Management of Resistant Hypertension in Diabetes

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HYPERTENSION

About half of subjects with diabetes have hypertension (54.6%), which is more than 2-fold compared with non-diabetic adults (22.7%).

Only 40% of them reaches the target goal of blood pressure < 130/80 mm Hg.

Prevalence

Diabetes 54.6%
Non-diabetes 22.7%

Control rate

Diabetes 39.5%
Non-diabetes 68.5%

DEFINITION OF HYPERTENSION: mean SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg, or use of antihypertensive medication

CONTROL RATE OF HYPERTENSION AMONG TREATMENT: BP < 130/80 mm Hg
Resistant Hypertension

- Blood pressure remaining above goal in spite of concurrent use of 3 antihypertensive agents of different classes.

- Ideally, 1 of the 3 agents should be a diuretic & all agents should be prescribed at optimal dose amounts.
Definition Highlights

• Use of diuretic recommended but not required before diagnosing resistant hypertension.

• Doses should be optimal but not necessarily maximal before diagnosing resistant hypertension.

• Controlled resistant hypertension: high blood pressure controlled but with use of 4 of more agents should be considered resistant.
## 2013 ESH/ESC Guidelines

### Blood pressure goals in hypertensive patients

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A SBP goal &lt;140 mmHg:</td>
<td>I</td>
<td>B</td>
<td>266, 269, 270</td>
</tr>
<tr>
<td>a) is recommended in patients at low–moderate CV risk;</td>
<td>I</td>
<td>A</td>
<td>270, 275, 276</td>
</tr>
<tr>
<td>b) is recommended in patients with diabetes;</td>
<td>I</td>
<td>A</td>
<td>270, 275, 276</td>
</tr>
<tr>
<td>c) should be considered in patients with previous stroke or TIA;</td>
<td>IIa</td>
<td>B</td>
<td>296, 297</td>
</tr>
<tr>
<td>d) should be considered in patients with CHD;</td>
<td>IIa</td>
<td>B</td>
<td>141, 265</td>
</tr>
<tr>
<td>e) should be considered in patients with diabetic or non-diabetic CKD.</td>
<td>IIa</td>
<td>B</td>
<td>312, 313</td>
</tr>
</tbody>
</table>

In elderly hypertensives less than 80 years old with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.

In fit elderly patients less than 80 years old SBP values <140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability.

In individuals older than 80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions.

A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated.

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CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack.

*a* Class of recommendation.

*b* Level of evidence.

*c* Reference(s) supporting levels of evidence.
### Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults with Hypertension

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Population</th>
<th>Goal BP, mm Hg</th>
<th>Initial Drug Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JNC 8</strong></td>
<td>General ≥60 y</td>
<td>&lt;150/90</td>
<td><strong>Nonblack</strong>: thiazide-type diuretic, ACEI, ARB, or CCB</td>
</tr>
<tr>
<td>2014 Hypertension guideline</td>
<td>General &lt;60 y</td>
<td>&lt;140/90</td>
<td><strong>Black</strong>: thiazide-type diuretic or CCB</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;140/90</td>
<td>Thiazide-type diuretic, ACEI, ARB, or CCB</td>
</tr>
<tr>
<td></td>
<td>CKD</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td><strong>NICE 2011</strong></td>
<td>General &lt;80 y</td>
<td>&lt;140/90</td>
<td>&lt;55 y: ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>General ≥80 y</td>
<td>&lt;150/90</td>
<td>≥55 y or black: CCB</td>
</tr>
<tr>
<td><strong>KDIGO 2012</strong></td>
<td>CKD no proteinuria</td>
<td>≤140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>CKD + proteinuria</td>
<td>≤130/80</td>
<td></td>
</tr>
</tbody>
</table>
Goals

• People with diabetes and hypertension should be treated to a systolic blood pressure goal of $<140 \text{ mmHg}$

• Lower systolic targets, such as $<130 \text{ mmHg}$, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden

• Patients with diabetes should be treated to a diastolic blood pressure $<80 \text{ mmHg}$
Critical Importance of Adequate Diuretic Therapy

- 23/32 patients referred for management of “resistant hypertension” had evidence of expanded extracellular volume by nuclear study
  - None had clinical evidence of expanded extracellular volume
  - All were already on diuretic therapy
Critical Importance of Adequate Diuretic Therapy

- Control improved in patients treated with potent thiazide diuretics (indapamide, metolazone, or larger doses of hctz, etc.) or given multiple daily doses of loop diuretics
- Patients with co-existent renal disease may require more intensive diuretic therapy
<table>
<thead>
<tr>
<th>Patient</th>
<th>Blood pressure (mm Hg)</th>
<th>Antihypertensive drugs</th>
<th>Blood pressure (mm Hg)</th>
<th>Antihypertensive drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>180/110</td>
<td>Moduretic, 1 dose daily; hydralazine, 25 mg bid; captopril, 50 mg bid; verapamil, 80 mg bid plus 160 mg at bedtime; clonidine, 0.1-mg patch weekly</td>
<td>160/90</td>
<td>Furosemide, 80 mg bid; captopril, 50 mg bid</td>
</tr>
<tr>
<td>2</td>
<td>184/114</td>
<td>Dyazide, 1 dose daily; nadolol, 80 mg/d; guanadrel, 10 mg bid; captopril, 25 mg tid</td>
<td>146/92</td>
<td>Furosemide, 160 mg bid; clonidine, 0.2 mg bid; captopril, 50 mg bid</td>
</tr>
<tr>
<td>3</td>
<td>142/88</td>
<td>Furosemide, 80/40 mg/d; labetalol, 600 mg bid; captopril, 50 mg tid; minoxidil, 10 mg bid</td>
<td>120/80</td>
<td>Furosemide, 200 mg bid; aldactone, 25 mg bid</td>
</tr>
<tr>
<td>4</td>
<td>182/106</td>
<td>Bumetinide, 1 mg bid; clonidine, 0.2-mg patch weekly</td>
<td>134/90</td>
<td>Furosemide, 80 mg bid; enalapril, 10 mg/d; clonidine, 0.1 mg bid</td>
</tr>
<tr>
<td>5</td>
<td>170/110</td>
<td>Dyazide, 1 dose daily; prazocin, 3 mg tid; captopril, 100 mg tid; metoprolol, 100 mg/d</td>
<td>122/78</td>
<td>Furosemide, 160 mg bid; captopril, 100 mg bid; metoprolol, 100 mg/d</td>
</tr>
</tbody>
</table>
Prevalence

• Prevalence is unknown, but observational and clinical trials suggest it is a common clinical problem.
• In a recent analysis of National Health and Nutrition Examination Survey (NHANES) participants being treated for hypertension, only 53% were controlled to <140/90 mm Hg. ¹
• Of NHANES participants with CKD, only 37% were controlled to <130/80 mm Hg² and only 25% of diabetic participants were controlled to <130/85 mm Hg.¹
• In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) after approximately 5 years of follow-up, 27% of participants were on 3 or more medications.³

In General Population - Low

In Specialized Clinics - 15%

In Clinical Trials* - 30%

*ALLHAT, CONVINCE, LIFE, INSIGHT
Patient Characteristics Associated with Resistant Hypertension

- High baseline blood pressure
- Older age
- Obesity
- Excessive dietary salt ingestion
- Chronic kidney disease
- Diabetes
- Left ventricular hypertrophy
- Female gender
Lifestyle Factors Contributing to Resistant Hypertension

- Obesity or overweight
- High salt diet
- Physical inactivity
- Ingestion of low-fiber, high-fat diet
- Heavy alcohol ingestion
Causes of Resistance to Hypertension Treatment

• Poor adherence with prescribed medications
• Inaccurate blood pressure measurement
• White coat hypertension & Pseudohypertension
• Secondary causes of HTN & interfering substance
The Importance of Adherence

- Only 1/2 to 2/3 of patients take at least 75% of prescribed antihypertensive medicines
  - of those taking < 75%, only 37% achieved BP goal
  - of those taking >= 75%, 81% achieved goal
Techniques to Improve Adherence

• Education of the patient
  – Increases awareness but less effect on behavior
• Minimize the number of pills
  – Combination pills (ACEi/diuretic, ARB/diuretic, ARB/Ca-blocker, etc.)
• Minimize the frequency
• Increase the frequency of visits
  – Use of care managers
Causes of Resistance to Hypertension Treatment

- Poor adherence with prescribed medications
- Inaccurate blood pressure measurement
- White coat hypertension & Pseudohypertension
- Secondary causes of HTN & interfering substance
Accurate Reading of Blood Pressure

- Cuff bladder encircle ≥80% pts arm
- Sphygmomanometer
- Deflate 2-3mm per second
- Siting comfortably
- Back supported
- Legs uncrossed
- Upper arm bared
- Cuff bladder at heart level

SBP INACCURATELY HIGH IF: patient is supine, crossed legs, cuff below the heart, arm unsupported, undersized cuff.

AHA guidelines
Causes of Resistance to Hypertension Treatment

• Poor adherence with prescribed medications

• Inaccurate blood pressure measurement

• White coat hypertension & Pseudohypertension

• Secondary causes of HTN & interfering substance
White Coat Hypertension

• 20-30% of Apparently Resistant Hypertension may be due to “White-Coat Hypertension”

• Patients with WCH have an increased risk of CV events and often have some degree of end organ damage

• Use home or ambulatory monitoring to sort out
### TABLE 7. Clinical indications for out-of-office blood pressure measurement for diagnostic purposes

<table>
<thead>
<tr>
<th>Clinical indications for HBPM or ABPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Suspicion of white-coat hypertension</td>
</tr>
<tr>
<td>- Grade I hypertension in the office</td>
</tr>
<tr>
<td>- High office BP in individuals without asymptomatic organ damage and at low total CV risk</td>
</tr>
<tr>
<td>• Suspicion of masked hypertension</td>
</tr>
<tr>
<td>- High normal BP in the office</td>
</tr>
<tr>
<td>- Normal office BP in individuals with asymptomatic organ damage or at high total CV risk</td>
</tr>
<tr>
<td>• Identification of white-coat effect in hypertensive patients</td>
</tr>
<tr>
<td>• Considerable variability of office BP over the same or different visits</td>
</tr>
<tr>
<td>• Autonomic, postural, post-prandial, siesta- and drug-induced hypotension</td>
</tr>
<tr>
<td>• Elevated office BP or suspected pre-eclampsia in pregnant women</td>
</tr>
<tr>
<td>• Identification of true and false resistant hypertension</td>
</tr>
</tbody>
</table>
Home and Ambulatory BP Monitoring (ABPM)

Often lower than office readings

### TABLE 6. Definitions of hypertension by office and out-of-office blood pressure levels

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office BP</td>
<td>⩾140</td>
<td>and/or ⩾90</td>
</tr>
<tr>
<td>Ambulatory BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime (or awake)</td>
<td>⩾135</td>
<td>and/or ⩾85</td>
</tr>
<tr>
<td>Nighttime (or asleep)</td>
<td>⩾120</td>
<td>and/or ⩾70</td>
</tr>
<tr>
<td>24-h</td>
<td>⩾130</td>
<td>and/or ⩾80</td>
</tr>
<tr>
<td>Home BP</td>
<td>⩾135</td>
<td>and/or ⩾85</td>
</tr>
</tbody>
</table>

BP, blood pressure.
Pseudohypertension

- Osler’s Maneuver (the radial artery remains palpable due to calcification and thickening despite inflation of cuff above systolic pressure)
  - Poorly reproducible
- “Dinamap”-like devices may be more accurate in this setting
- Direct Intra-arterial measurement is the only definitive way to establish the diagnosis, but this is uncommonly done
Causes of Resistance to Hypertension Treatment

• Poor adherence with prescribed medications

• Inaccurate blood pressure measurement

• White coat hypertension & Pseudohypertension

• Secondary causes of HTN & interfering substance
Secondary Causes of Resistant Hypertension

Common

• Obstructive sleep apnea

• Renal parenchymal disease

• Primary aldosteronism

• Renal artery stenosis
Secondary Causes of Resistant Hypertension

Uncommon

• Pheochromocytoma
• Cushing’s disease
• Hyperparathyroidism
• Aortic coarctation
• Intracranial tumor
Primary Aldosteronism and Diabetes

• Type 2 diabetic patients are frequently affected by hypertension, and approximately 50–75% fail to achieve satisfactory blood pressure control. This is one cause of the high incidence of cardiovascular complications, such as heart failure, stroke, and kidney disease.

• A close relationship between aldosterone and insulin resistance has been demonstrated: hyperinsulinemia stimulates the production of aldosterone, and an excess of mineralocorticoids can cause the resistant hypertension observed in diabetic patients.
Type 2 diabetic patients with resistant hypertension should be screened for primary aldosteronism

J. J. Mukherjee, C. M. Khoo, A. C. Thai, S. B. Chionh, Lim Pin, K. O. Lee

Abstract
BP control in diabetic patients is often poor. The contribution of secondary hypertension due to undiagnosed PA in hypertensive type 2 diabetic patients is not well studied. We prospectively screened 100 consecutive Asian type 2 diabetic patients with difficult-to-control or resistant hypertension for PA. PAC (pmol/L) to PRA (ng/mL/h) ratio was measured; those with PAC-to-PRA ratio >550 (corresponding PAC >415) underwent intravenous 0.9% SLT. Patients with PAC ≥140 following SLT had CT adrenals and bilateral AVS. Thirteen patients (13%) were confirmed to have PA, and all had resistant hypertension. Eight had a surgically correctable form of PA. Patients with PA had higher mean (SD) systolic [159.0 (10.6) vs. 146.0 (10.7) mmHg, p=0.001] and diastolic BP [94.6 (6.0) vs. 87.6 (5.9) mmHg, p=0.001], lower serum potassium [3.5 (0.6) vs. 4.3 (0.5) mmol/L, p=0.001], and higher PAC [679.3 (291.0) vs. 239.5 (169.4) pmol/L, p=0.001]. Identification and institution of definitive treatment for PA resulted in better BP control and in a reduction in the use of antihypertensive medications. Our findings demonstrate a high prevalence of PA in type 2 diabetic patients with resistant hypertension. Systematic screening for PA in this select group is recommended, as targeted treatment improves BP control.
Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial

Christina S. Oxlund, Jan E. Henriksen, Lise Tarnow, Karoline Schousboe, Jeppe Gram, and Ib A. Jacobsen

Background: The increased risk of cardiovascular morbidity and mortality associated with arterial hypertension is particularly pronounced in patients with type 2 diabetes mellitus. Blood pressure control is, therefore, decisively important but often not sufficiently achieved.

Objective: The primary objective of this study was to evaluate the antihypertensive effect of low dose spironolactone added to triple therapy for resistant hypertension in patients with type 2 diabetes measured by ambulatory monitoring. Secondary objectives were to evaluate the effects on glycaemic control and urinary albumin excretion as well as adverse effects.

Methods: In a multicentre, double-blind, randomized, placebo-controlled study 119 patients with blood pressure at or above 130/80 mmHg despite triple antihypertensive therapy were included. One tablet of 25 mg spironolactone or placebo was added to previous treatment and increased to two if blood pressure below 130/80 mmHg was not achieved after 4 weeks. Blood pressure was measured by ambulatory monitoring at baseline and after 16 weeks.

Results: The study was completed by 112 patients, 57 randomized to spironolactone and 55 to placebo. Average daytime placebo-corrected blood pressure was reduced by 8.9 (4.7–13.2)/3.7 (1.5–5.8) mmHg. Also office blood pressure, night-time, 24-h and pulse pressures were reduced significantly. Urinary albumin/creatinine ratio was significantly reduced in the spironolactone group. Glycaemic control remained unchanged. Hyperkalemia was the most frequent adverse event leading to dose reduction in three cases and discontinuation in one, whereas gynaecomastia was not reported.

Conclusion: Low dose spironolactone exerts significant BP and urinary albumin creatinine ratio lowering effects in high-risk patients with resistant hypertension and type 2 diabetes mellitus.
Substances that Can Interfere with Blood Pressure Control

- **Non-Narcotic Analgesics**
  - Non-steroidal anti-inflammatory agents including aspirin
  - Selective COX-2 inhibitors

- **Sympathomimetic agents**
  - decongestants
  - diet pills
  - cocaine

- **Stimulants**
  - methylphenidate
  - dexamethasone
  - dextroamphetamine
  - amphetamine, methamphetamine
  - modafinil
Substances that Can Interfere with Blood Pressure Control

- Alcohol
- Oral contraceptives
- Cyclosporine
- Erythropoietin
- Natural licorice
- Herbal compounds - ephedra - ma huang
Exclude pseudoresistance

Identify and reverse contributing factor

Discontinue and/or minimize interfering substance

Screen of secondary causes of Hypertension

Diagnosis of true resistant Hypertension
Treatment of Resistant Hypertension

Non-Pharmacologic Recommendations

- Weight loss
- Regular exercise (at least 30 min most days of the week)
- Low dietary salt ingestion (<100 mEq sodium/24-hr)
- Moderate alcohol ingestion (no more than 2 drinks per day for most men and 1 drink per day for women or lighter weight persons)
- Ingestion of low-fat, high-fiber diet
- Treat obstructive sleep apnea if present
Treatment of Resistant Hypertension

Pharmacologic Recommendations

• Withdrawal or down titration of interfering substances as possible

• Use of a long-acting thiazide diuretic, preferably chlorthalidone

• Combine agents with different mechanisms of action

• Recommended triple regimen of
  - ACE inhibitor or ARB
  - Calcium channel blocker
  - Thiazide diuretic

_Hypertension_. 2008 Jun;51(6):1403-19
Treatment of Resistant Hypertension

- Consider addition of mineralocorticoid receptor antagonist

- Use of loop diuretic may be necessary in patients with CKD (creatinine clearance <30 mL/min)
Non Pharmacological Approaches

The following procedures are invasive and irreversible

• Implantable pulse generators – perivascular carotid sinus leads to be surgically implanted

• Renal Denervation
Renal Sympathetic Activation: Efferent Nerves
Kidney as Recipient of Sympathetic Signals

- Renin Release → RAAS activation
- Sodium Retention
- Renal Blood Flow

Renal Efferent Nerves
Renal Sympathetic Activation: Afferent Nerves
Kidney as Origin of Central Sympathetic Drive

- Vasoconstriction
- Atherosclerosis
- Insulin Resistance
- Sleep Disturbances
- Renal Afferent Nerves
  - ↑ Renin Release → RAAS activation
  - ↑ Sodium Retention
  - ↓ Renal Blood Flow
  - Hypertrophy
  - Arrhythmia
  - Oxygen Consumption
Kidneys, in response to ischemia, send afferent sympathetic signals to the brain that disinhibit the nuclei tractus solitarii (NTS), increasing sympathetic outflow.

The NTS in the brainstem control efferent sympathetic signals from the brain to various organs of the body. Sympathetic signals raise blood pressure by increasing the heart rate, constricting arteries, and, in the kidney, increasing renin release and sodium and fluid retention.

In the renal denervation procedure, a specially designed catheter is positioned in the renal artery, and radiofrequency energy is applied to the endoluminal surface.
Renal Nerve Anatomy

- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia
Renal Nerve Anatomy Allows a Catheter-Based Approach

- Renal artery access via standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF generator
  - Automated
  - Low power
  - Built-in safety algorithms
Initial Cohort – Reported in the *Lancet*, 2009:  
- First-in-man, non-randomized  
- Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)  
- 12-month data

**Expanded Cohort*** – This Report (Symplicity HTN-1):  
- Expanded cohort of patients (n=153)  
- 36-month follow-up

*Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)
Symplicity HTN-1: BP Reductions through 3 years

**BP change (mmHg)**

- **1 M** (n=143): -19
- **3 M** (n=148): -21
- **6 M** (n=144): -22
- **12 M** (n=130): -26
- **18 M** (n=107): -26
- **24 M** (n=59): -15
- **30 M** (n=24): -14
- **36 M** (n=24): -19

**P<0.01 for ∆ from BL for all time points**

*Systolic BP*

*Diastolic BP*

*Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)*
**Purpose:** To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial.

**Patients:** 106 patients randomized 1:1 to treatment with renal denervation vs. control.

**Clinical Sites:** 24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence).
Symplicity HTN-2 Trial

- Treatment-resistant HTN population
- BL OBP 178/97 mmHg
- 49 Renal Denervation, 51 Control
- Age 58 years
- BMI 31 kg/m²
- 40% with Diabetes
- eGFR 77*
- Avg # meds 5.2
- Renal Denervation and Control groups generally well-matched

Inclusion Criteria:
- Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)
- Stable drug regimen of 3+ more anti-HTN medications
- Age 18-85 years

Exclusion Criteria:
- Haemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- eGFR < 45 mL/min/1.73m² (MDRD formula)
- Type 1 diabetes mellitus
- Contraindication to MRI
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months

*MDRD, ml/min/1.73m²
Symplicity HTN-2: Patient disposition

Assessed for Eligibility (n=190)

Excluded During Screening, Prior to Randomisation (n=84)
- BP < 160 at Baseline Visit (after 2 weeks of medication compliance confirmation) (n=36; 19%)
- Ineligible anatomy (n=30; 16%)
- Declined participation (n=10; 5%)
- Other exclusion criteria discovered after consent (n=8; 4%)

Randomised (n=106)

Allocated to RDN
n=52 Treated
n=49 Analysable

Allocated to Control
n=54 Control
n=51 Analysable

Crossover
n=46

Per protocol, 6-mo Post-RDN (Crossover)
n=35

Not-per-protocol*, 6-mo Post-RDN (Crossover)
n=9

2 LTFU

* Crossed-over with ineligible BP (<160 mmHg)

Screening

6-month Primary End-Point

12-month Post-Randomisation

12-month post-RDN
n=47
### Primary Endpoint:  
- **84%** of RDN patients had ≥10 mmHg reduction in SBP  
- **10%** of RDN patients had no reduction in SBP

### Latest Follow-up:  
- **Control crossover** (n = 35): -24/-8 mmHg (Analysis is on patients with SBP ≥ 160 mmHg at 6 M)

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**Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Esler, M.)**
Symplicity HTN-2: Lancet Conclusions

• Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, resulted in significant reductions in BP.

• The magnitude of BP reduction can be predicted to affect the development of hypertension-related diseases and mortality.

• The technique was applied without major complications.

• This therapeutic innovation, based on the described neural pathophysiology of essential hypertension, affirms the crucial relevance of renal nerves in the maintenance of BP in patients with hypertension.

• Catheter-based renal denervation is beneficial for patients with treatment-resistant essential hypertension.

Symplicity 3 HTN Trial

- 535 patients with resistant HTN in 87 US medical centers
- Intervention: Radiofrequency ablation vs sham control.
- Randomization: 2/3 intervention, 1/3 Sham
- Endpoints: safety and efficacy at 6 months
- Results: did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control.

Figure 1. Primary Efficacy End Point.
A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The I bars indicate standard deviations.
### Therapeutic strategies in patients with resistant hypertension

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
<th>Ref.(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>I</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin should be considered, if no contraindication exists.</td>
<td>II(^a)</td>
<td>B</td>
<td>604, 606, 607, 608</td>
</tr>
<tr>
<td>In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation may be considered.</td>
<td>II(^b)</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>
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.

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.

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

\(^{a}\)Class of recommendation.

\(^{b}\)Level of evidence.

\(^{c}\)Reference(s) supporting levels of evidence.
Conclusions

• Patients with RHTN should be screened for reversible causes of hypertension, such as renal artery stenosis, primary aldosteronism, and obstructive sleep apnea. Patients should be counseled about potentially modifiable lifestyle factors, such as sodium intake, weight loss, diet, and exercise.

• Combination therapy with different antihypertensive classes is crucial in the effective treatment of RHTN. This should ideally include a thiazide-like diuretic.

• The role of aldosterone excess in the pathogenesis of RHTN is being increasingly recognized, and addition of a mineralocorticoid receptor antagonist as a fourth-line antihypertensive agent is recommended.

• Overall, renal denervation and carotid baroreceptor stimulation should be restricted to resistant hypertensive patients at particularly high risk, after fully documenting the inefficacy of additional antihypertensive drugs to achieve BP control.