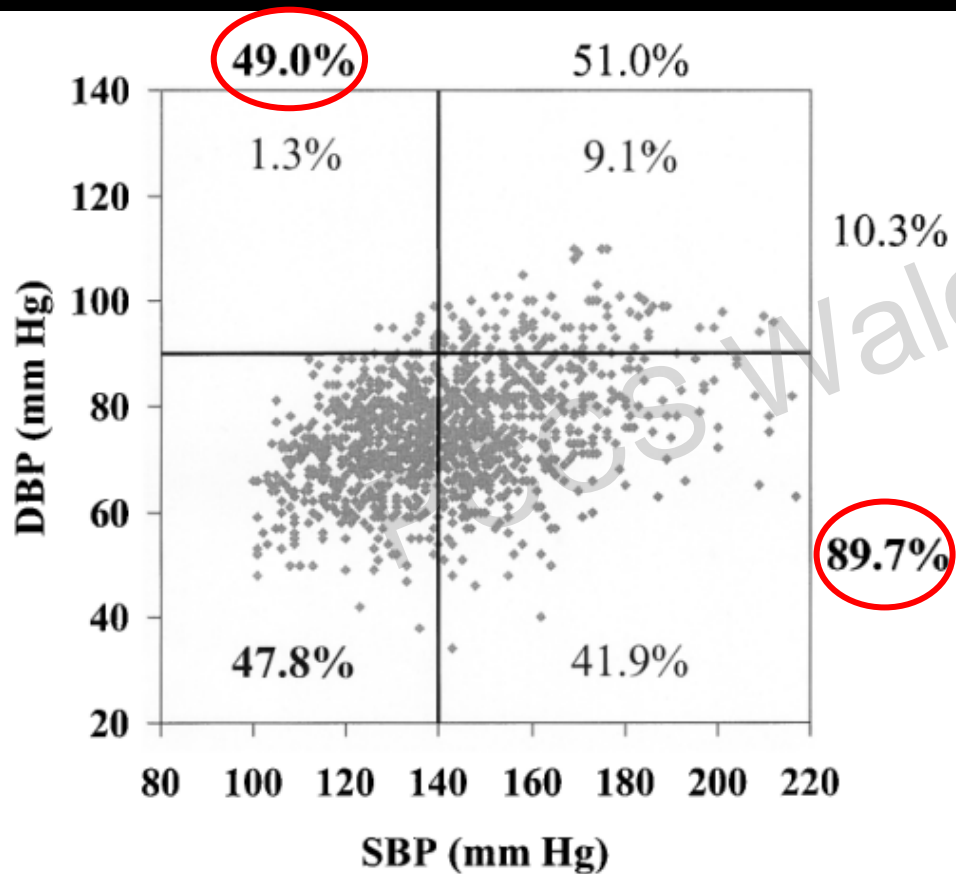
Isolated systolic hypertension is difficult to treat...

PCCS Wales Conference

Differential Control of Systolic and Diastolic Blood Pressure

Factors Associated With Lack of Blood Pressure Control in the Community

Donald M. Lloyd-Jones, Jane C. Evans, Martin G. Larson, Christopher J. O'Donnell,
Edward J. Roccella, Daniel Levy



Pathogenesis of Drug-Resistant Hypertension

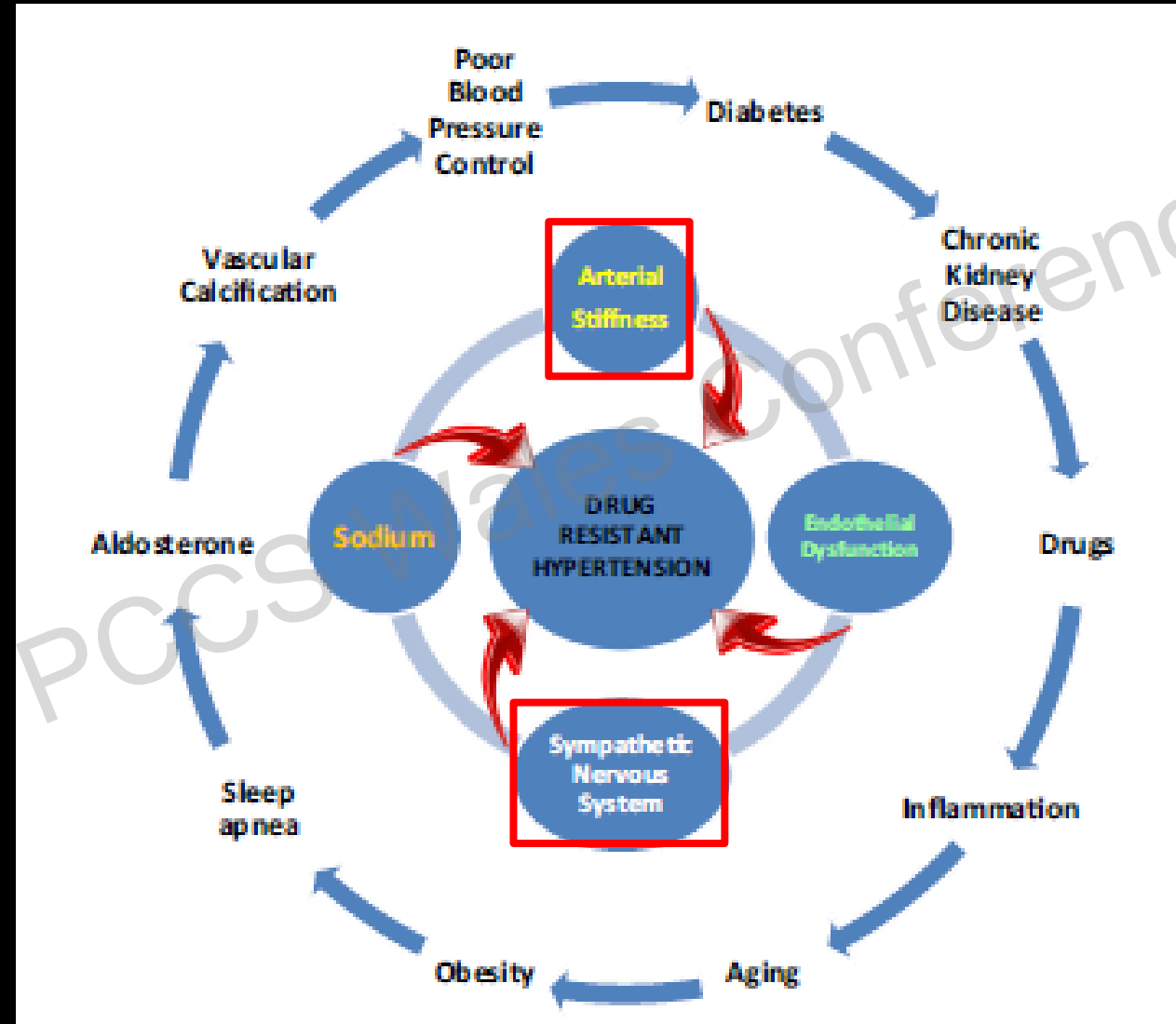
Raymond R. Townsend, MD

Summary: More is known about the epidemiology of drug-resistant hypertension than particular pathogenic factors and pathways. Several recurring themes, however, seem evident on using insight from epidemiology and general knowledge of the pathophysiology of hypertension. Specifically, 4 main pathways converge on drug resistance including sodium handling, sympathetic nervous system activation, endothelial dysfunction, and arterial stiffness. These factors, and the various pathways and elements contributing to them, are

Pathogenesis of Resistant Hypertension...?

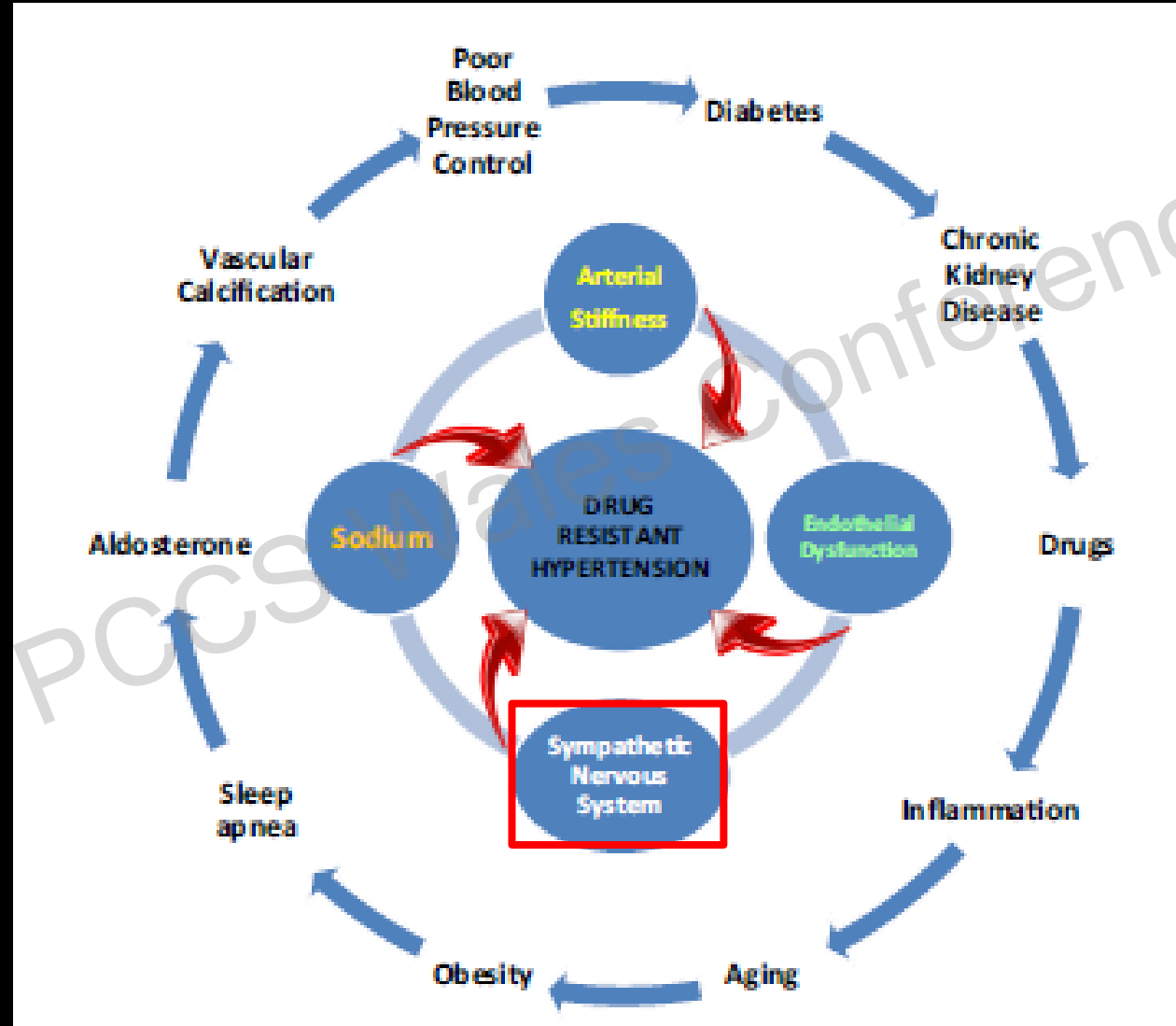
Pathogenesis of Drug-Resistant Hypertension

Raymond R. Townsend, MD

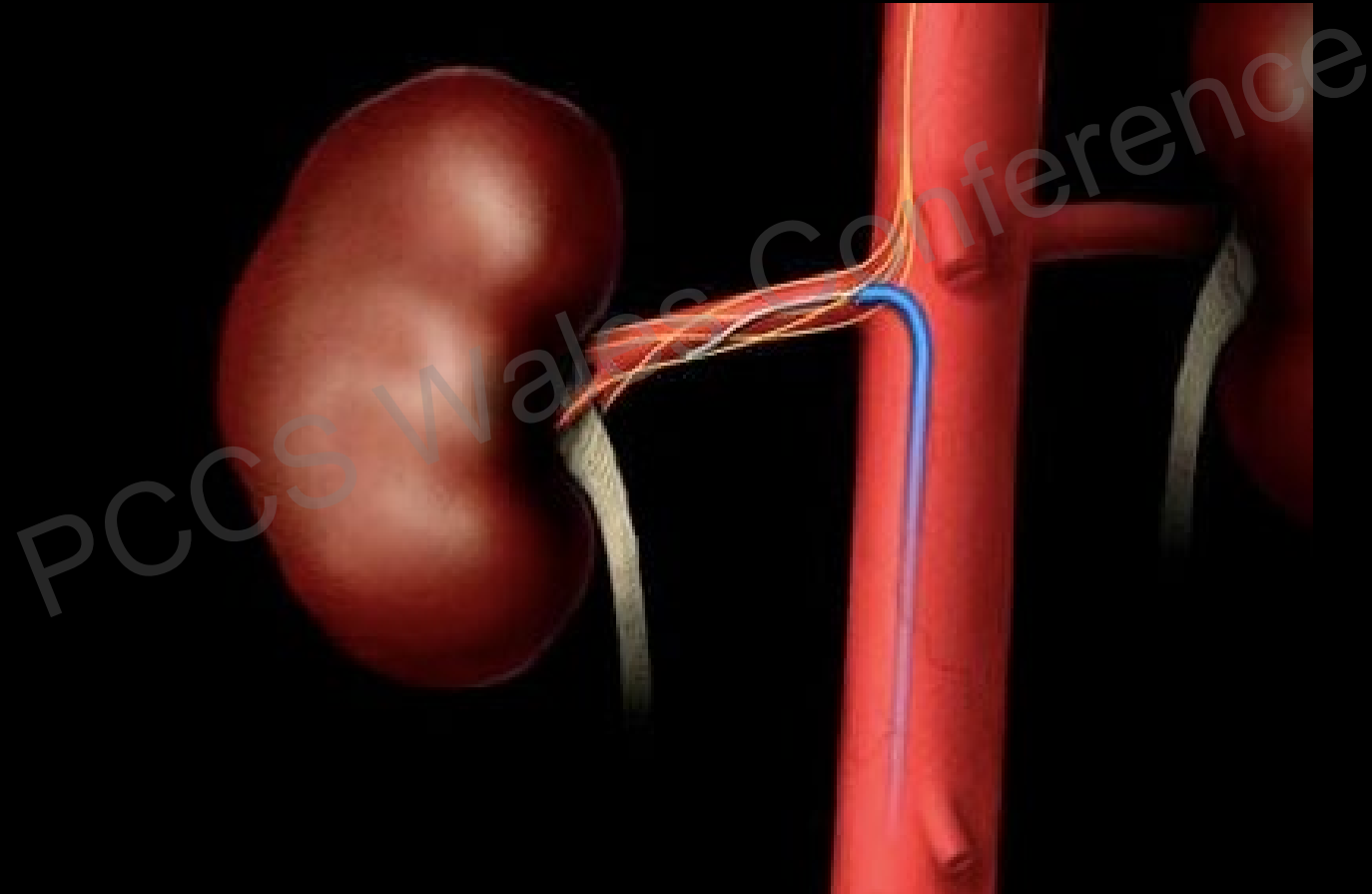


Pathogenesis of Drug-Resistant Hypertension

Raymond R. Townsend, MD

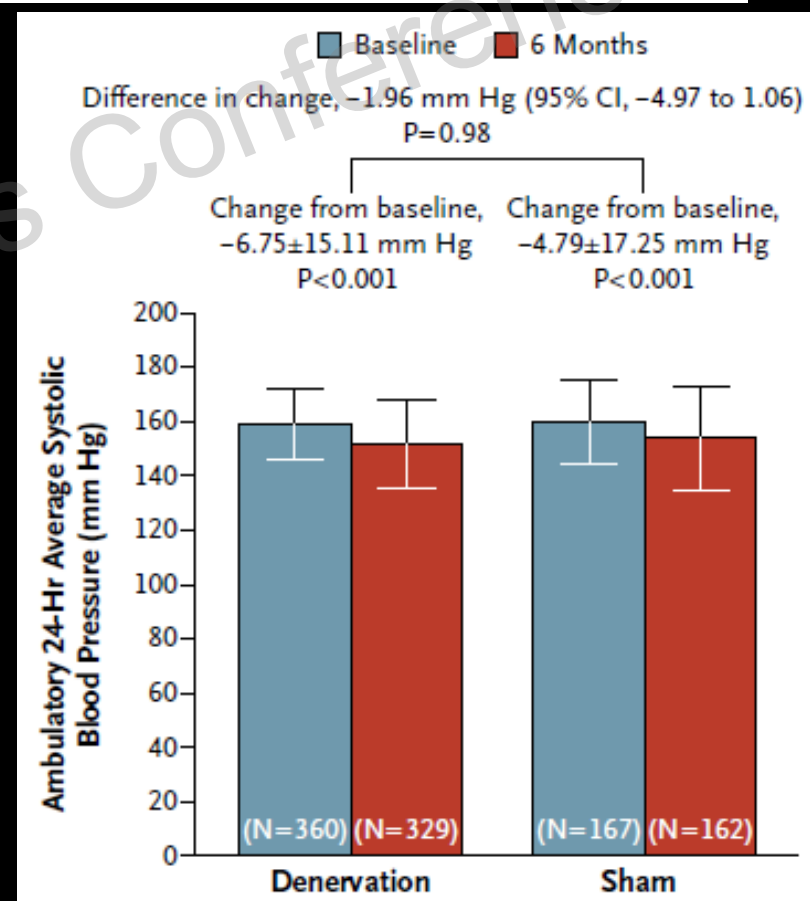
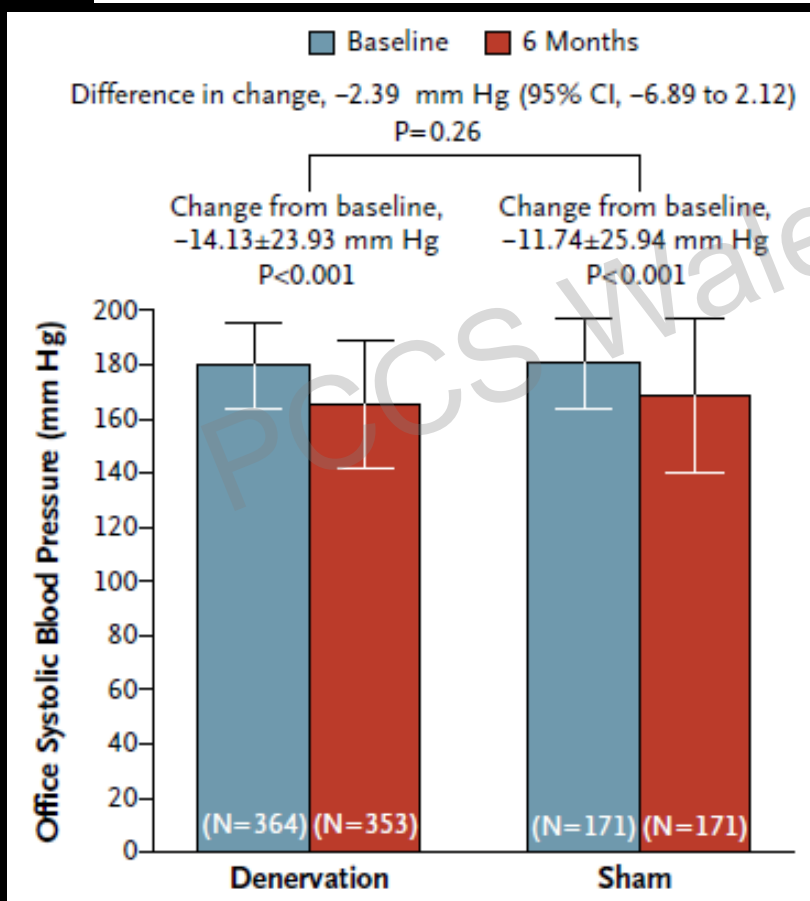


Renal Denervation

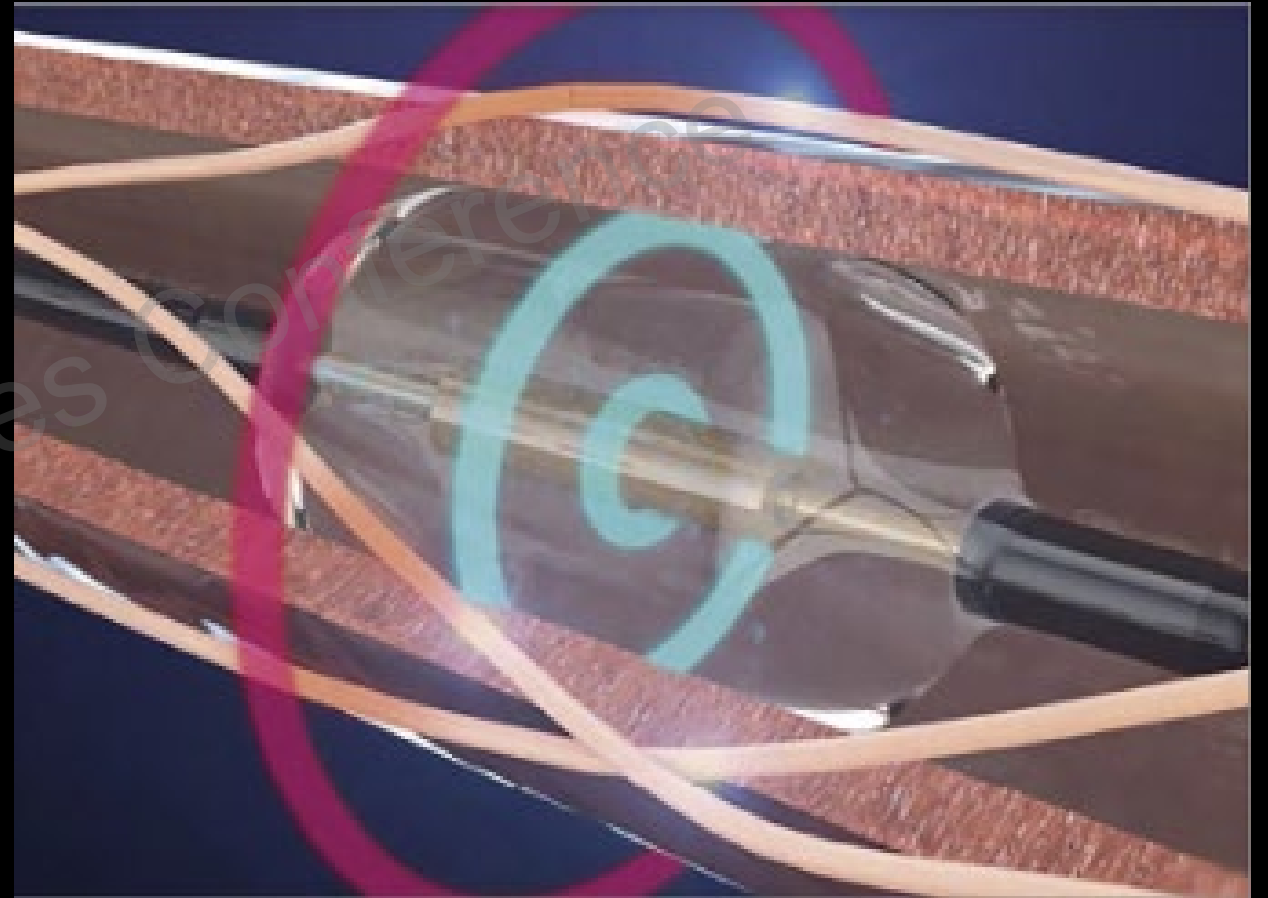
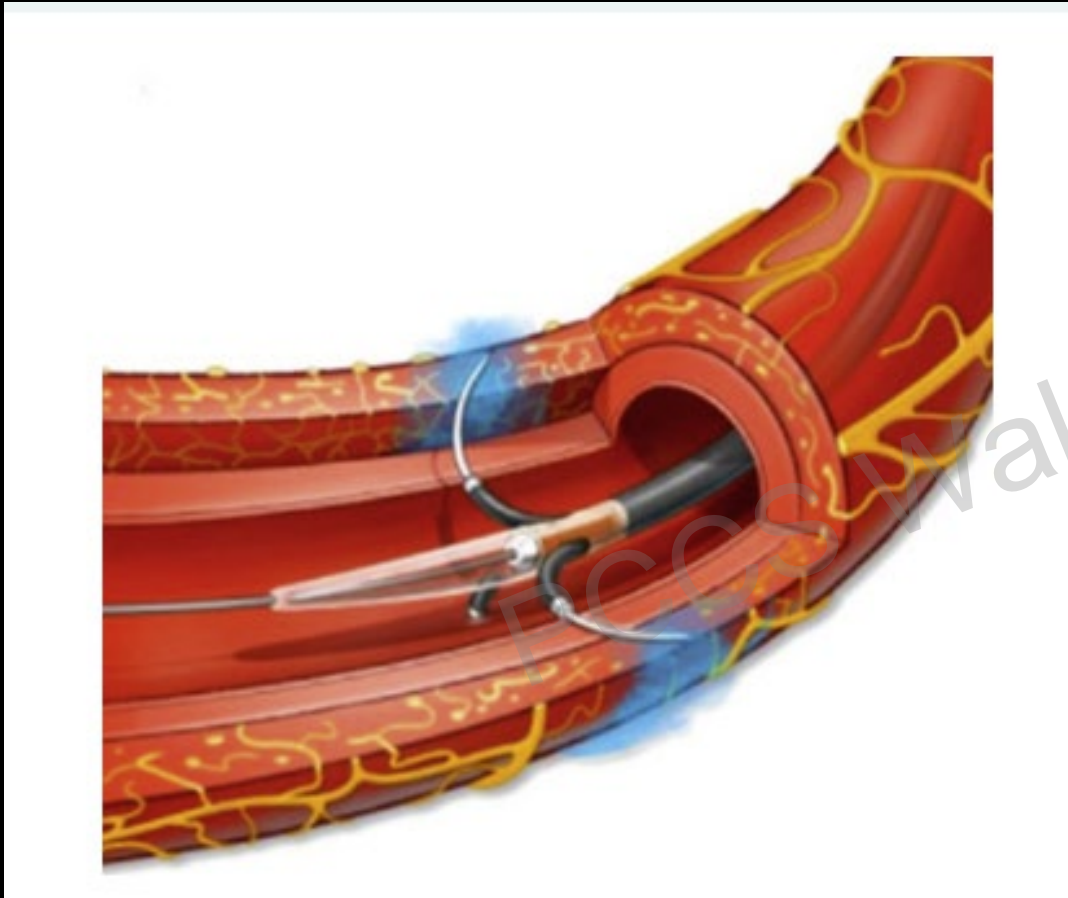


A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators*

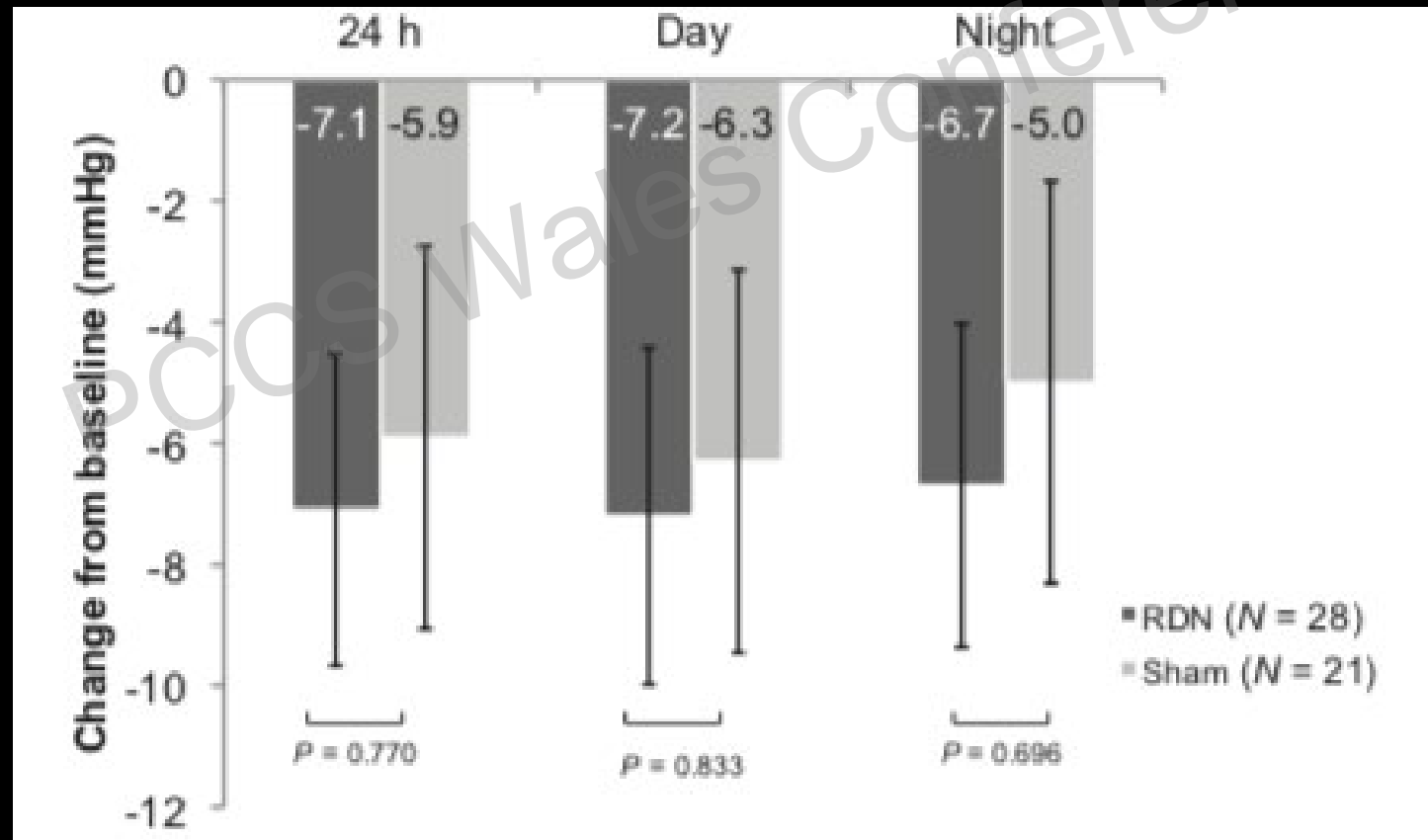


Ultrasound Renal Denervation



Phase II randomized sham-controlled study of renal denervation for individuals with uncontrolled hypertension – WAVE IV

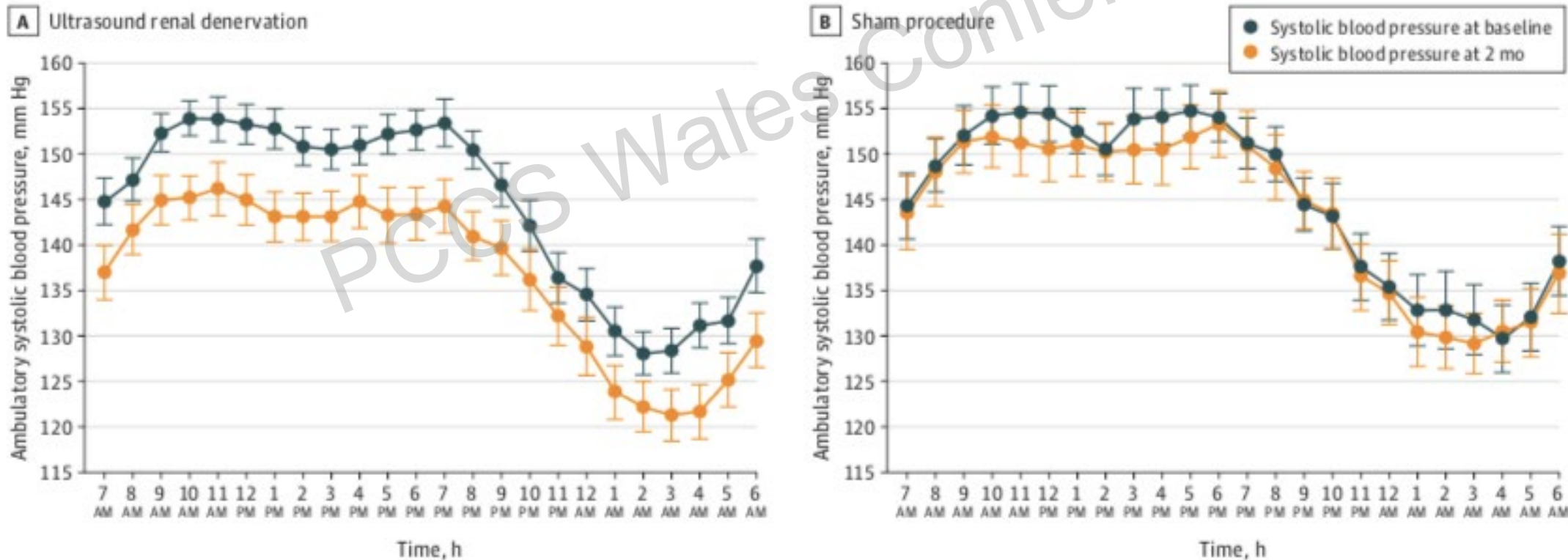
Roland E. Schmieder^a, Christian Ott^a, Stefan W. Toennes^b, Peter Bramlage^c, Michael Gertner^d, Omar Dawood^e, Peter Baumgart^f, Benjamin O'Brien^{g,h}, Indranil Dasguptaⁱ, Georg Nickenig^j, John Ormiston^k, Manish Saxena^g, Andrew S.P. Sharp^l, Horst Sievert^m, Jindrich Spinar^{n,o}, Zdenek Starek^p, Joachim Weil^q, Ulrich Wenzel^r, Adam Witkowski^s, and Melvin D. Lobo^g



Endovascular Ultrasound Renal Denervation to Treat Hypertension The RADIANCE II Randomized Clinical Trial

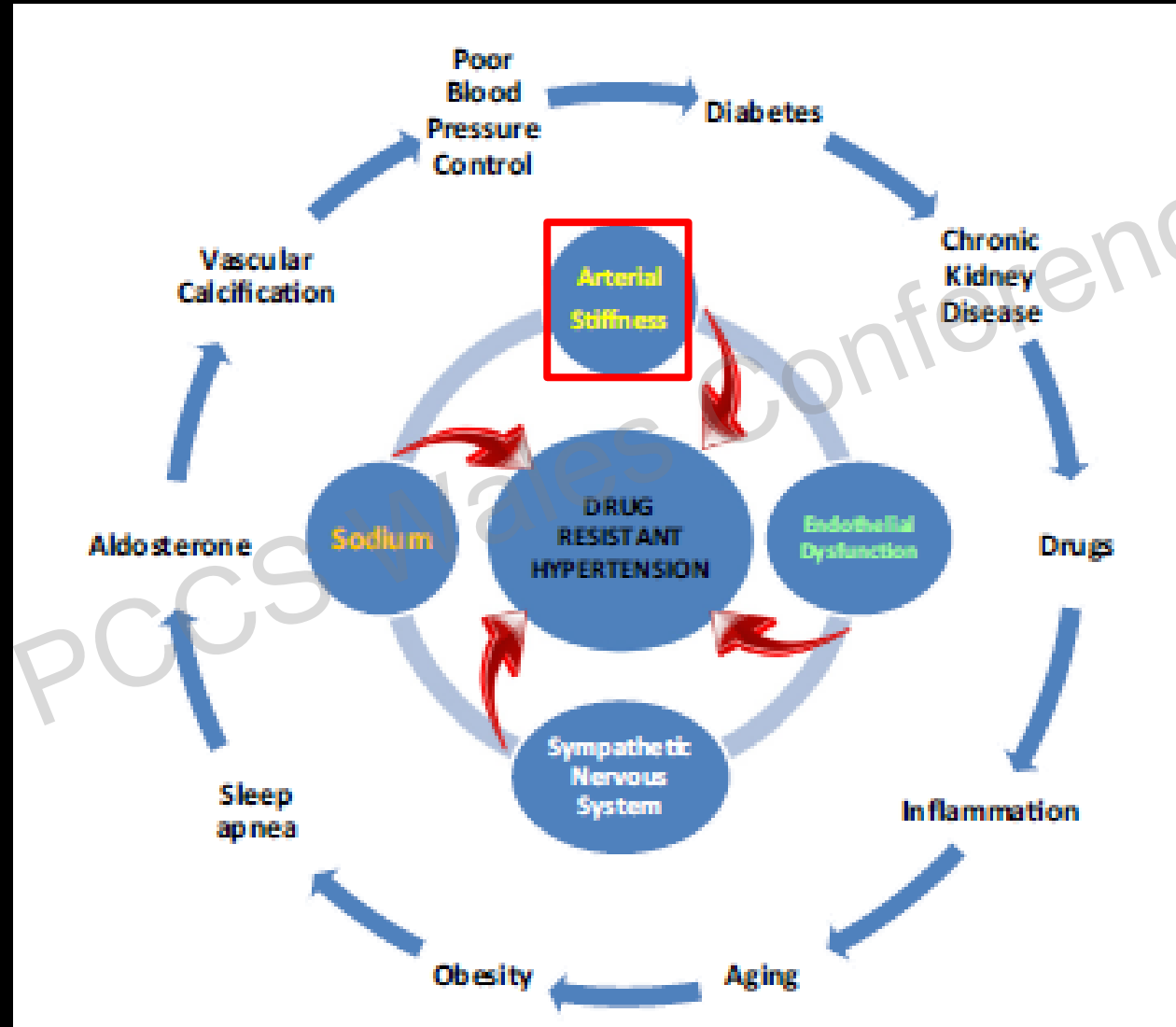
Michel Azizi, MD, PhD; Manish Saxena, MBBS, MSc; Yale Wang, MD; J. Stephen Jenkins, MD;
Chandan Devireddy, MD; Florian Rader, MD, MSc; Naomi D. L. Fisher, MD; Roland E. Schmieder, MD;
Felix Mahfoud, MD, MA; Jason Lindsey, MD; Kintur Sanghvi, MD; Thomas M. Todoran, MD, MS; John Pacella, MD;
John Flack, MD; Joost Daemen, MD, PhD; Andrew S. P. Sharp, MD; Philipp Lurz, MD, PhD; Michael J. Bloch, MD;
Michael A. Weber, MD; Melvin D. Lobo, PhD; Jan Basile, MD; Lisa Claude, MS; Helen Reeve-Stoffer, PhD;
Candace K. McClure, PhD; Ajay J. Kirtane, MD, SM; for the RADIANCE II Investigators and Collaborators

Azizi et al., JAMA
2023;329(8):651-661.



Pathogenesis of Drug-Resistant Hypertension

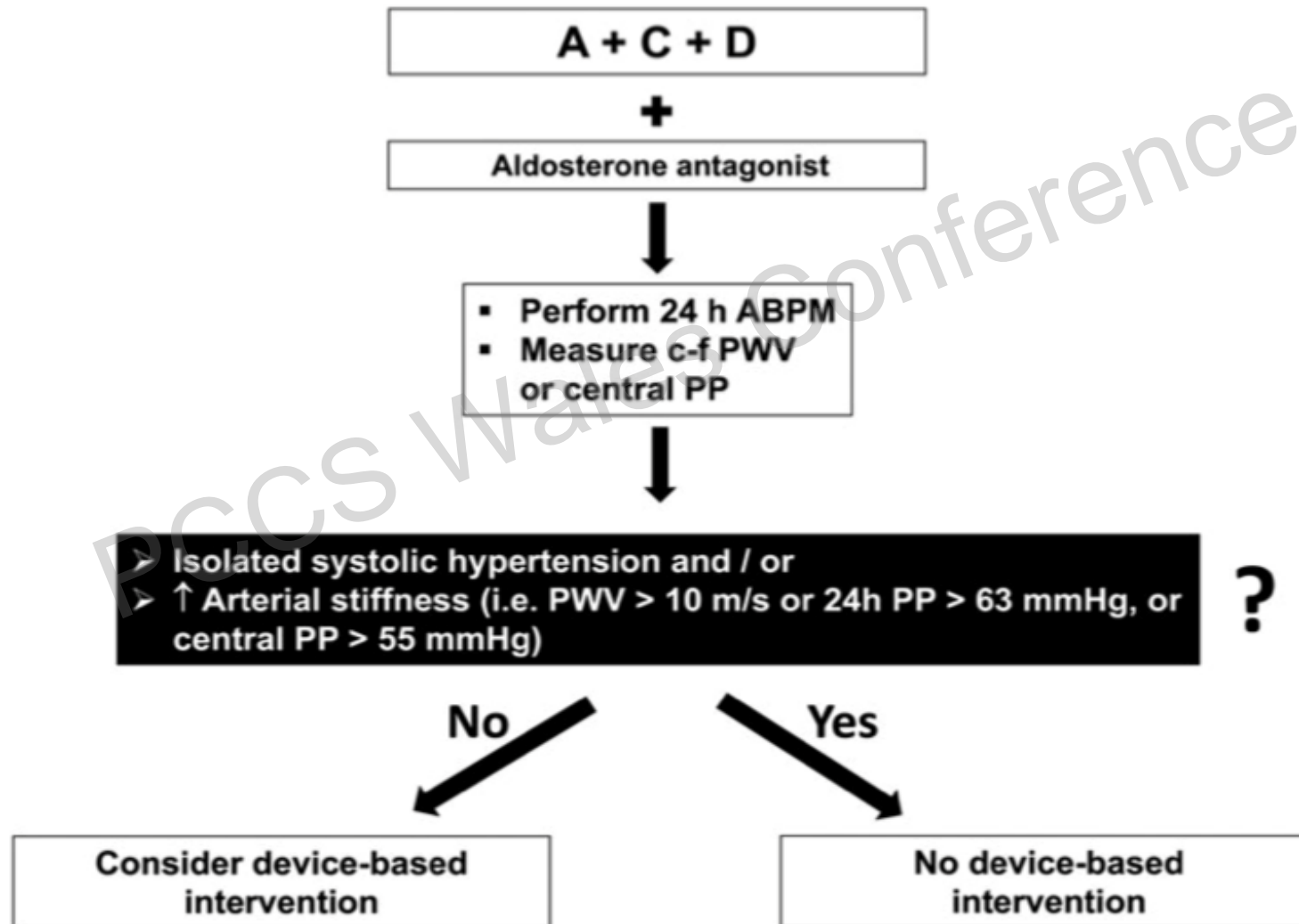
Raymond R. Townsend, MD



Resistant hypertension: what the cardiologist needs to know

Stefano F. Rimoldi¹, Franz H. Messerli^{1,2*}, Sripal Bangalore², and Urs Scherrer^{1,3}

¹Department of Cardiology and Clinical Research, University Hospital, Bern, Switzerland; ²Division of Cardiology, St Luke's-Roosevelt Hospital Center, New York, NY, USA; and ³Facultad de Ciencias, Departamento de Biología, Universidad de Tarapacá, Arica, Chile



Arterial Stiffness as a Cause of Resistant Hypertension?

Thomas G. Pickering, MD, DPhil

Table. Characteristics Associated With Resistant Hypertension and Corresponding Changes in Arterial Stiffness

CHARACTERISTIC	RESISTANT HYPERTENSION	INCREASED ARTERIAL STIFFNESS
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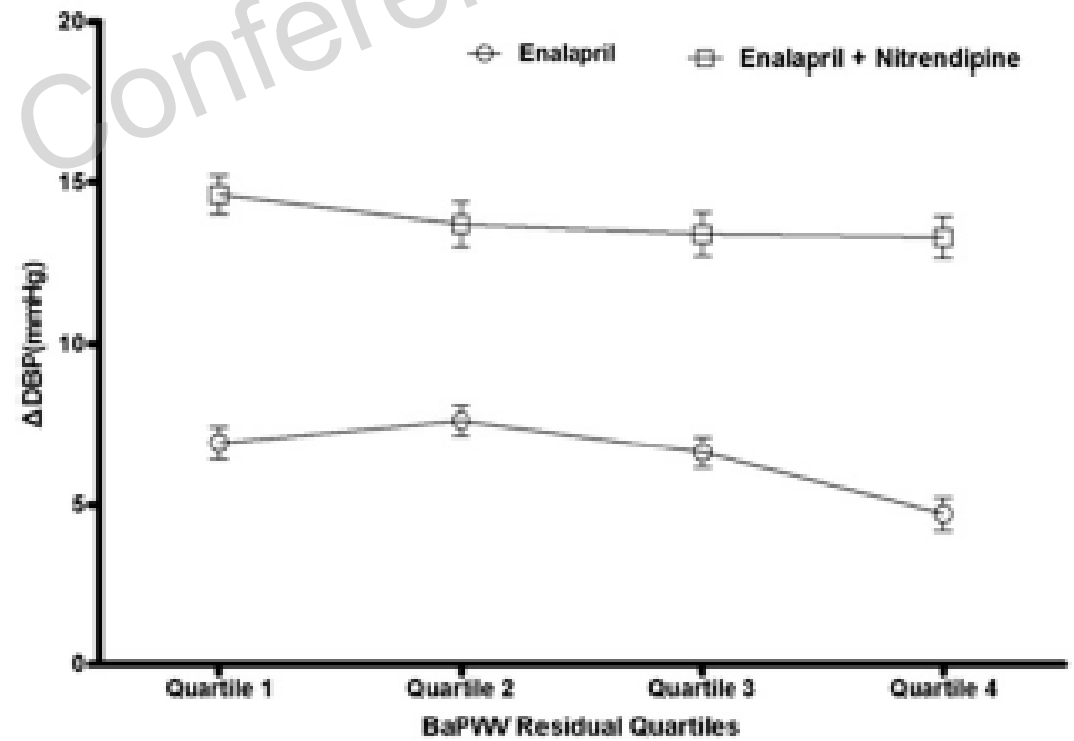
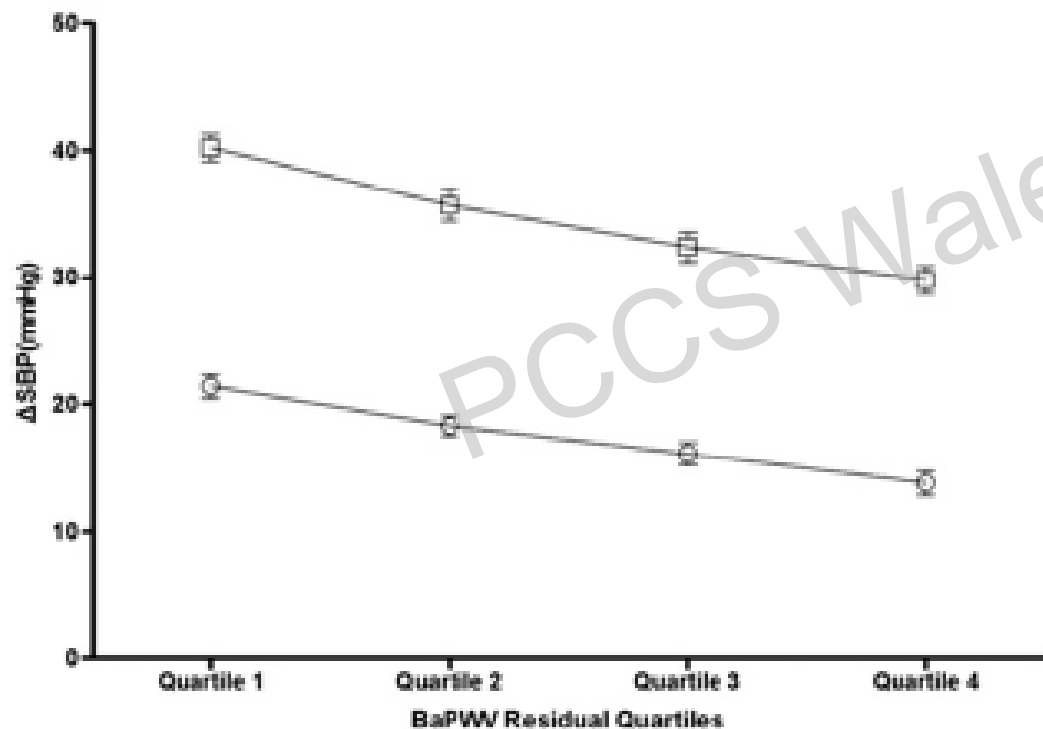
Adapted from Epstein.¹

A prospective study on pulse wave velocity (PWV) and response to anti-hypertensive treatments



PWV determines BP control

Meili Zheng^a, Yong Huo^{b,*}, Xiaobin Wang^c, Xin Xu^d, Xianhui Qin^d, Genfu Tang^e, Houxun Xing^e, Fangfang Fan^b, Jianping Li^b, Yan Zhang^b, Binyan Wang^d, Xiping Xu^d, Xinchun Yang^{a,**}, Yundai Chen^f, Geng Qian^f



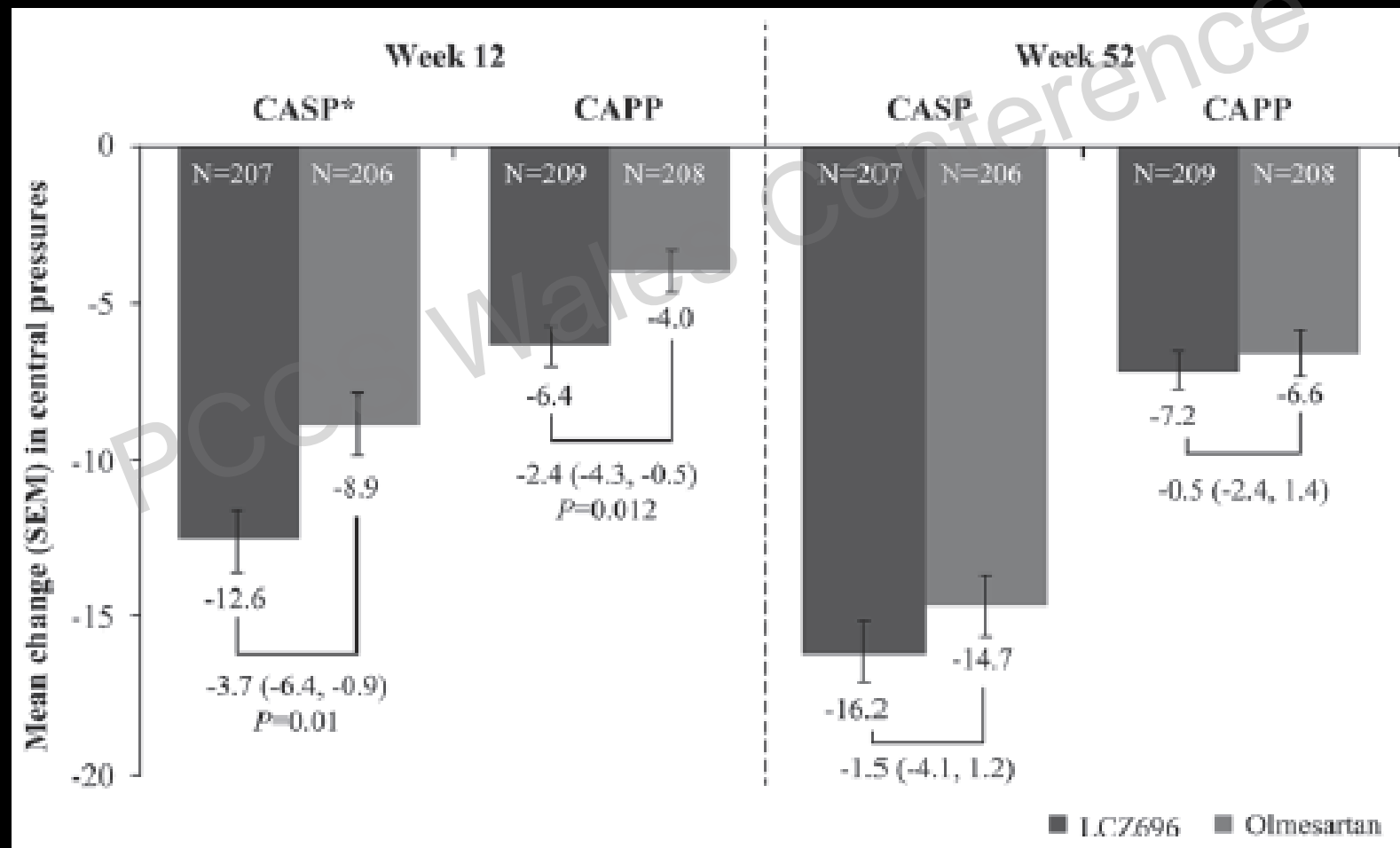
Novel Treatments...

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Effects of Sacubitril/Valsartan Versus Olmesartan on Central Hemodynamics in the Elderly With Systolic Hypertension

The PARAMETER Study

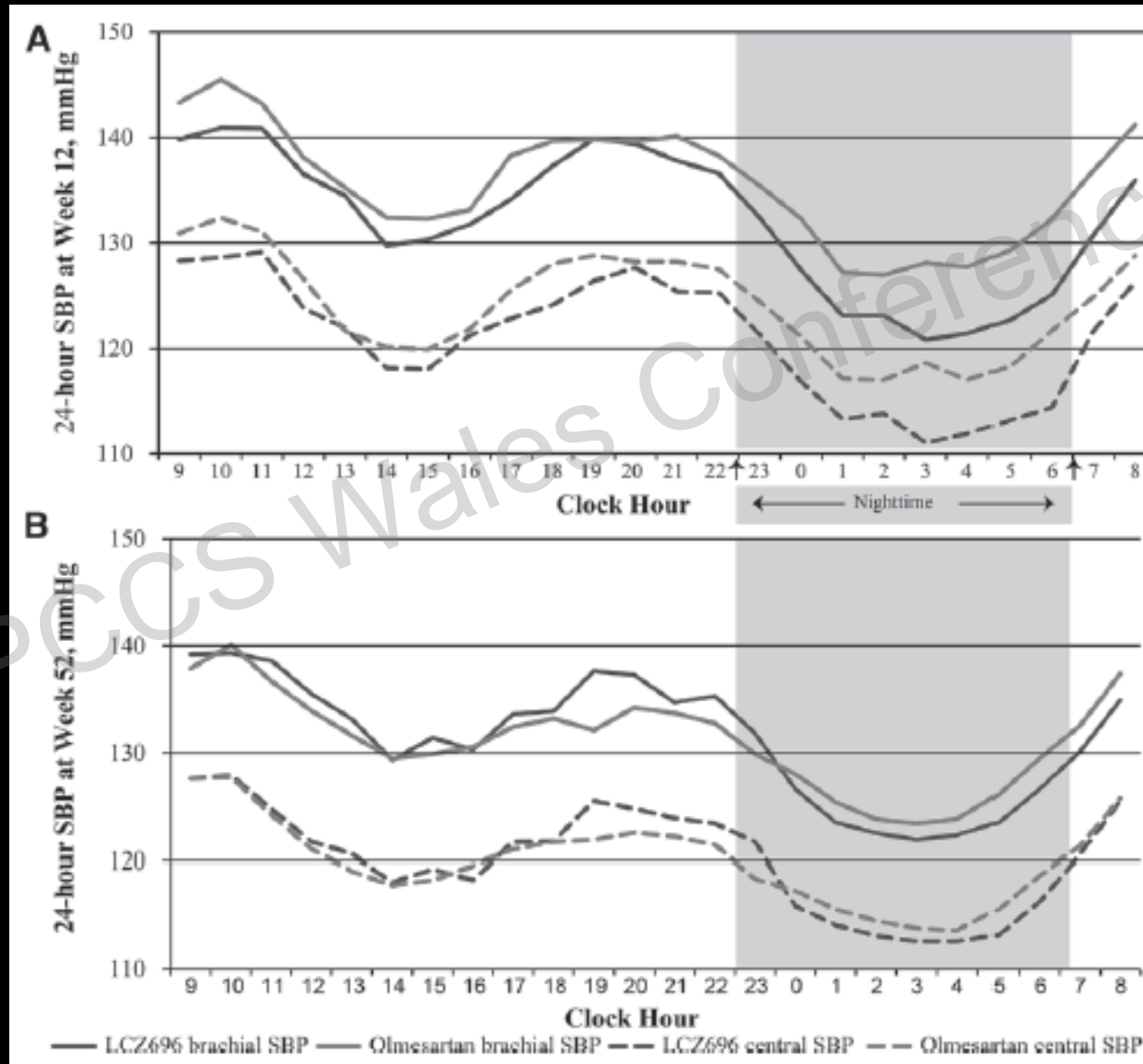
Bryan Williams, John R. Cockcroft, Kazuomi Kario, Dion H. Zappe, Patrick C. Brunel, Qian Wang, Weinong Guo



Williams et al.,
Hypertension.
2017;69(3):411-420.

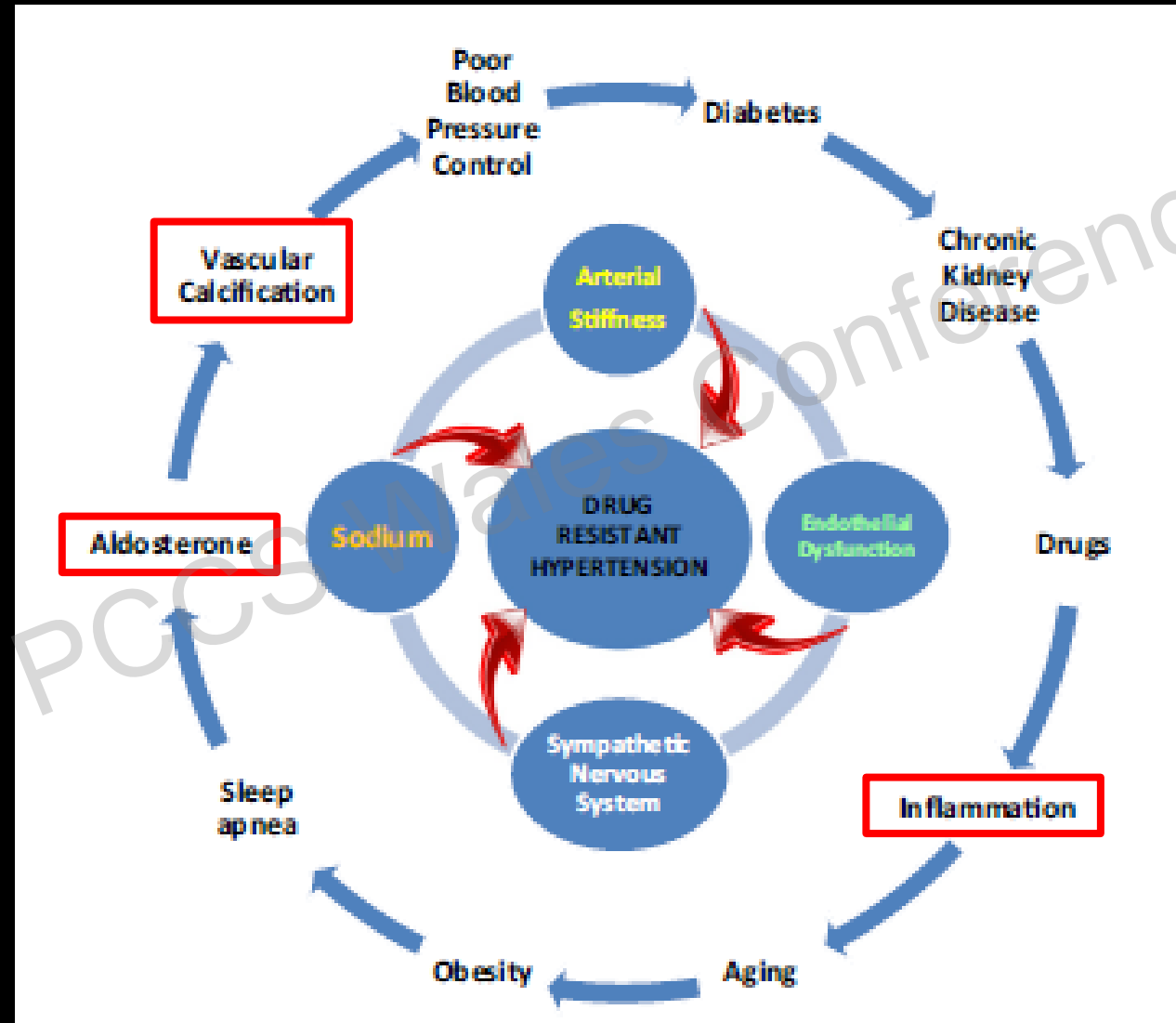
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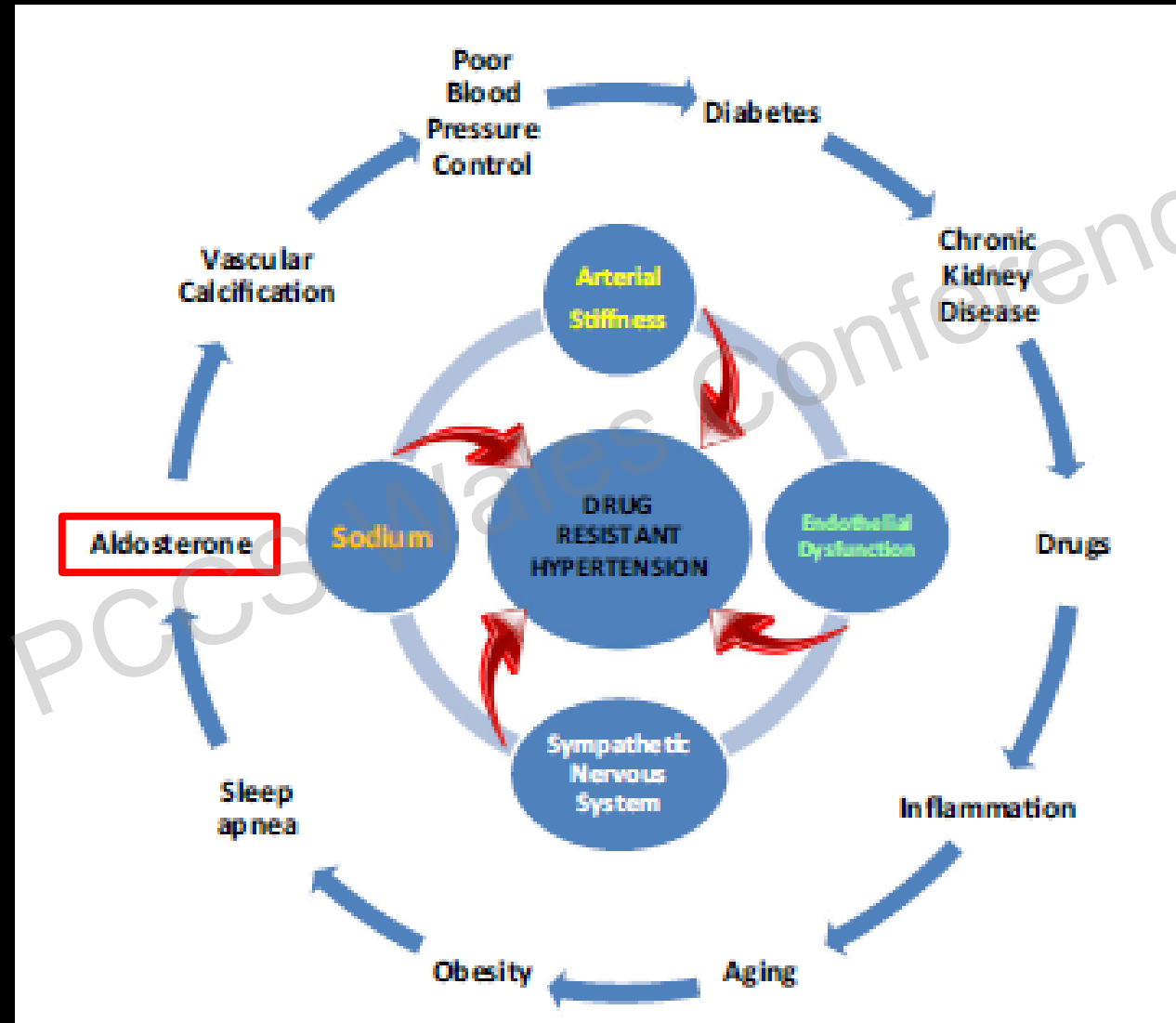
Pathogenesis of Drug-Resistant Hypertension

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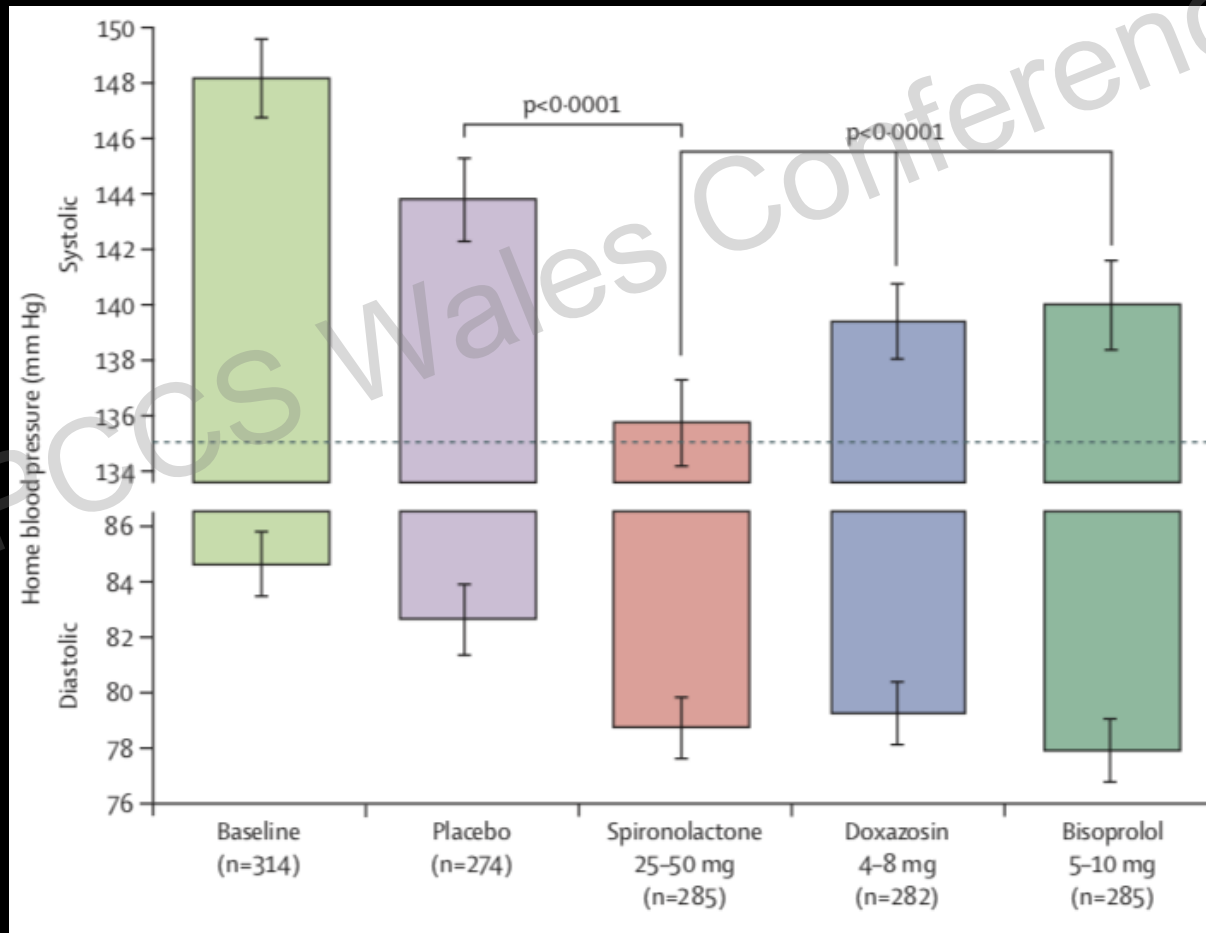
Pathogenesis of Drug-Resistant Hypertension

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Spiroonolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group*



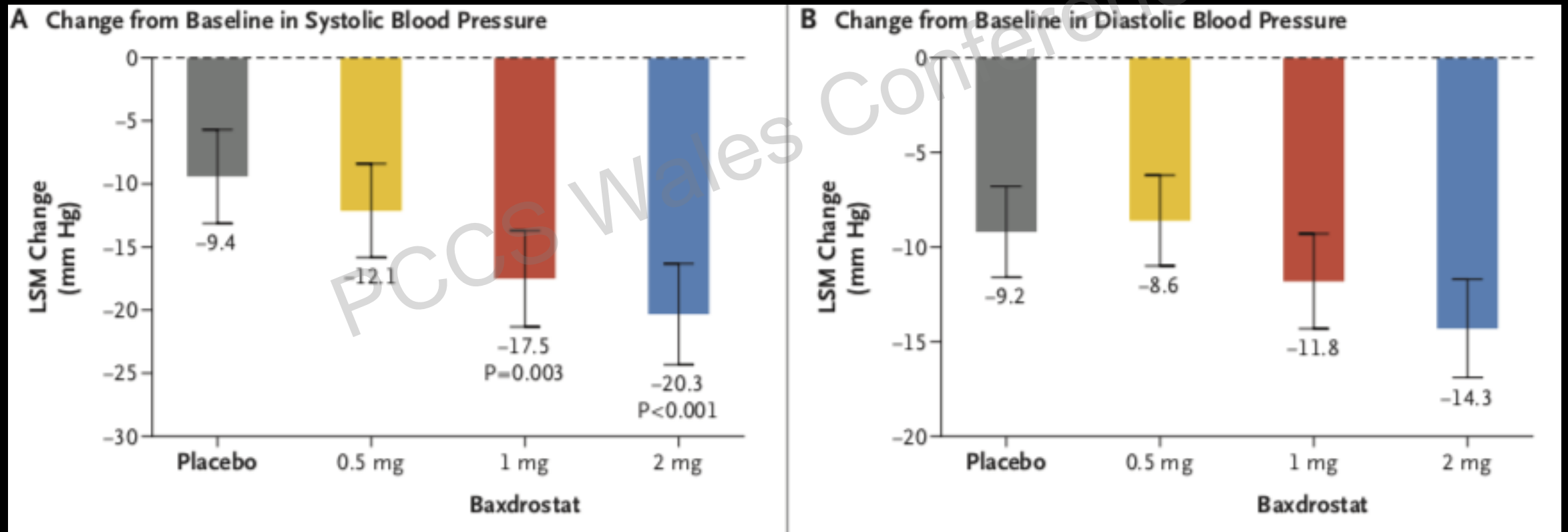
Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

Mason W. Freeman, M.D., Yuan-Di Halvorsen, Ph.D., William Marshall, M.D., Mackenzie Pater, Ph.D., Jon Isaacsohn, M.D., Catherine Pearce, D.H.Sc., Brian Murphy, M.D., M.P.H., Nicholas Alp, M.D., Ajay Srivastava, M.D., Deepak L. Bhatt, M.D., M.P.H., and Morris J. Brown, M.D., for the BrigHTN Investigators*

Aldosterone Synthesis Inhibition

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

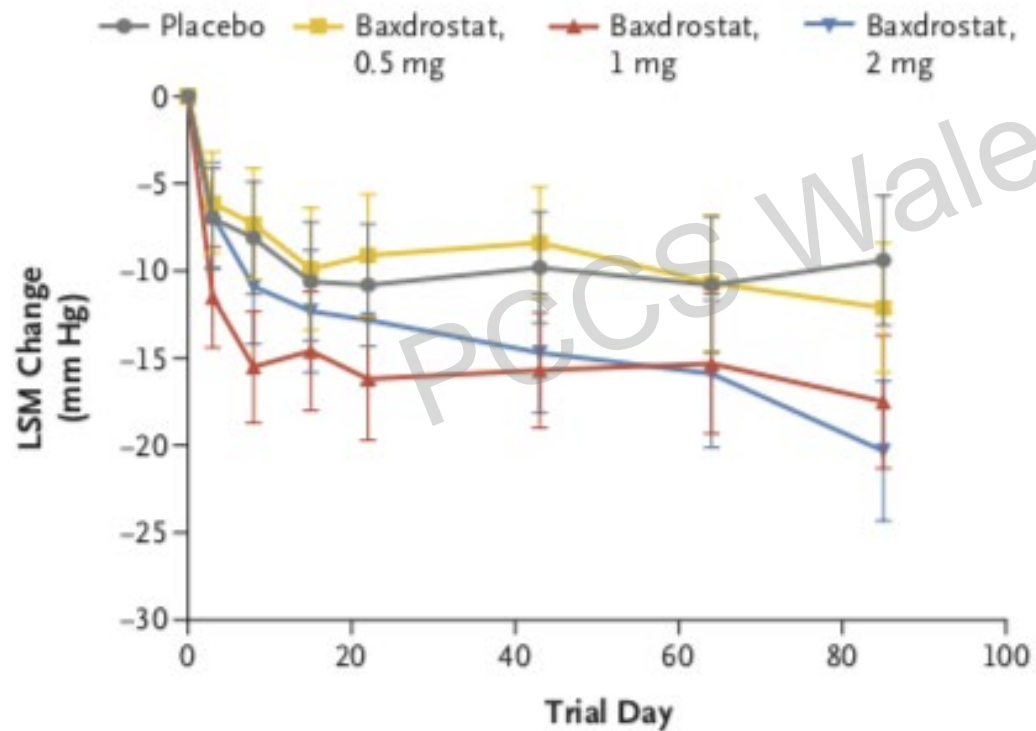
Mason W. Freeman, M.D., Yuan-Di Halvorsen, Ph.D., William Marshall, M.D., Mackenzie Pater, Ph.D., Jon Isaacsohn, M.D., Catherine Pearce, D.H.Sc., Brian Murphy, M.D., M.P.H., Nicholas Alp, M.D., Ajay Srivastava, M.D., Deepak L. Bhatt, M.D., M.P.H., and Morris J. Brown, M.D., for the BrightHTN Investigators*



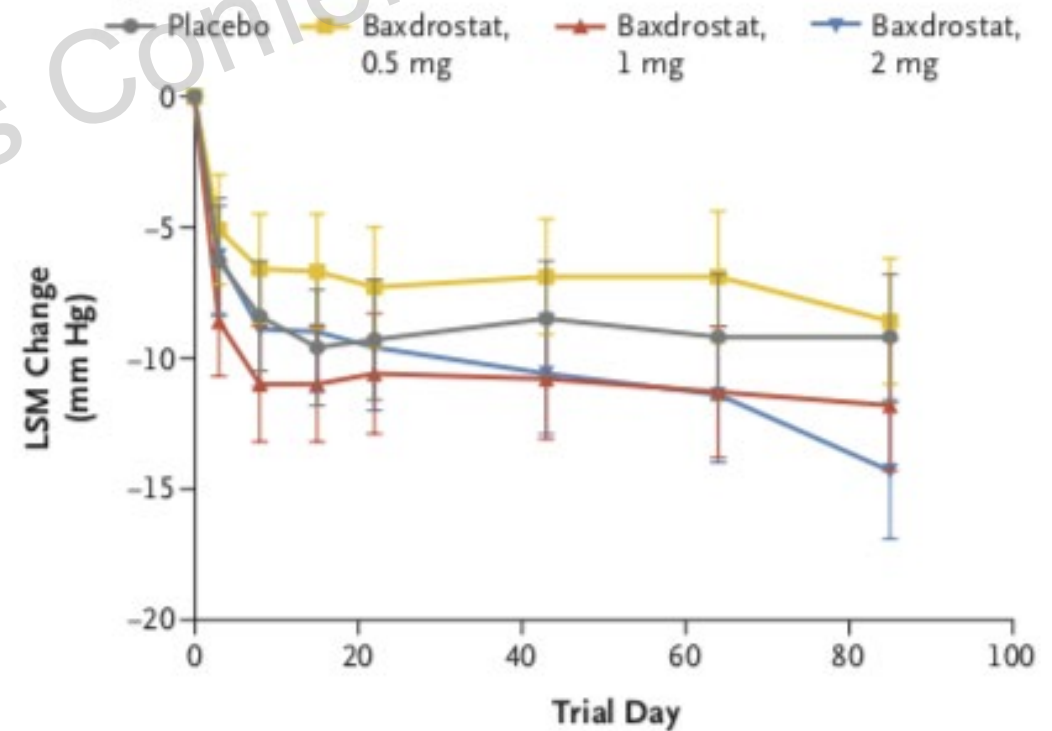
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C Change in Systolic Blood Pressure over Time



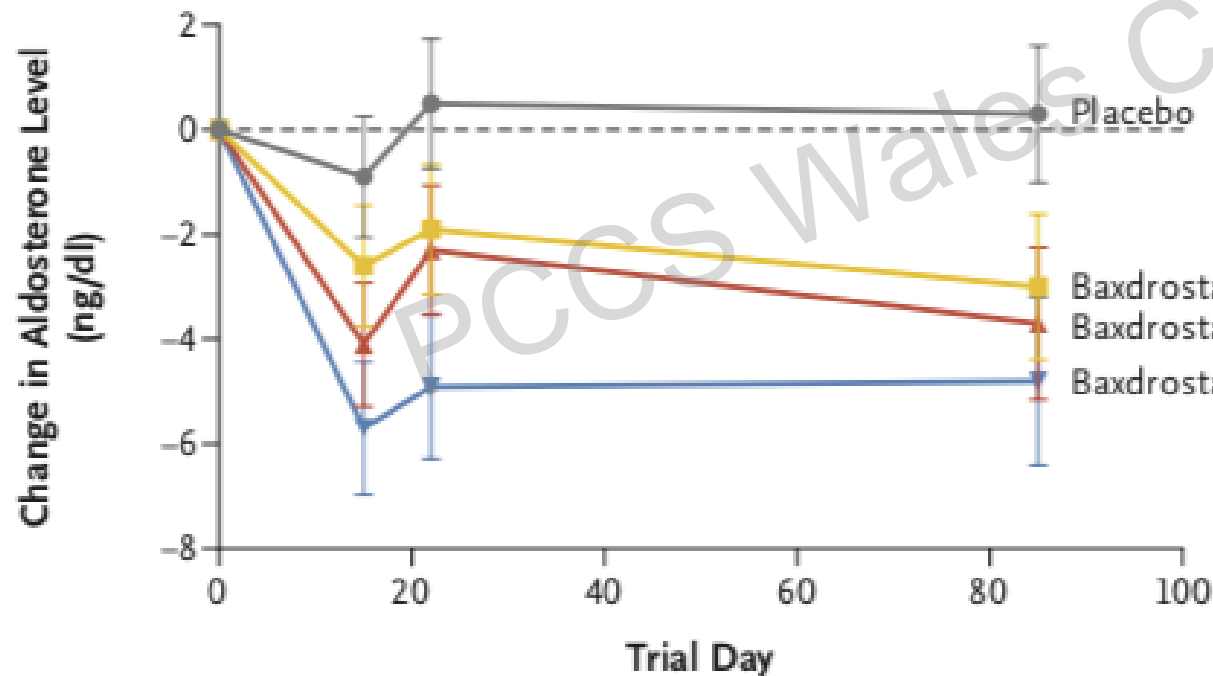
D Change in Diastolic Blood Pressure over Time



Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

Mason W. Freeman, M.D., Yuan-Di Halvorsen, Ph.D., William Marshall, M.D., Mackenzie Pater, Ph.D., Jon Isaacsohn, M.D., Catherine Pearce, D.H.Sc., Brian Murphy, M.D., M.P.H., Nicholas Alp, M.D., Ajay Srivastava, M.D., Deepak L. Bhatt, M.D., M.P.H., and Morris J. Brown, M.D., for the BrightTN Investigators*

B Serum Aldosterone

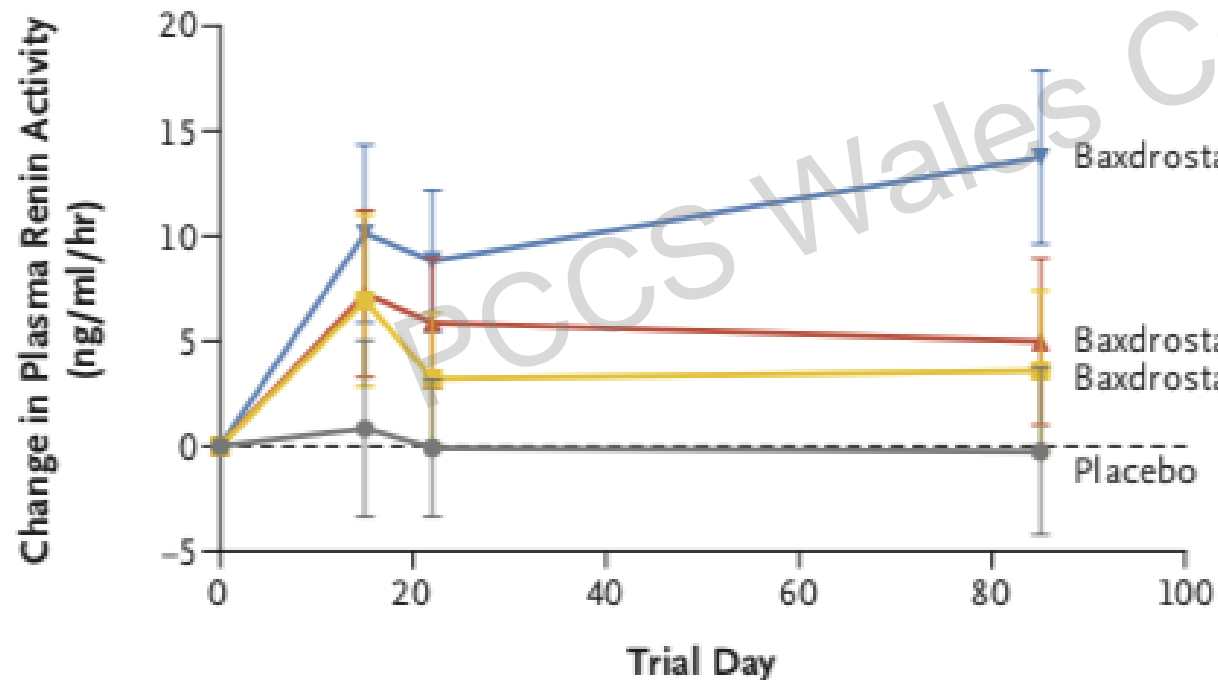


	Mean (\pm SD) Baseline Serum Aldosterone Level ng/dl
Placebo	6.7 \pm 4.8
Baxdrostat, 0.5 mg	6.9 \pm 4.2
Baxdrostat, 1 mg	7.9 \pm 5.8
Baxdrostat, 2 mg	8.4 \pm 5.5

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

Mason W. Freeman, M.D., Yuan-Di Halvorsen, Ph.D., William Marshall, M.D., Mackenzie Pater, Ph.D., Jon Isaacsohn, M.D., Catherine Pearce, D.H.Sc., Brian Murphy, M.D., M.P.H., Nicholas Alp, M.D., Ajay Srivastava, M.D., Deepak L. Bhatt, M.D., M.P.H., and Morris J. Brown, M.D., for the BrighTN Investigators*

C Plasma Renin Activity



	Mean (\pm SD) Baseline Plasma Renin Activity ng/ml/hr
Placebo	4.5 \pm 6.7
Baxdrostat, 0.5 mg	3.1 \pm 5.2
Baxdrostat, 1 mg	5.2 \pm 10.8
Baxdrostat, 2 mg	6.7 \pm 10.4

Take Home Messages for Resistant Hypertension

- Consider mechanisms involved in resistant hypertension: ISH is increasingly common and difficult to treat to target
- Consider expert referral
- Try to exclude poor compliance
- 24hr BP measurement
- Spironolactone is useful as a 4th line agent
- Consider non-pharmacological therapy (devices)
- New pharmacological agents in pipeline