

AZIENDA OSPEDALIERA  
SANT' ANDREA

UNIVERSITÀ DI ROMA "LA SAPIENZA"  
SECONDA FACOLTÀ  
DI MEDICINA E CHIRURGIA



*Regione Lazio*



SAPIENZA  
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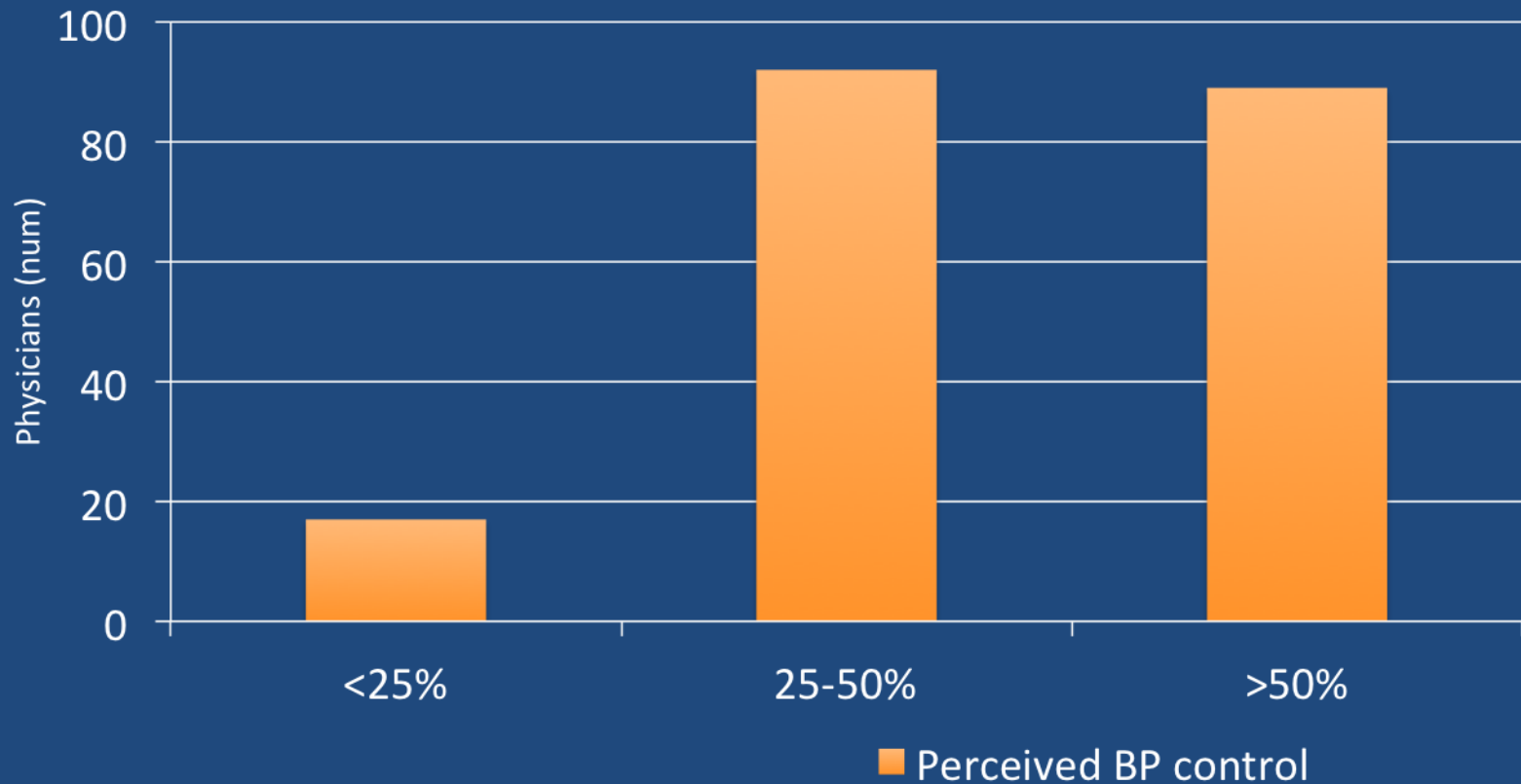
# Current Issues on Resistant Hypertension

- Relatively Low Prevalence in HT population (lower in general population)
- Not Uniform Diagnostic Criteria by International Guidelines
- Different Diagnostic Approaches (Clinic BP or ABPM)
- Different Professional Figures involved in the clinical management (HT Specialist, Cardiologist, Nephrologist, GP, others)
- Various Pharmacological Options (combination strategies)
- New Non-Pharmacological Strategies (Carotid Stimulation or RDN)

# True Resistant Hypertension or Challenging Hypertension?

The gap between perceived and attained BP  
control in the daily clinical practice

# In what percentage of hypertensive patients do you achieve the recommended BP goals?



A sample of 203 cardiologists operating in outpatient clinics and randomly selected amongst members of the largest Italian Outpatient Cardiologist Association (ARCA) were interviewed by e-mail, in April-May 2007.

# BP Stratification in Hypertensive Patients enrolled in Hypertension Surveys in Italy

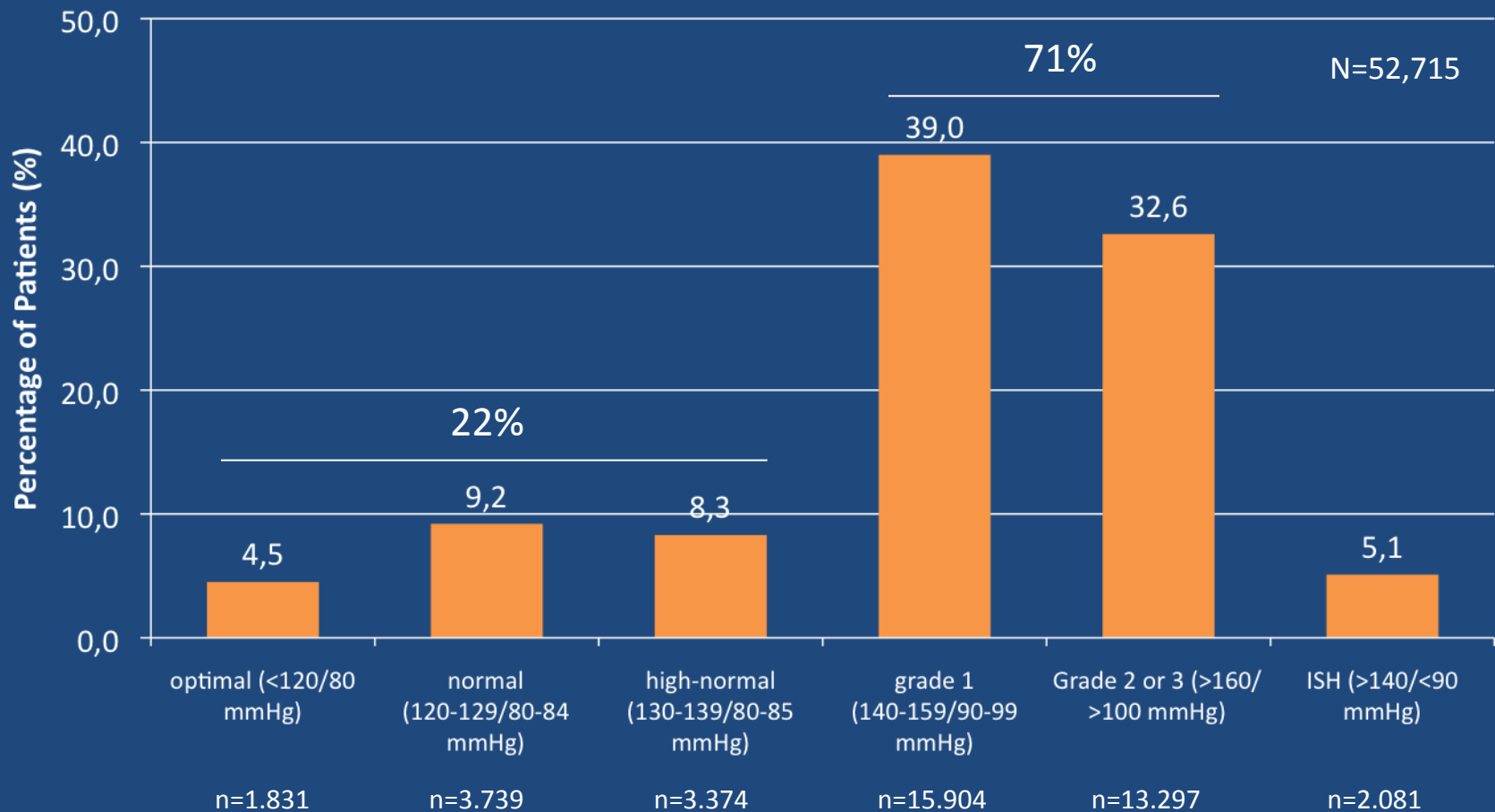
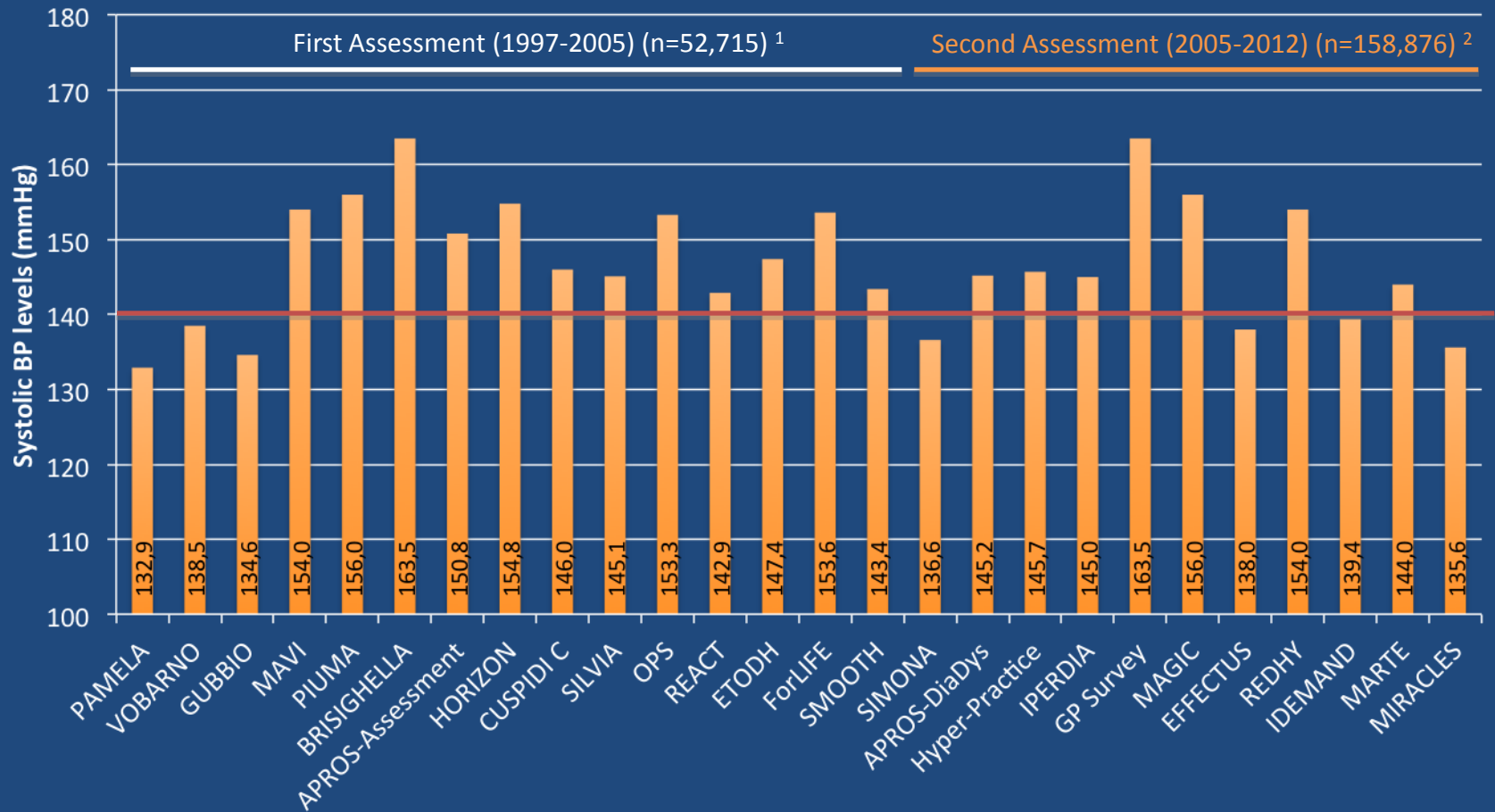


Figure 1a

# Systolic BP levels in Patients included in Hypertension Surveys performed in Italy between 1997-2012



1. Volpe M, Tocci G, et al. J Hypertens 2007;25(7):1491-8.

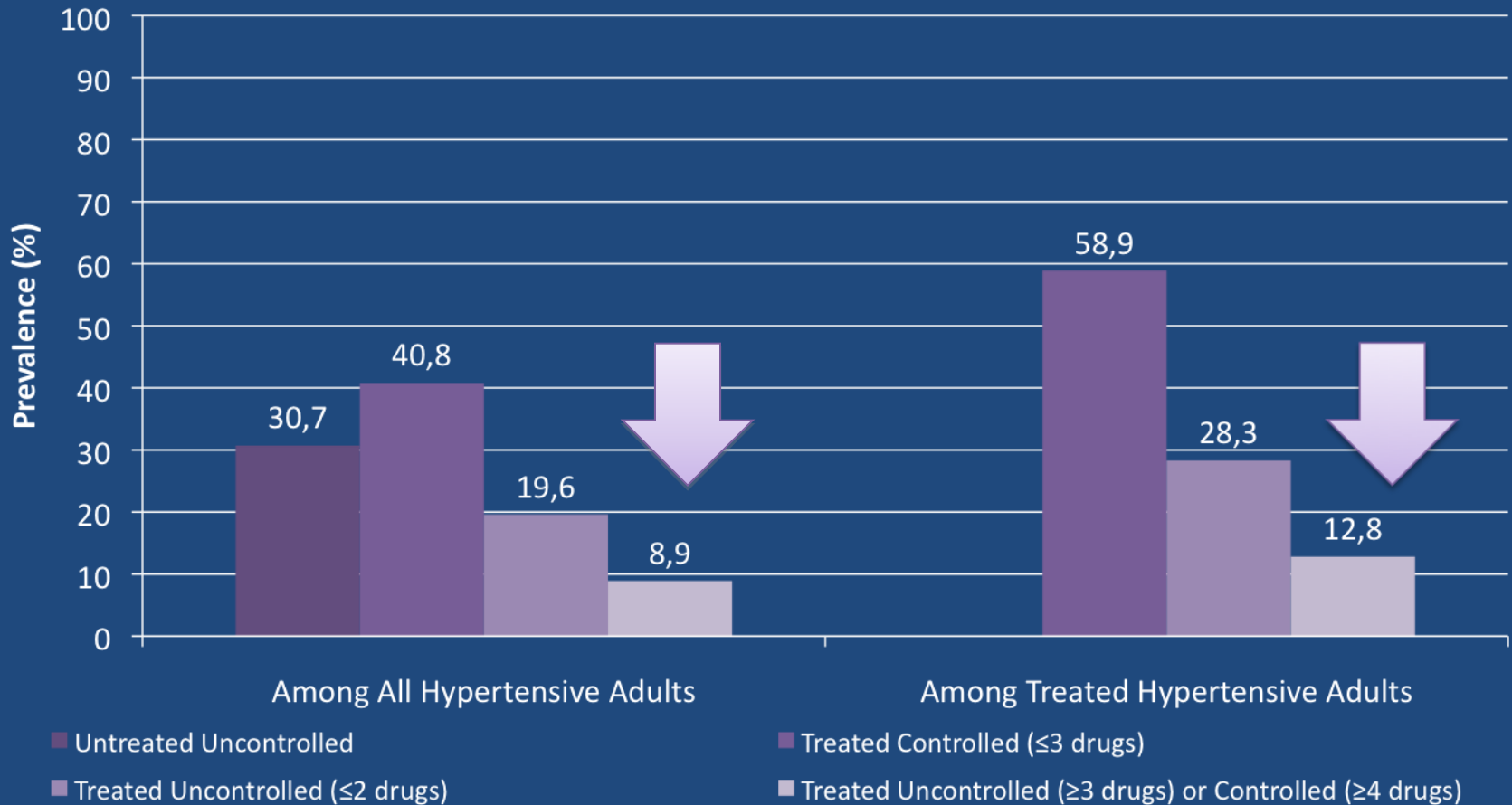
2. Tocci G, Volpe M, et al. J Hypertens 2012;30:1065-74.

# Epidemiology of Resistant Hypertension in Italy

Popolazione Italia (35-75 anni)		32.060.564	ISTAT 2010
	Uomini	15.660.931	
	Donne	16.399.633	
Popolazione ipertesa (PB $\geq$ 140/90 mmHg)		BP (%)	Analisi SIIA (Società Italiana dell'Ipertensione Arteriosa)
	Uomini	53% 8.285.396	
	Donne	45% 7.356.970	
Popolazione totale "ipertesi"		15.642.366	Onusko et al. 2003
Popolazione affetta da ipertensione secondaria		10% 1.564.237	
Popolazione totale "ipertesi" candidabile al trattamento		14.078.129	
Popolazione ipertesa non trattata		43% 6.053.596	Tocci et al. 2012
Popolazione ipertesa trattata		57% 8.024.534	
Popolazione ipertesa trattata sotto controllo		37% 2.969.077	Tocci et al. 2012
Popolazione ipertesa trattata <u>NON</u> sotto controllo		63% 5.055.456	
<b>1° scenario</b>			A.Filippi et al. 2009
Popolazione ipertesa NON controllata & resistente (terapia $\geq$ 3 farmaci) di grado 2-3		5,7% 288.161	
Popolazione target (candidabile alla RDN) - terapia $\geq$ 3 farmaci		50% 144.081	
Impatto % (RDN vs popolazione ipertesa) - terapia $\geq$ 3 farmaci		0,92%	Expert opinion
<b>2° scenario</b>			A.Filippi et al. 2009
Popolazione ipertesa NON controllata & resistente (terapia $\geq$ 4 farmaci) di grado 2-3		2,6% 132.958	
Popolazione target - terapia $\geq$ 4 farmaci (candidabile alla RDN)		50% 66.479	
Impatto % (RDN vs popolazione ipertesa) - terapia $\geq$ 4 farmaci		0,42%	Expert opinion

Reference

# Classification of Adults with Hypertension in the United States





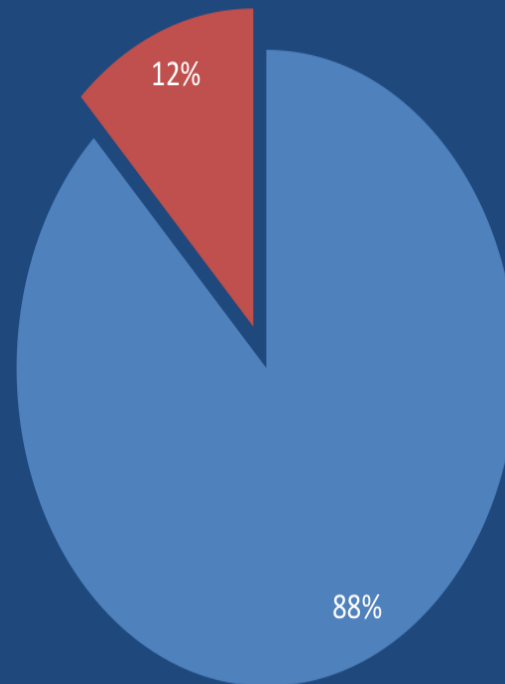
Clinical Features of 8295 Patients With Resistant Hypertension Classified on the Basis of 24-hour ABPM:

## Prevalence of Resistant Hypertension

The CARDIORISC-MAPAPRES project has been promoted by the **Spanish Society of Hypertension** with the support of an educational grant from Lacer Spain.

More than 1000 investigators (**primary care physicians and referral units**) have participated by including patients with suspected hypertension or previously diagnosed hypertensive patients on pharmacological treatment. The present analysis was performed in a **cohort of 68045 patients**.

All the investigators were supplied by an **automated ABPM monitor (SpaceLabs 90207)**. Data obtained were transferred to a central database along with a case report form also common from all the participants.



■ Controlled or treated with less than 3 drugs ■ Refractory Hypertension

# Not Uniform Definitions of Resistant Hypertension

United States		Europe	
JNC 7 (2003) <sup>1</sup> Failure to reach BP goal (<140/90 mmHg or <130/80 mmHg in high-risk patients) in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic.	AHA (2008) <sup>2</sup> BP that remains above goal ( $\geq 140/90$ mmHg or $\geq 130/80$ mmHg in high-risk patients) despite concurrent use of 3 antihypertensive agents of different classes (ideally one of which is a diuretic, and all agents are optimized)	ESH (2007) <sup>3</sup> BP $\geq 140/90$ mmHg (or $\geq 130/80$ mmHg in high-risk patients) despite treatment with at least 3 drugs (including a diuretic) in adequate doses and after exclusion of spurious hypertension such as isolated office hypertension and failure to use large cuffs on large arms	BHS (2011) <sup>4</sup> Someone whose BP is not controlled to <140/90 mmHg, despite optimal or best-tolerated doses of third-line treatment.

1. Chobanian AV et al. JAMA. 2003;289:2560-2572;

2. Calhoun DA et al. Circulation. 2008;117:e510-526;

3. Mancia G et al. J Hypertens. 2007;25:1105-1187;

4. NCGC. Available at: <http://www.nice.org.uk/nicemedia/live/12167/54727/54727.pdf>. Accessed Nov 19 2011.

# Patients' characteristics at baseline

- 1097 patients treated as of June 26, 2013
  - 86% with SBP  $\geq$ 140 mmHg
  - 66% of patients treated according to ESC Consensus paper on Renal Denervation<sup>1</sup>
    - SBP  $\geq$  160 mm Hg ( $\geq$  150 mmHg Diabetes II), 3+ meds, including diuretic
  - 13% with BP  $\geq$ 180/100 mmHg
- Co-Morbidities Include:
- Diabetes II 38.2%
  - Renal Disease 30.1%
  - Sleep Apnea 16.9%
  - Hx of Cardiac Disease 49%
  - Heart Failure 9.2%
  - Atrial Fibrillation 12.6%
  - LVH 15.9%

# Blood Pressure levels and Antihypertensive Tx at baseline

Drugs	Proportions
Baseline BP (mm Hg)	164/89 $\pm$ 24/16
Number of classes anti-HTN meds (mean)	4.39 $\pm$ 1.33
Diuretic (%)	76%
Aldosterone blocker (%)	21%
ACE (%)	34%
ARB (%)	65%
Beta-Blocker (%)	77%
Calcium Channel Blocker (%)	75%
Alpha adrenergic Blocker(%)	34%
Vasodilator (%)	14%
Direct Renin Inhibitor (%)	7%


Stratification of total CV risk in categories of low, moderate, high and very high risk according to SBP and DBP and prevalence of RFs, asymptomatic OD, diabetes, CKDstage or symptomatic CVD.

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High-normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	Low Risk	Low Risk	Moderate Risk	High Risk
1-2 RF	Moderate Risk	Moderate Risk	High Risk	Very High Risk
≥3 RF	High Risk	High Risk	Very High Risk	Very High Risk
OD, CKD stage 3 or Diabetes	High Risk	High Risk	High Risk	High to Very High Risk
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	Very High Risk	Very High Risk	Very High Risk	Very High Risk

No clear positioning of Resistant Hypertension within Global CV Risk Stratification

Subjects with a high normal office but a raised out-of-office BP(masked hypertension) have a CV risk in the hypertension range. Subjects with a high office BP but normal out-of-office BP (white-coat hypertension), particularly if there is no diabetes, OD, CVD or CKD, have lower risk than sustained hypertension for the same office BP.

# Distribution of Patients according to 2013 ESH/ESC Global Cardiovascular Risk Stratification



Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	High normal SBP 130-139 or DBP 85-89 (n=71)	Grade 1 HT SBP 140-159 or DBP 90-99 (n=292)	Grade 2 HT SBP 160-179 or DBP 100-109 (n=373)	Grade 3 HT SBP ≥ 180 or DBP ≥ 110 (n=295)
No other RF	0.0%	5.6%	6.7%	11.4%
1-2 RF	93.8%	51.9%	49.5%	45.7%
≥ 3 RF	6.3%	42.6%	43.8%	42.9%
OD, CKD stage 3 or diabetes	71.8%	72.9%	64.9%	66.4%
Symptomatic CVD, CKD stage ≥ 4 or diabetes with OD/RFs	54.9%	62.7%	55.5%	56.6%

# Not All Refractory Hypertension is True Treatment-Resistant Hypertension

- Not all patients who fail to respond to antihypertensive therapy have true treatment-resistant hypertension
- Long-term outcomes vary substantially among the various subtypes of refractory hypertension
- Optimal treatment modalities and approach to management vary among subtypes

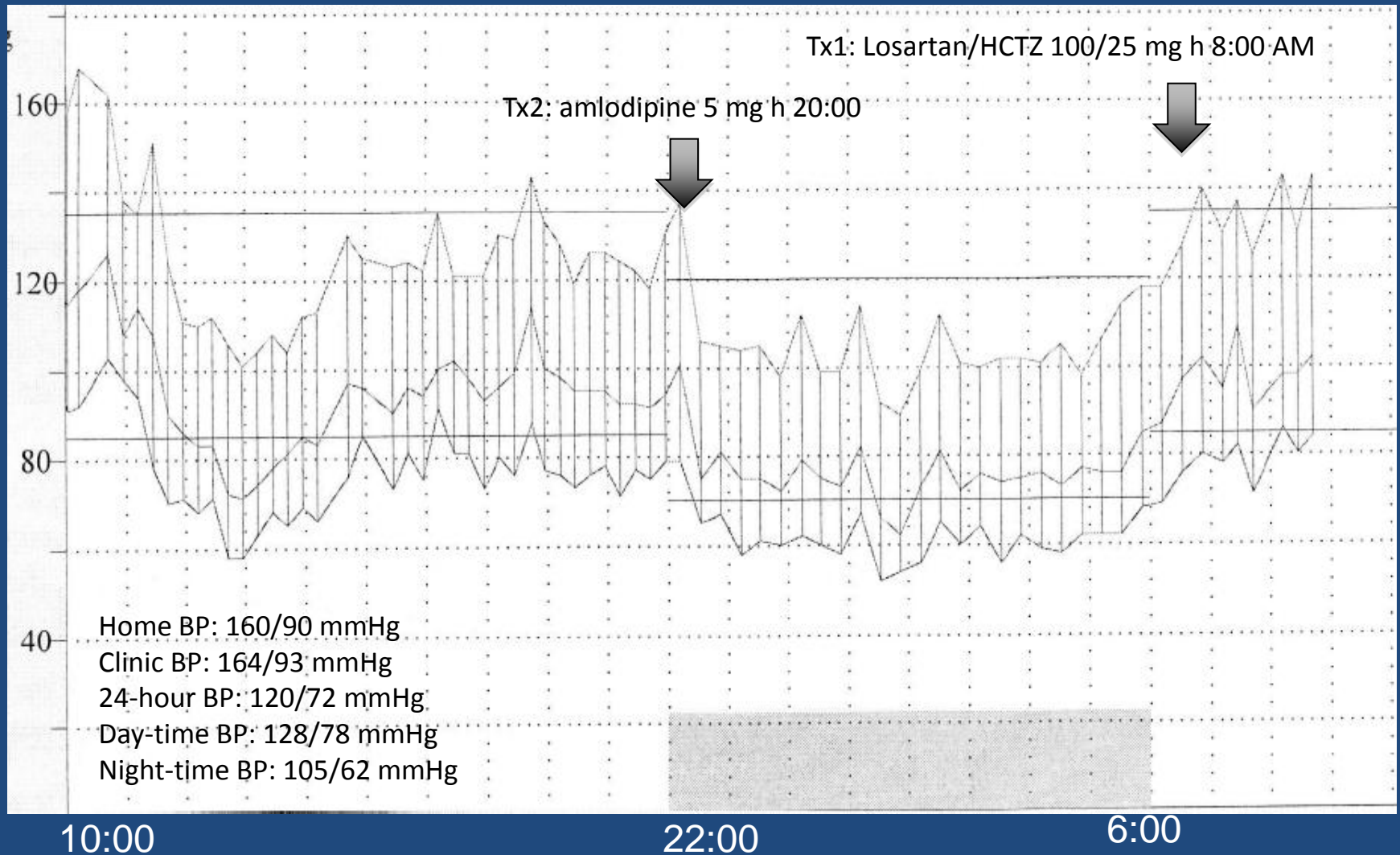
Secondary Hypertension <sup>1</sup>	Pseudoresistance <sup>1,2</sup>	Masked Hypertension <sup>2</sup>	White coat hypertension <sup>2</sup>	True treatment-resistant hypertension* <sup>3</sup>
Hypertension elicited or exacerbated by other drugs or diseases	Apparent hypertension due to lack of adherence, poor BP measurement technique	Clinic BP <140/90 mm Hg; daytime BP >135 or >85 mm Hg	Clinic BP ≥140 or ≥90 mm Hg; daytime BP <135/85 mm Hg	BP ≥140/90 mm Hg despite adequate doses of ≥3 drugs (including diuretic) after exclusion of spurious hypertension

1. Calhoun DA et al. Circulation. 2008;117:e510-526;

2. Pierdomenico SD et al. Am J Hypertens. 2005;18:1422-1428;

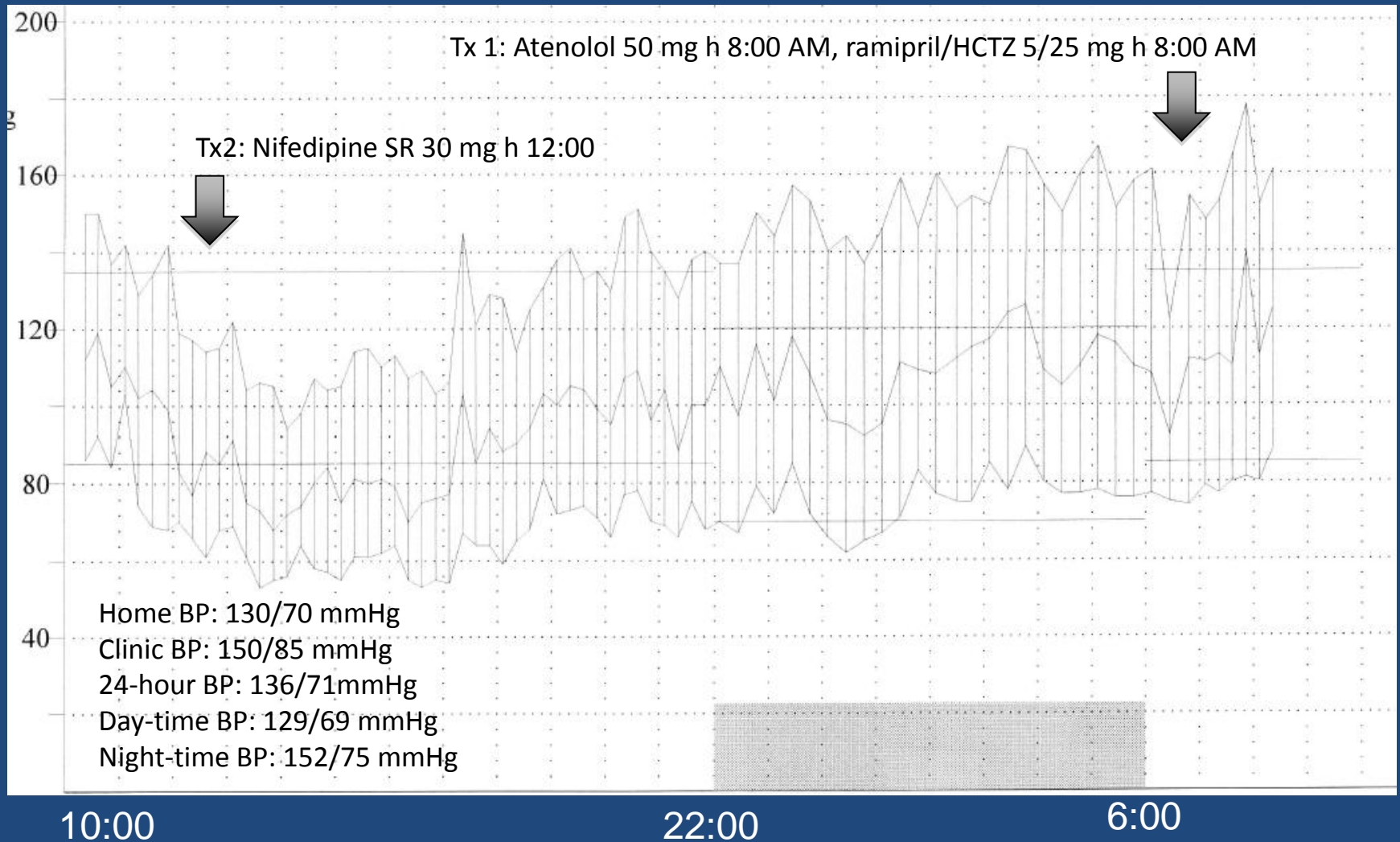
3. Mancia G et al. J Hypertens. 2013;31:1281-1357.

# White-Coat Hypertension

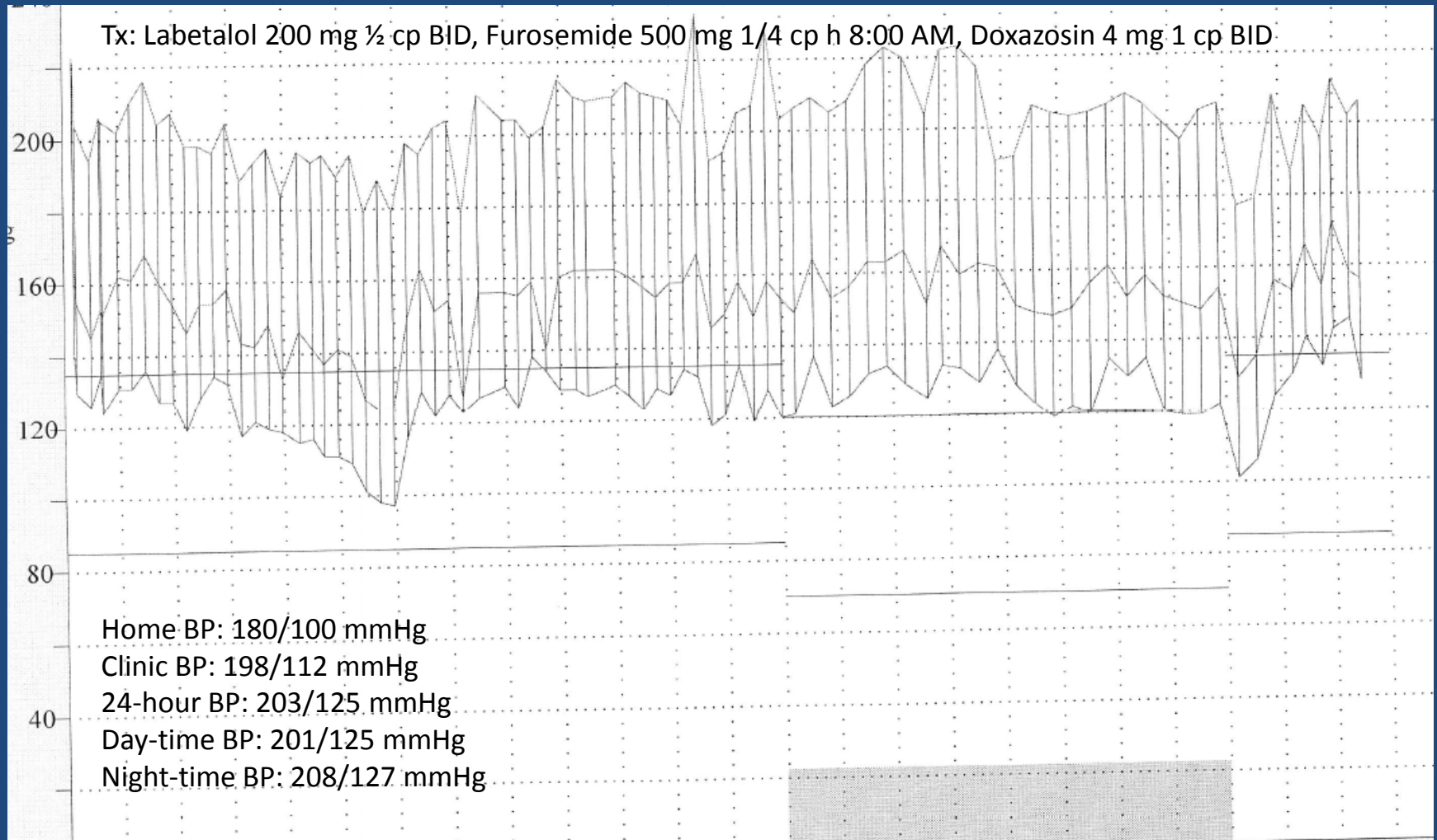




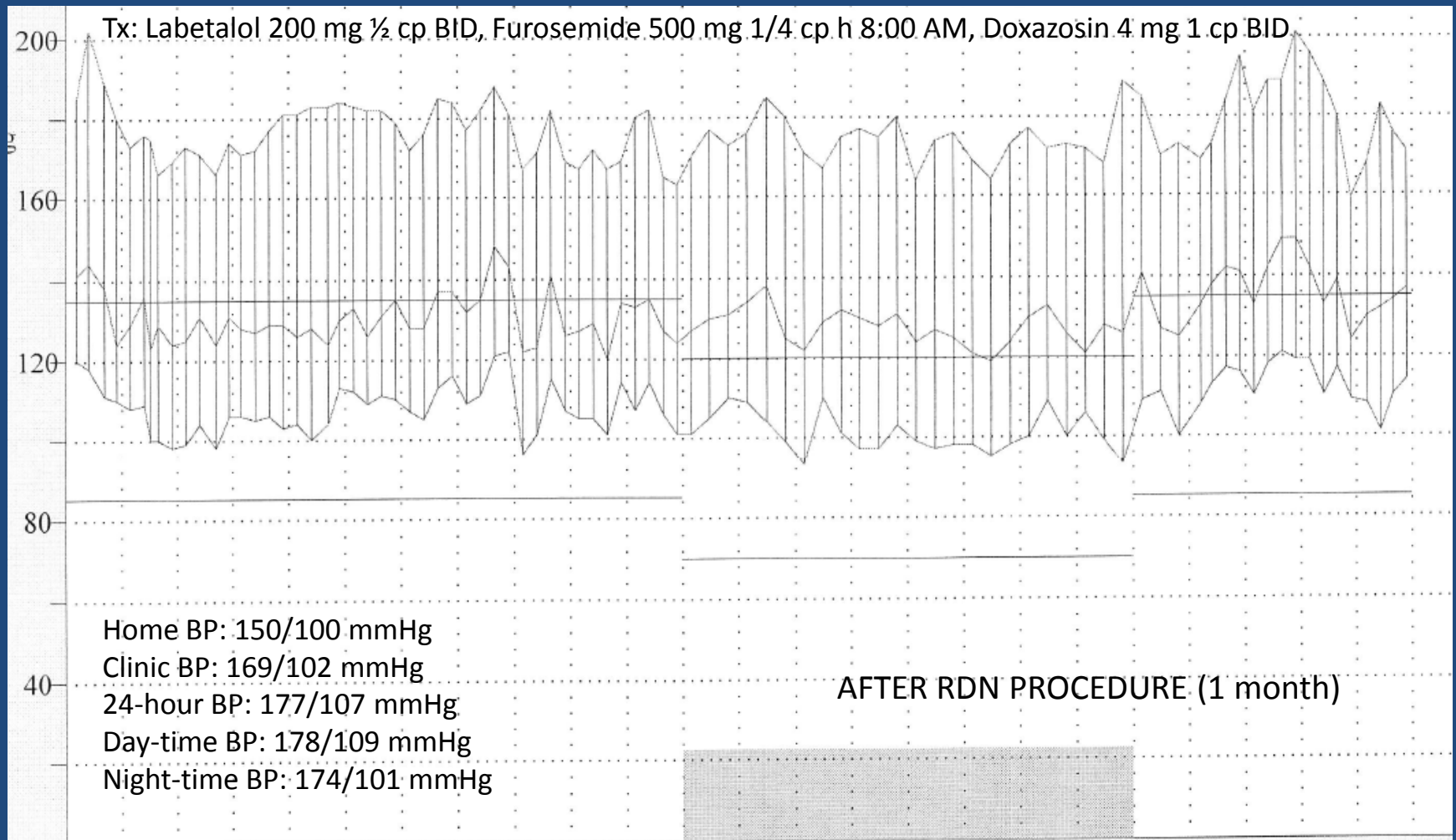
# Out-of-Office Uncontrolled Hypertension



# True Resistant Hypertension in patients with multiple drug intolerance: Before Renal Denervation



# True Resistant Hypertension in patients with multiple drug intolerance: Effect of Renal Denervation at 1-month



# Hypertension Unit: How to properly diagnose and treat Resistant Hypertension

BP >140/90 mmHg in hypertensive patients receiving at least 3 antihypertensive drugs, including a diuretic, at adequate (full) doses

Check any discrepancies among office, home and 24-hour ambulatory BP measurements

Normal home and high clinic and ambulatory BP levels  
**Office-Resistant Hypertension**

All BP above limits

Normal home and ambulatory and high clinic BP levels:  
**Pseudo-Resistant Hypertension**

**Check patient's adherence to antihypertensive drug prescriptions**

Check patient's assumption of any interfering drug or substance

Identify and treat possible causes of secondary hypertension and any concomitant condition that may persistently keep BP levels elevated \*

**Optimize and titrate pharmacologic and non-pharmacologic therapies**

Refer patient to Hypertension Center

# Is resistant hypertension really resistant ?

## Causes of Pseudo-Resistant Hypertension

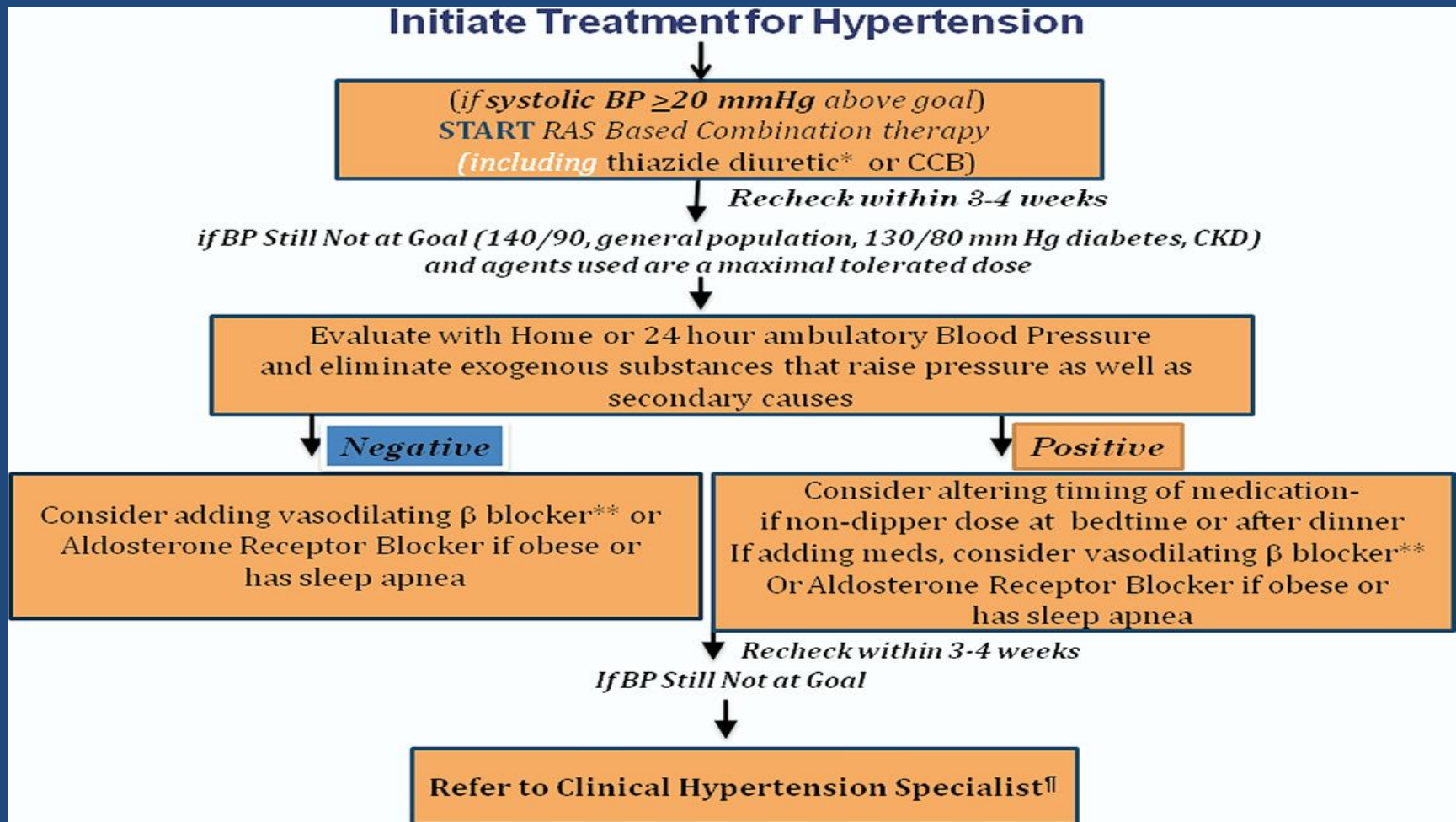
- Heavily calcified or arteriosclerotic arteries that are difficult to compress (in elderly persons)
- Improper blood pressure measurement
- White-coat effect
- Poor patient's adherence
  - Side effects of medication
  - Complicated dosing schedules
  - Poor relations between doctor and patient
  - Inadequate patient education
  - Memory or psychiatric problems
  - Costs of medication
- Related to antihypertensive medication
  - Inadequate doses
  - Inappropriate combinations
- Physician inertia (failure to change or increase dose regimens when not at goal)

# Factors Contributing to Resistant Hypertension

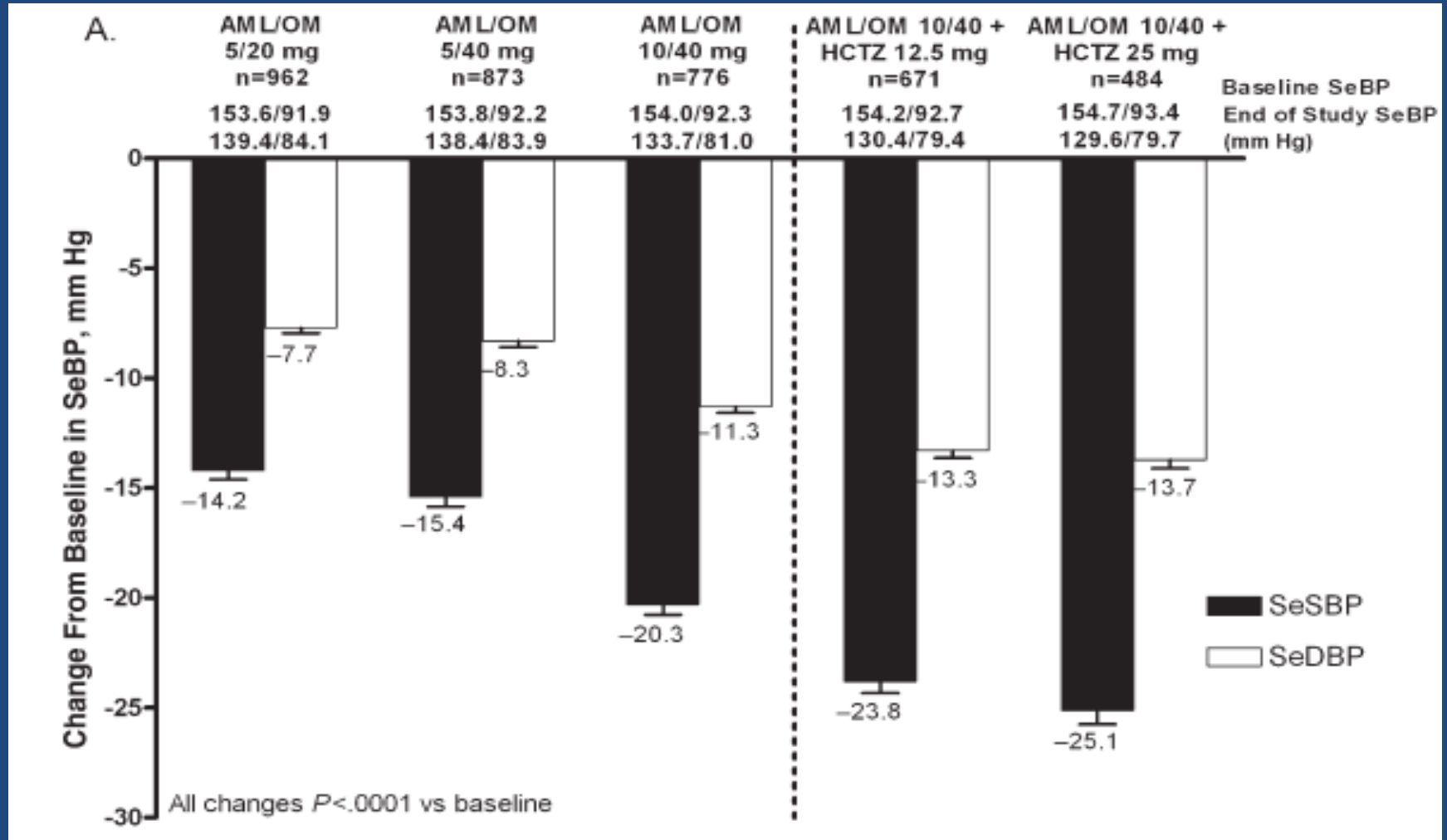
- **Drug-induced**
  - Nonsteroidal anti-inflammatory drugs (including cyclo-oxygenase-2 inhibitors)
  - Sympathomimetics (decongestants, anorectics)
  - Cocaine, amphetamines, other illicit drugs
  - Oral contraceptive hormones
  - Adrenal steroid hormones
  - Erythropoietin
  - Cyclosporine and tacrolimus
  - Licorice (included in some chewing tobacco)
  - Over-the-counter dietary and herbal supplements (e.g., ginseng, yohimbine, ma huang, bitter orange)
- **Excess alcohol intake**
- **Volume overload**
  - Excess sodium intake
  - Volume retention from kidney disease
  - Inadequate diuretic therapy
- **Associated conditions**
  - Obesity
  - Diabetes mellitus
  - Older age
- **Identifiable causes of hypertension**
  - Renal parenchymal disease
  - Renovascular disease
  - Primary aldosteronism
  - Obstructive sleep apnea
  - Pheochromocytoma
  - Cushing's syndrome
  - Thyroid diseases
  - Aortic coarctation
  - Intracranial tumors



# An Approach to Achieve BP Goal in Resistant Hypertension



Change from baseline  
 in seated cuff systolic (SeSBP) and diastolic (SeDBP) blood pressure levels  
 with different combination therapies based on olmesartan/amlodipine/HCTZ





# Treatment strategies and choice of drugs in patients with resistant hypertension

Recommendations	Class	Level
In resistant hypertensive patients it is recommended that physicians check whether the drugs included in the existing multiple drug regimen have any BP lowering effect, and withdraw them if their effect is absent or minimal.	I	C
Mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin should be considered, if no contraindication exists.	IIa	B
In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation may be considered.	IIb	C
Until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, it is recommended that these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centers.	I	C
It is recommended that the invasive approaches are considered only for truly resistant hypertensive patients, with clinic values $\geq 160$ mmHg SBP or $\geq 110$ mmHg DBP and with BP elevation confirmed by ABPM.	I	C

# Potential Upcoming Options for Treating Resistant Hypertension

- **Pharmacological Options**
  - Aldosterone Synthase Inhibitors
  - NEP inhibitors (Omapatrilat- compassionate use)
  - New Aldosterone Antagonists (Eplerenone, others)
  - Clonidine Extended Release
  - Endothelin Antagonists
- **Non-pharmacological Options**
  - Renal Artery Denervation
  - Carotid Baroreflex Stimulation

# How to manage difficult-to-treat patients with resistant hypertension?

**POSITION PAPER**

## Denervazione delle arterie renali nel trattamento dell'ipertensione arteriosa resistente: definizione della patologia, selezione dei pazienti e descrizione della procedura

Documento di Indirizzo 2012  
della Società Italiana dell'Ipertensione Arteriosa (SIIA)

Massimo Volpe<sup>1</sup>, Enrico Agabiti-Rosei<sup>2</sup>, Ettore Ambrosioni<sup>3</sup>, Santina Cottone<sup>4</sup>, Cesare Cuspidi<sup>5</sup>, Claudio Borghi<sup>3</sup>, Nicola De Luca<sup>6</sup>, Francesco Fallo<sup>7</sup>, Claudio Ferri<sup>8</sup>, Giuseppe Mancia<sup>5</sup>, Alberto Morganti<sup>9</sup>, Maria Lorenza Muiesan<sup>10</sup>, Riccardo Sarzani<sup>11</sup>, Leonardo Sechi<sup>12</sup>, Giuliano Tocci<sup>1</sup>, Agostino Virdis<sup>13</sup>

Volpe M, et al. G Ital Cardiol (Rome) 2012 Dec;13(12):846-5  
Ipertensione Prev Cardiovasc 2013; *in press*  
High Blood Press Cardiovasc Prev 2012 Dec;19(4):237-44

# Current Issues on Renal Denervation in Resistant Hypertension

1. Eligible candidates (BP thresholds, Therapeutic Regimen, Out-of-Office measure of BP)
2. Predictors of test success
3. Measures to estimate effectiveness of the renal nerve ablation procedure
4. Efficacy measures
5. Effect on hard outcomes in hypertension
6. Clinical codification of the specific procedure for reimbursement
7. Cost/benefit

## Medtronic Announces U.S. Renal Denervation Pivotal Trial Fails to Meet Primary Efficacy Endpoint While Meeting Primary Safety Endpoint (1/2)

- MINNEAPOLIS - January 9, 2014 - Medtronic, Inc. (NYSE: MDT) today announced that its U.S. pivotal trial in renal denervation for treatment-resistant hypertension, SYMPLICITY HTN-3, **failed to meet its primary efficacy endpoint**. The trial **met its primary safety endpoint**, and the trial's Data Safety Monitoring Board (DSMB) concluded that there were no safety concerns in the study.
- In light of the product's demonstrated safety profile, including the SYMPLICITY HTN-3 findings, **no specific action is currently indicated for patients who have had the renal denervation procedure with the SYMPLICITY system**. Patients should consult with their physician regarding any questions they may have about their treatment.
- Based on these clinical trial findings, **Medtronic intends to formulate a panel of independent advisors made up of physicians and researchers who will be asked to make recommendations about the future of the global hypertension clinical trial program**, as well as provide advice on continued physician and patient access to the Symplicity technology in countries with regulatory approvals.

## Medtronic Announces U.S. Renal Denervation Pivotal Trial Fails to Meet Primary Efficacy Endpoint While Meeting Primary Safety Endpoint (2/2)

Pending this panel review, the company intends to:

1. Suspend enrolment in the three countries where renal denervation hypertension trials are being conducted for regulatory approvals (SYMPLICITY HTN-4 in the U.S., HTN-Japan and HTN-India).
2. Begin informing clinical trial sites and investigators, global regulatory bodies, and customers of these findings and decisions.
3. Continue to ensure patient access to the SYMPLICITY technology at the discretion of their physicians in markets where it is approved.
4. Continue the Global SYMPLICITY post-market surveillance registry and renal denervation studies evaluating other non-hypertension indications.

# Conclusive Remarks

- Diagnosis of Resistant Hypertension should be certified by Excellence Hypertension Centers after comprehensive medical history evaluation and full BP profile assessment.
- Triple combination therapy with HCTZ and long-lasting and well-tolerated RAS blockers plus dihydropyridinic CCBs should be applied to improve BP control.
- If BP goals are not achieved after 4-6 weeks, either beta-blockers (especially if CAD or CHF) or upstream (renin inhibitors) or downstream (antialdosterone) modulation or others should be considered.
- Drugs with proven efficacy (reduced CV mortality and sustained antihypertensive effect) and tolerability, that can be administered once daily, should be always preferred.
- Current studies on RDN have been halted, including SYMPLICITY-HTN3 and ENLIGHT-HTN4.

Thank you for Your Attention!

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# How to improve BP control in daily clinical practice of hypertension?

## POSITION PAPER

### Strategie per migliorare il controllo della pressione arteriosa in Italia: dalla stratificazione del rischio cardiovascolare globale alla terapia di combinazione

Documento di Indirizzo 2012  
della Società Italiana dell'Ipertensione Arteriosa (SIIA)

Massimo Volpe<sup>1</sup>, Ettore Ambrosioni<sup>2</sup>, Claudio Borghi<sup>2</sup>, Santina Cottone<sup>3</sup>, Cesare Cuspidi<sup>4</sup>,  
Nicola De Luca<sup>5</sup>, Francesco Fallo<sup>6</sup>, Claudio Ferri<sup>7</sup>, Alberto Morganti<sup>8</sup>, Maria Lorenza Muiesan<sup>9</sup>,  
Riccardo Sarzani<sup>10</sup>, Leonardo Sechi<sup>11</sup>, Agostino Virdis<sup>12</sup>, Giuliano Tocci<sup>1</sup>, Enrico Agabiti-Rosei<sup>13</sup>,  
Bruno Trimarco<sup>6</sup>, Alessandro Filippi<sup>14</sup>, Giuseppe Mancia<sup>4</sup>

# Uncontrolled Hypertension

