CONGRESSO
INTERREGIONALE
SIIA
PIEMONTE - LIGURIA - VALLE D'AOSTA

Torino, 09 ottobre 2021

IPERTENSIONE ARTERIOSA RESISTENTE IN PAZIENTE CON INTOLLERANZE A FARMACI ANTI-IPERTENSIVI: TRATTAMENTO CON DENERVAZIONE RENALE

Chiara Lopez MD

Società Italiana dell'Ipertensione Arteriosa
Lega Italiana contro l'Ipertensione Arteriosa
Sezione interregionale Piemonte-Liguria-Valle d'Aosta

III SESSIONE

IPERTENSIONE DI DIFFICILE CONTROLLO
Moderatori: G. Antonucci (Genova), T. Marchese (Chieri)

15.00 Ipertensione e uso di FANS ***E. Delsignore (Vercelli)***

15.12 Ipertensione arteriosa resistente in paziente con intolleranze a farmaci antiipertensivi: trattamento con denervazione renale ***C. Lopez (Torino)***

15.24 Non farsi ingannare dalle apparenze ***A. Piazza (Genova)***

15.36 Ipertensione Arteriosa e ponatinib ***R. Galliano (Cuneo)***

15.48 Ipertensione arteriosa in corso di ESA ***A. Lisi (Aosta)***

16.00 Discussione

M.C. 56 anni ♂

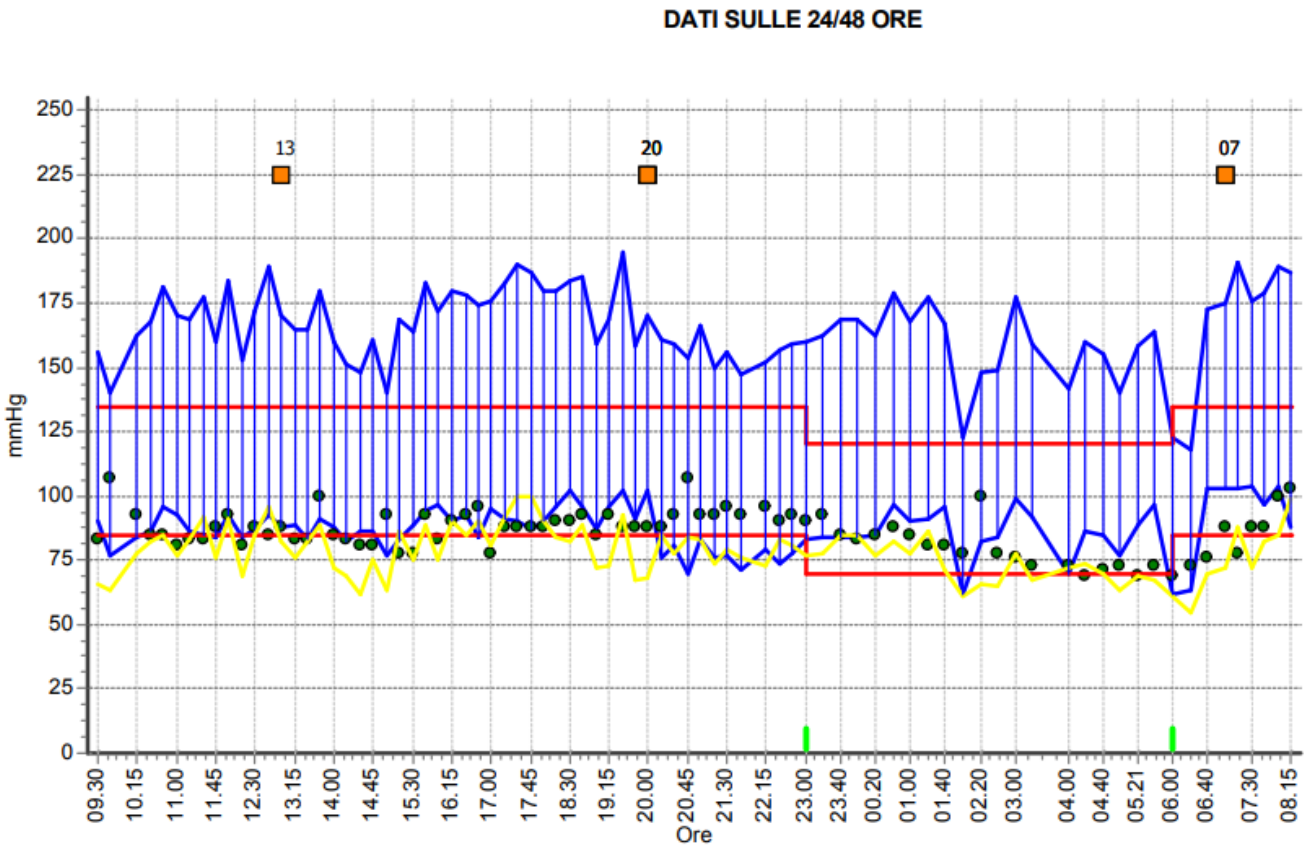
Inviato c/o Nostro centro per «**ipertensione arteriosa di difficile controllo**». Per quanto riguarda le complicanze si segnalano **cardiopatia ipertensiva** (Ecocardiogramma: FE 62% lieve IVSX, pattern diastolico di primo grado, dilatazione Asx), **nefropatia ipertensiva** (creatinina 1.30 mg/dl con macroalbuminuria positiva) e **vasculopatia TSA subclinica** (IMT> 0.9 mm a livello delle CCA bilaterlmente).

In trattamento con Doxazosina 4 mg 1cp x2/die, Ramipril/HCT 5/25 mg 1cp/die, Lercanidipina 20 mg 1cp/die.

Familiarità positiva per ipertensione e CVD non precoci. Ex fumatore.

In APR:

- Policitemia vera Jak2+;
- Steatosi epatica.



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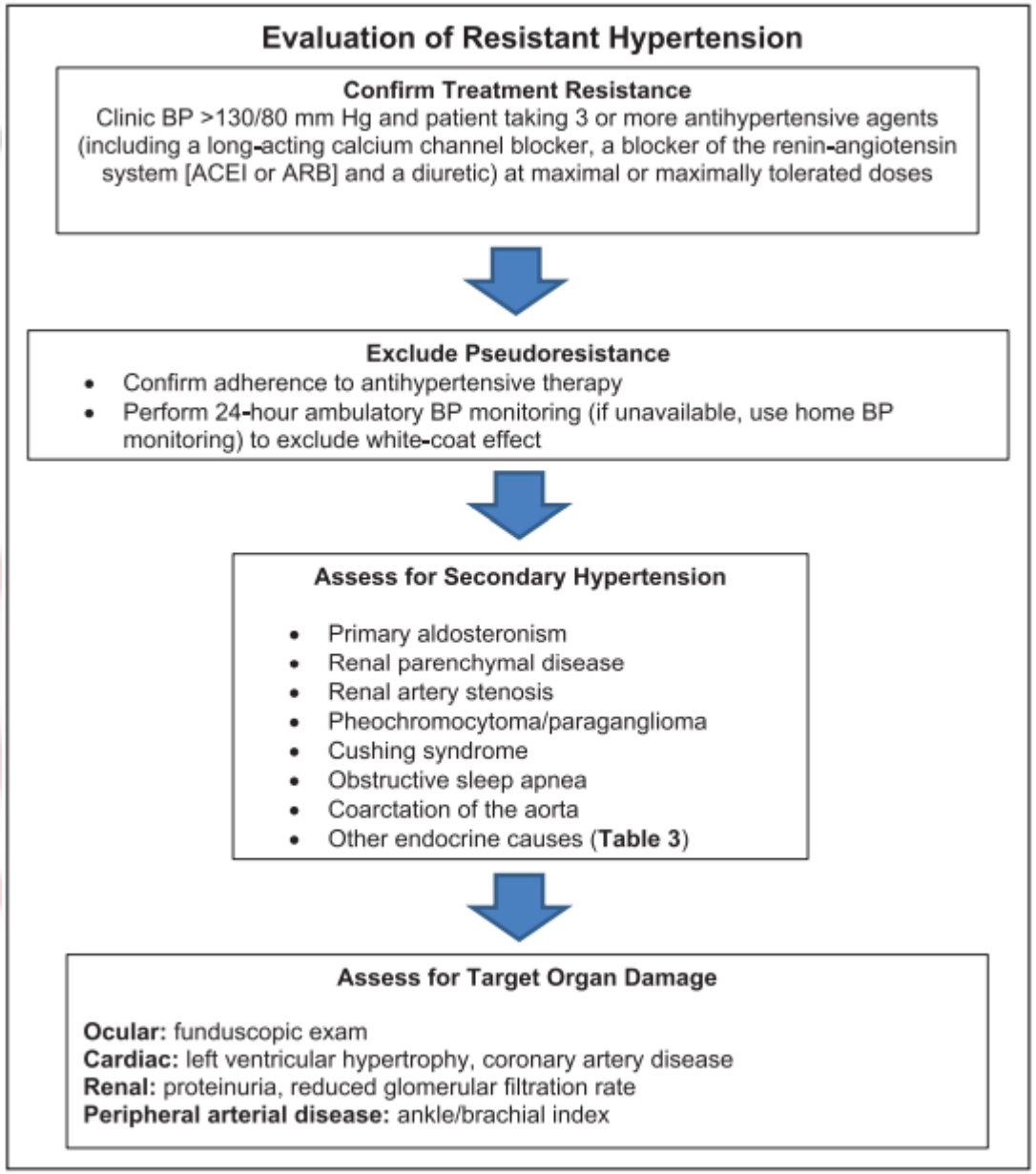
Iposodiemia in corso di HCT

Ipertensione arteriosa etichettabile come RESISTENTE/PSEUDORESISTENTE

Management dell'ipertensione resistente



Carey RM, Calhoun DA, Bakris GL et al. Resistant hypertension: detection, evaluation and management. A scientific statement from American Heart Association (AHA). Hypertension 2018;

Management dell'ipertensione resistente

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8.1.2 Pseudo-resistant hypertension

Several possible causes of pseudo-resistant hypertension should be evaluated and ruled out before concluding that the patient has resistant hypertension:

(1) **Poor adherence to prescribed medicines** is a frequent cause of pseudo-resistant hypertension, occurring in ≤50% of patients assessed by therapeutic drug monitoring, and is directly related to the number of tablets prescribed[315] (see section 10).

(2) **White-coat phenomenon** (in which office BP is elevated but BP is controlled at ABPM or HBPM) is not uncommon in these patients, hence the recommendation to confirm office hypertension with ABPM or HBPM before confirming the diagnosis of resistant hypertension.

(3) **Poor office BP measurement technique**, including the use of cuffs that are too small relative to the arm circumference, can result in a spurious elevation of BP.

(4) **Marked brachial artery calcification**, especially in older patients with heavily calcified arteries.

(5) **Clinician inertia**, resulting in inadequate doses or irrational combinations of BP-lowering drug therapies.

Other causes of resistant hypertension

(1) Lifestyle factors, such as obesity or large gains in weight, excessive alcohol consumption, and high sodium intake.

(2) Intake of vasopressor or sodium-retaining substances, drugs prescribed for conditions other than hypertension, some herbal remedies, or recreational drug use (cocaine, anabolic steroids, etc.) (see *Table 24*).

(3) Obstructive sleep apnoea (usually, but not invariably, associated with obesity).

(4) Undetected secondary forms of hypertension (see *section 8.2*).

(5) Advanced HMOD, particularly CKD or large-artery stiffening.

Resistant hypertension is associated with older age (especially >75 years), male sex, black African origin, higher initial BP at diagnosis of hypertension, highest BP ever reached during the patient's lifetime, frequent outpatient visits, obesity, diabetes, atherosclerotic disease and HMOD, CKD, and a Framingham 10 year coronary risk score >20%.[383,384]

Cause di pseudoresistenza

Williams B, Mancia G, Spiering W et al. 2018 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). Blood Pressure 2018

TENTATIVO DI OTTIMIZZAZIONE TERAPEUTICA:

- STOP DOXAZOSINA, RAMIPRIL/HCT E LERCANIDIPINA
- AVVIA CLONIDINA TTS2 1 CEROTTO/SETT;
- AVVIA RAMIPRIL/AMLODIPINA 10/10 MG 1 CP E ATENOLOLO/CLORTALIDONE 100/25 MG 1CP/DIE;
- AVVIA SPIRONOLATTONE 25 MG 1CP/DIE.

EVIDENZA DI IPOSODIEMIA ANCHE CON CLORTALIDONE E DI IPERKALIEMIA CON SPIRONOLATTONE A BASSE DOSI

TD: Atenololo 100 mg 1cp, Ramipril/Amlodipina 10/10 mg 1cp, Torasemide 10 mg 2cp, Isosorbide mononitrato 20 mg 1cp x3, Clonidina TTS 2 1 cerotto/sett, Aliskiren 300 mg 1cp

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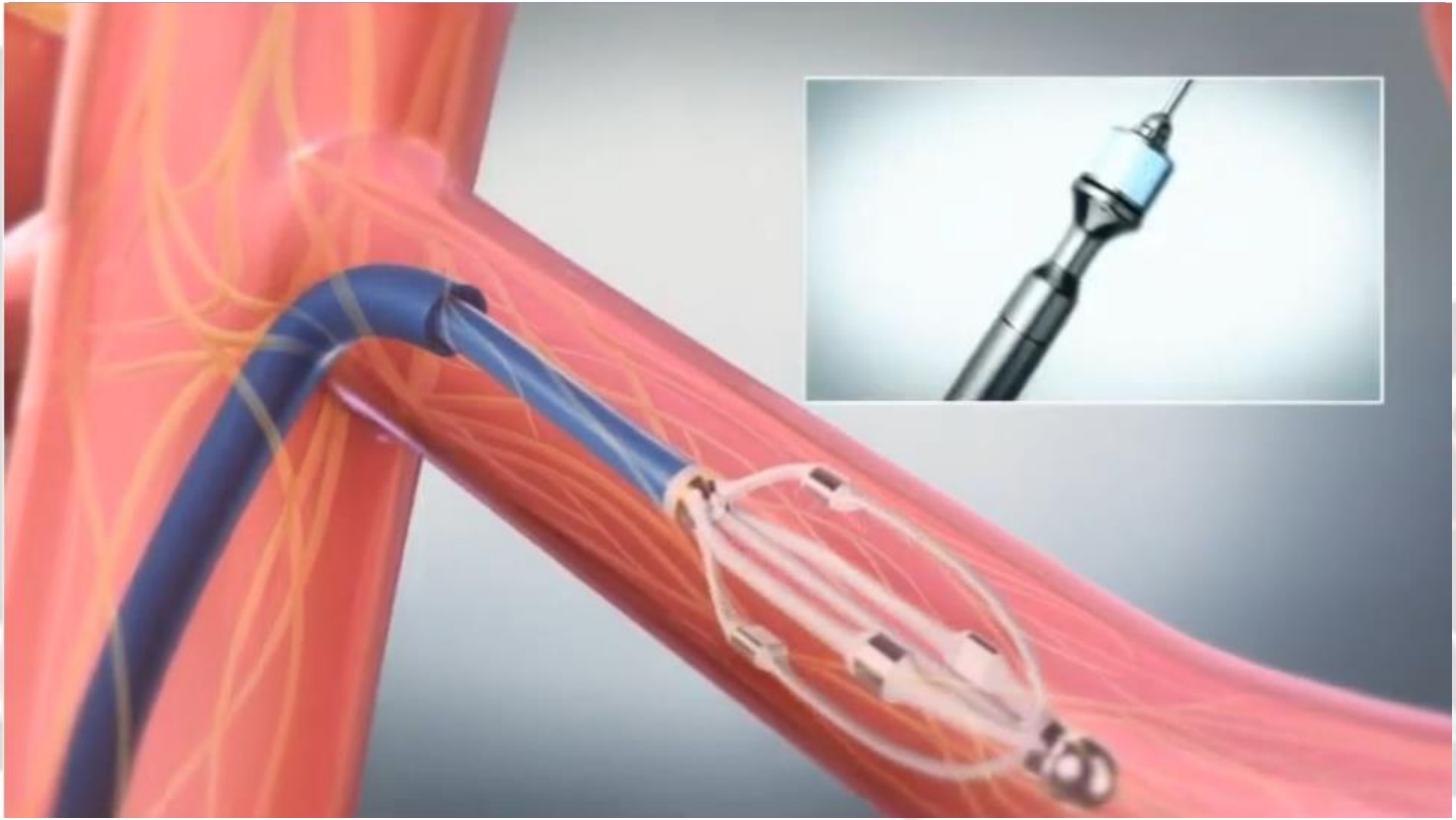
IPERTENSIONE ARTERIOSA REFRATTARIA ESSENZIALE PLURICOMPLICATA:

mancato raggiungimento del target pressorio in un soggetto iperteso, nonostante l'utilizzo corrente di 5 o più farmaci anti-ipertensivi di differenti classi, alla massima dose consentita o tollerata, incluso un diuretico e comunemente un ACE-inibitore o ARBs e un CCB.

Unger T, Borghi C, Charchar F et al. 2020 International Society of Hypertension (ISH) global hypertension practice guidelines. Journal of Hypertension 2020



IL PRIMO TRIAL PROSPETTICO RANDOMIZZATO CONTROLLATO SULLA TERAPIA CON DENERVAZIONE RENALE

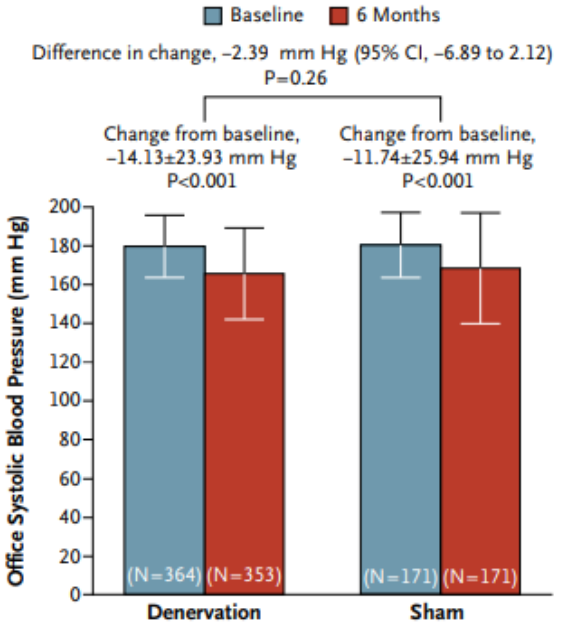


Figure 1. Primary Efficacy End Point.

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.

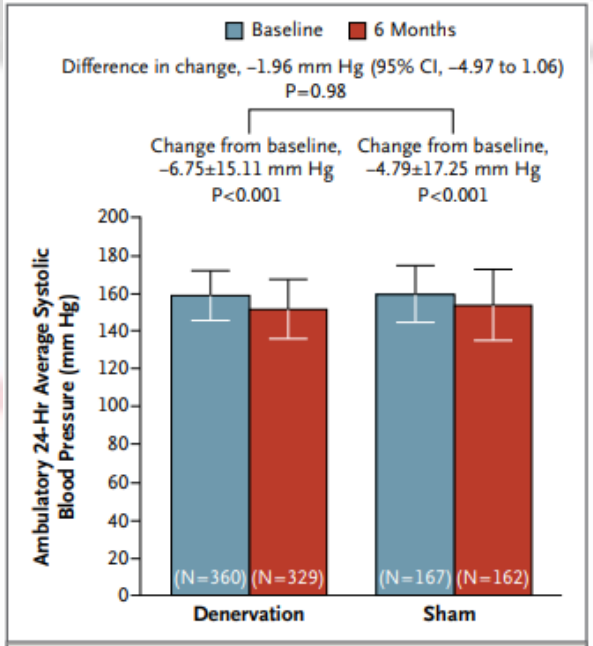


Figure 2. Secondary Efficacy End Point.

A significant change from baseline to 6 months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2 mm Hg. The I bars indicate standard deviations.

The first sham-controlled prospective randomized study in the field of renal ablation therapy, SYMPLICITY HTN-3, showed little to no effect of renal denervation therapy in a severely drug treatment–resistant population.[404] The failure of this most rigorously designed randomized sham-control study to meet the efficacy end points raised several methodological concerns, including alterations in patient behavior in adherence to their multidrug pharmacological regimens and inadequate denervation resulting from technical failure of the catheter, the interventional proceduralist, or both.[405]

Bhatt, DL, Kandzari, DE et al; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370:1393–1401

DENERHTN TRIAL

The Renal Denervation for Hypertension (DENERHTN) trial was a prospective, open-label randomised controlled trial with blinded endpoint evaluation in patients with resistant hypertension, done in 15 French tertiary care centres specialised in hypertension management. Eligible patients aged 18–75 years received indapamide 1·5 mg, ramipril 10 mg (or irbesartan 300 mg), and amlodipine 10 mg daily for 4 weeks to confirm treatment resistance by ambulatory blood pressure monitoring before randomisation. Patients were then randomly assigned (1:1) to receive either renal denervation plus an SSAHT regimen (renal denervation group) or the same SSAHT alone (control group). The randomisation sequence was generated by computer, and stratified by centres. For SSAHT, after randomisation, spironolactone 25 mg per day, bisoprolol 10 mg per day, prazosin 5 mg per day, and rilmenidine 1 mg per day were sequentially added from months two to five in both groups if home blood pressure was more than or equal to 135/85 mm Hg. The primary endpoint was the mean change in daytime systolic blood pressure from baseline to 6 months as assessed by ambulatory blood pressure monitoring. The primary endpoint was analysed blindly. The safety outcomes were the incidence of acute adverse events of the renal denervation procedure and the change in estimated glomerular filtration rate from baseline to 6 months. This trial is registered with ClinicalTrials.gov, number NCT01570777.

Findings

Between May 22, 2012, and Oct 14, 2013, 1416 patients were screened for eligibility, 106 of those were randomly assigned to treatment (53 patients in each group, intention-to-treat population) and 101 analysed because of patients with missing endpoints (48 in the renal denervation group, 53 in the control group, modified intention-to-treat population). The mean change in daytime ambulatory systolic blood pressure at 6 months was −15·8 mm Hg (95% CI −19·7 to −11·9) in the renal denervation group and −9·9 mm Hg (−13·6 to −6·2) in the group receiving SSAHT alone, a baseline-adjusted difference of −5·9 mm Hg (−11·3 to −0·5; p=0·0329). The number of antihypertensive drugs and drug-adherence at 6 months were similar between the two groups. Three minor renal denervation-related adverse events were noted (lumbar pain in two patients and mild groin haematoma in one patient).

Azizi, M, Sapoval, M, Gosse et al.; Renal Denervation for Hypertension (DENERHTN) investigators. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. Lancet. 2015

SPYRAL HTN-OFF MED TRIAL

Methods: SPYRAL HTN-OFF MED was a multicentre, international, single-blind, randomised, sham-controlled, proof-of-concept trial. Patients were enrolled at 21 centres in the USA, Europe, Japan, and Australia. Eligible patients were drug-naive or discontinued their antihypertensive medications. Patients with an office systolic blood pressure (SBP) of 150 mm Hg or greater and less than 180 mm Hg, office diastolic blood pressure (DBP) of 90 mm Hg or greater, and a mean 24-h ambulatory SBP of 140 mm Hg or greater and less than 170 mm Hg at second screening underwent renal angiography and were randomly assigned to renal denervation or sham control. Patients, caregivers, and those assessing blood pressure were blinded to randomisation assignments. The primary endpoint, change in 24-h blood pressure at 3 months, was compared between groups. Drug surveillance was done to ensure patient compliance with absence of antihypertensive medication. The primary analysis was done in the intention-to-treat population. Safety events were assessed at 3 months. This study is registered with ClinicalTrials.gov, number NCT02439749.

Findings: Between June 25, 2015, and Jan 30, 2017, 353 patients were screened. 80 patients were randomly assigned to renal denervation (n=38) or sham control (n=42) and followed up for 3 months. Office and 24-h ambulatory blood pressure decreased significantly from baseline to 3 months in the renal denervation group: 24-h SBP -5·5 mm Hg (95% CI -9·1 to -2·0; p=0·0031), 24-h DBP -4·8 mm Hg (-7·0 to -2·6; p<0·0001), office SBP -10·0 mm Hg (-15·1 to -4·9; p=0·0004), and office DBP -5·3 mm Hg (-7·8 to -2·7; p=0·0002). No significant changes were seen in the sham-control group: 24-h SBP -0·5 mm Hg (95% CI -3·9 to 2·9; p=0·7644), 24-h DBP -0·4 mm Hg (-2·2 to 1·4; p=0·6448), office SBP -2·3 mm Hg (-6·1 to 1·6; p=0·2381), and office DBP -0·3 mm Hg (-2·9 to 2·2; p=0·8052). The mean difference between the groups favoured renal denervation for 3-month change in both office and 24-h blood pressure from baseline: 24-h SBP -5·0 mm Hg (95% CI -9·9 to -0·2; p=0·0414), 24-h DBP -4·4 mm Hg (-7·2 to -1·6; p=0·0024), office SBP -7·7 mm Hg (-14·0 to -1·5; p=0·0155), and office DBP -4·9 mm Hg (-8·5 to -1·4; p=0·0077). Baseline-adjusted analyses showed similar findings. There were no major adverse events in either group.

Townsend RR, Mahfoud F, et al; SPYRAL HTN-OFF MED Trial Investigators. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial.Lancet. 2017

LA POSIZIONE DELLE LINEE GUIDA

Device-based therapies for hypertension

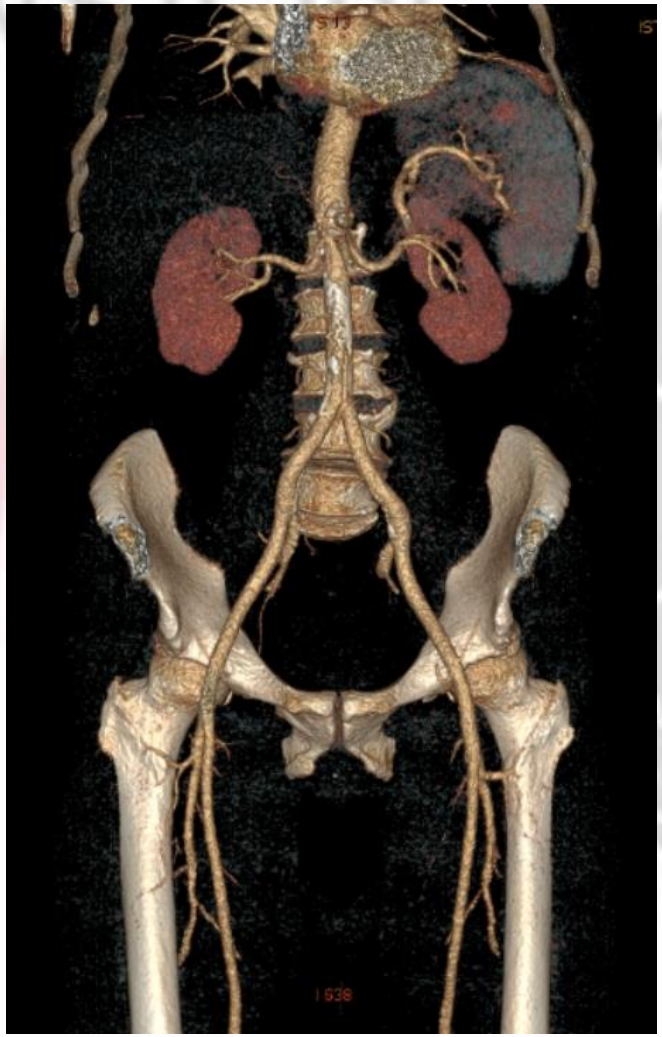
Recommendation	Class[a]	Level[b]
Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.[367,368]	III	B

RCT = randomized controlled trial.
[a]Class of recommendation.
[b]Level of evidence.

Williams B, Mancia G, Spiering W et al. 2018 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). Blood Pressure 2018

TORNANDO AL CASO CLINICO….

PREVIA VALUTAZIONE DELLA MORFOLOGIA RENALE, MEDIANTE ANGIOTC, IN DATA 29/06/2021 IL PAZIENTE E’ STATO SOTTOPOSTO A PROCEDURA DI DENERVAZIONE RENALE PERCUTANEA, SENZA COMPLICANZE.



A 3 MESI DALLA PROCEDURA INVASIVA….

PER POTER DEFINIRE L’OUTCOME DEL TRATTAMENTO, SARA’ NECESSARIO UN TEMPO DI FOLLOW-UP MAGGIORMENTE PROLUNGATO

TAKE HOME MESSAGES 1

- **L'ipertensione arteriosa resistente** non è una condizione così rara, **la sua prevalenza va dal 12% al 18% dei soggetti adulti ipertesi in trattamento** e aumenta in alcune sottocategorie di pazienti, come in quelli con IRC;
- **L'ipertensione arteriosa refrattaria** è una condizione che interessa circa **il 10% degli ipertesi resistenti;**
- Prima di etichettare un paziente come iperteso resistente risulta fondamentale:
  - confermare la resistenza al trattamento mediante esecuzione di ABPM o HBPM;
  - **escludere le cause di pseudoresistenza**, in particolare l'abuso di sale con la dieta e la mancata aderenza alla terapia prescritta;
  - **escludere le secondarietà tensive.**

Carey RM, Calhoun DA, Bakris GL et al. Resistant hypertension: detection, evaluation and management. A scientific statement from American Heart Association (AHA). Hypertension 2018;

TAKE HOME MESSAGES 2

- Dopo aver confermato la diagnosi di ipertensione arteriosa resistente essenziale è **importante l'ottimizzazione della terapia anti-ipertensiva** nel tentativo di raggiungere il target pressorio;
- In caso di ipertensione arteriosa resistente non compensata/refrattaria, specie in presenza di danno d'organo ipertensione mediato**, si può valutare l'opportunità di sottoporre il paziente ad un trattamento invasivo dell'ipertensione**, come la denervazione renale, preferibilmente **nell'ambito di un trial clinico sperimentale**;
- Pertanto tali trattamenti possono rappresentare **una valida strategia terapeutica, con buoni risultati nel breve termine**, in accordo con gli outcome dei più recenti trial sperimentali in merito;
- Tuttavia, per poterne estendere l'indicazione **mancano ancora i dati di sicurezza ed efficacia a lungo termine.**

Carey RM, Calhoun DA, Bakris GL et al. Resistant hypertension: detection, evaluation and management. A scientific statement from American Heart Association (AHA). Hypertension 2018;

Williams B, Mancia G, Spiering W et al. 2018 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). Blood Pressure 2018

Chiara.lopez@unito.it