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CRITICAL ANALYSIS OF STUDIES THAT HAVE CHANGED RECENT CLINICAL PRACTICE: ARTERIAL HYPERTENSION

ANÁLISE CRÍTICA DOS ESTUDOS QUE MUDARAM A PRÁTICA CLÍNICA RECENTE: HIPERTENSÃO ARTERIAL

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ABSTRACT

The three studies that have had an important influence on the clinical practice of who works with arterial hypertension were the SIMPLICITY HTN-3, PATHWAY 2 and SPRINT studies. The SIMPLICITY HTN-3 study raised doubts around a procedure that was already being used in clinical practice, the denervation of the sympathetic renal nerve through radiofrequency wave ablation. It was the first study with a control group that did not show a difference between the specific blood pressure control outcomes in patients with resistant hypertension. Therefore, the Simplicity HTN 3 Study modified clinical practice in the sense that all hypertension guidelines are unanimous in stating that currently such a procedure should be reserved for specific clinical investigation laboratories researching the method and should not be used as an established treatment option. The PATHWAY2 study consolidated the use of the mineralocorticoid receptor blocker (spironolactone) as the fourth drug in the resistant arterial hypertension treatment flowchart. The results were so impactful that the European guideline for arterial hypertension changed its orientation around the pharmacological sequence of resistant hypertension treatment substantially. Finally, the SPRINT study demonstrated the need for intervention in patients with arterial hypertension with pressure values below 140/90 mmHg, depending on the amount of additional cardiovascular risk in those patients. The results of the SPRINT study promoted changes to or inclusions of its data in various national and international guidelines, such as the Brazilian Society of Cardiology, the American Heart Association and the European Society of Cardiology.

Keywords: Antihypertensive Agentes; Hypertension; Evidence – Based Practice.

RESUMO

Os três estudos que tiveram importante influência na prática clínica de quem trabalha com hipertensão arterial foram os estudos SIMPLICITY HTN-3, PATHWAY 2 e SPRINT. O estudo SIMPLICITY HTN-3 pôs a dúvida um procedimento que já estava sendo utilizado na prática clínica, qual seja, denervação do nervo simpático renal através de ablação por ondas de radiofrequência. Foi o primeiro estudos com grupo controle que não mostrou diferença entre os desfechos específicos de controle da pressão arterial em pacientes com hipertensão resistente. Portanto, o estudo SIMPLICITY HTN 3 modificou a prática clínica no sentido de que todas as diretrizes de hipertensão são unânimes em afirmar que tal procedimento atualmente deva ser reservado para laboratórios específicos de investigação clínica do método e não deve ser empregado como opção estabelecida de tratamento. O estudo PATHWAY 2 consolida o uso do bloqueador de receptor de mineralocorticoides (espironolactona) como o quarto medicamento no fluxograma de tratamento da hipertensão arterial resistente. Os resultados foram tão impactantes que a diretriz europeia de hipertensão arterial mudou substancialmente a orientação da sequência farmacológica do tratamento. Por fim, o estudo SPRINT demonstrou a necessidade de intervenção em pacientes com hipertensão arterial com valores pressóricos abaixo de 140/90 mmHg na dependência da quantidade de risco adicional dos pacientes. Os resultados do estudo SPRINT motivaram alterações ou inclusões de seus dados em várias diretrizes nacionais e internacionais, tais como Sociedade Brasileira de Cardiologia, American Heart Association e European Society of Cardiology.

Descritores: *Anti-Hipertensivos; Hipertensão; Prática Clínica Baseada em Evidênicas.*

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In arterial hypertension, some concepts are not well defined yet, requiring studies with better design for a more precise methodological configuration. Most guidelines generally recommend blood pressure targets lower than 140/90 mmHg, but intervention studies suggest that lower target values could benefit hypertension patient. SPRINT study contributed to a more evident concept regarding blood pressure goals. PATHWAY-2 study evaluated the use of the fourth drug in resistant hypertension. We have been using spironolactone for years following the blockade of the renin angiotensin aldosterone system associated with calcium channel and diuretic antagonists, but somewhat empirically, based more on case series and small studies. PATHWAY-2 study provided some evidence of the logical use of spironolactone in resistant hypertension contributing to the pathophysiological understanding of the process. Simplicity HTN-3 study was a milestone in understanding when renal denervation, a panacea after Simplicity 1 and 2, actually contributed to blood pressure reduction when there was true control. All three of these studies were important not only in changing clinical management but also contributing to new pathophysiological concepts of hypertension.

SPRINT" STUDY

SPRINT (Systolic Blood Pressure Intervention Trial),[1] study sponsored by the National Heart, Lang, and Blood Institute (NHLBI), is an open-label, controlled clinical trial in which 9361 hypertensive patients in the United States were randomized, with recruitment between November 2001 and March 2013, to assess whether a treatment goal for systolic blood pressure (SBP) less than 120 mmHg (intensive treatment - IT) would reduce clinical events more than a target for SBP less than 140 mmHg (standard treatment - ST) recommended in major international and national hypertension guidelines such as the European Society of Cardiology (ESC) / European Society of Hypertension (ESH)[2] and the American College of Cardiology (ACC) / American Heart Association (AHA)[3] and the Brazilian Society of Cardiology (Hypertension[4] and Cardiogeriatrics[5]).

At the recommendation of the Data and Safety Monitoring Committee, the study was discontinued early on August 20, 2015, after an average follow-up of 3.26 years (mean SBP of 121.5 mmHg in the IT group and 134.6 mmHg in the ST group), from an initial planning for five years, due to the lower number of endpoints in the intensive treatment group, with statistical significance.

Blood pressures were obtained from an average of three in-office self-measurements, without the supervision of any healthcare professional, using an automatic, non-invasive digital measuring device (oscillometric method), with arm monitor (Model 907, Omron Healthcare).

Inclusion criteria were age ≥ 50 years, SBP between 130 and 180 mmHg and high cardiovascular risk (at least one of the following criteria: risk ≥ 15% at 10 years by Framingham score or clinical or subclinical cardiovascular disease or age ≥ 75 years or chronic kidney disease).

Exclusion criteria were diabetes mellitus, previous stroke, secondary systemic arterial hypertension or symptomatic heart failure (HF) in the last six months or left ventricular ejection fraction <35%, among others.

IT group (mean number of antihypertensive drugs = 2.8) had a significant reduction in primary composite endpoints: myocardial infarction (MI) or other acute coronary syndromes (ACS), CVA, acute HF or cardiovascular death (5.2% vs. 6.8%; p <0.001) and in some of the individual or secondary: AMI (2.1% vs. 2.5%; p = 0.19) or other ACS (0.9% vs 0.9%; p = 0.99), CVA (1.3% vs. 1.5%; p = 0.5%), CI (1.3% vs. 2.1%; p = 0.002), CV death (0.8% vs. 1.4%; p = 0.005) or death from any cause (3.3% vs. 4.5%; p = 0.003) when compared to ST group (1.8 medications).

In Sprint study, *"the NNT (number needed to achieve result with the treatment) to prevent primary outcome events, death from any cause, and cardiovascular death during the study's median 3.26 years was 61,90 and 172 respectively".*

When analyzing the data, it was found that the statistically significant benefit in favor of a more aggressive target in the primary composite endpoint was due to the decrease in CV deaths and for any cause, mainly due to the HF aspect in the secondary endpoints. However, more serious adverse events occurred in the most severe BP (IT) reduction group, namely: hypotension (2.4% vs. 1.4%, p = 0.001), syncope (2.3% vs. 1, 7%; p = 0.05), electrolyte disorders (3.1% vs. 2.3%; p = 0.02) and of these, hyponatremia (3.8% vs. 2.1%; p <0.001) and hypokalemia (2.4% vs. 1.6%; p = 0.006) and acute renal injury - AKI (4.1% vs. 2.5%; p <0.001).

Given this scenario, despite the benefit of reducing HF, the cost was a significant increase in AKI. In these patients, in order to achieve the aggressive goal, the physician should pay special attention to renal function and electrolyte disorders, especially in older patients.

It was observed that the benefit in all-cause deaths occurred only around two years, and for the primary composite endpoint, near the first year. A surprise in the study was that despite a 13.1 mmHg reduction between mean SBP of 134.6 mmHg in the ST group and 121.5 mmHg in the IT group, there was no benefit in CVA reduction at the mean follow-up of 3.26 years.

The strengths of the study were the large sample size and population diversity with 2636 elderly ≥ 75 years (28% of patients included).

The study's weaknesses refer to the non-inclusion of patients with low and moderate risk, diabetes mellitus, previous CVA, institutionalized elderly, more severe hypertension and individuals <50 years of age. In this study, in which the average age, in years, was 67.9 ± 9.4 in IT group and 67.9 ± 9.5 in the ST, the probable concerns about hormonal variability (menstrual cycle), fear of women becoming pregnant and the consequent risk of teratogenicity do not justify the disparity in the inclusion of only 36% of participants being female in IT group and 35.2% in ST group; can lead to underrepresentation.

Another aspect that we considered as a weak point of the study was the presentation of the result graph with the mean and confidence interval and not the mean with the standard deviation of this mean. We would need to look at the standard deviation to know if the mean represents well the values of most patients. If the standard deviation is large there will be an overlap of results. As is usual in randomized clinical trials the results appear as mean and standard deviation and in this case of SPRINT study we can speculate that these results were masked for some reason (this study probably showed a large standard deviation that may have contaminated the results in their proper interpretation, mean. Sprint study concluded: *"Targeting a systolic blood pressure of less than 120 mmHg*

compared to less than 140 mmHg in patients at high risk for cardiovascular events (CVE), but without diabetes resulted in lower fatal and nonfatal CVE rates and death for any cause".

The results of Sprint study motivated changes or additions of its data to several national and international guidelines, such as SBC, AHA and ESC, among others.

We transcribed below the translations of some of these points mentioned in these guidelines:

7th Brazilian Arterial Hypertension Guideline[4]

"This guideline chose to recommend a blood pressure target lower than 130/80 mmHg for high CV risk patients except diabetics and patients with ACD due to an increase in fatal and nonfatal CV events when the pressure was <120/70 mmHg, particularly with diastolic blood pressure (DBP) <60 mmHg. Thus, for these patients, the target should be within a narrower safety range (<130/80 mmHg, but not <120/70 mmHg)".

6th Ambulatory Blood Pressure Monitoring Guidelines and 4th Residential Blood Pressure Monitoring Guidelines[6]

"Perspectives. In Systolic Blood Pressure Intervention Trial (Sprint) study, a new BP measurement modality was used without the presence of the healthcare professional. Thus, the patient, after being properly trained, performed his/her own measurement in a room reserved for this purpose. Sprint participants followed a protocol in which they waited in a quiet room for five minutes; then an automatic device measures blood pressure three times at intervals of several minutes, recording the values obtained".

Update on the Cardiogeriatrics Guidelines of the Brazilian Society of Cardiology[5]

"The recommendations of the III Guidelines on Cardiogeriatrics, for the elderly ≥ 65 years old, without frailty criteria, considering a robust elderly, are of SBP levels ≤ 130 mmHg. For patients ≤ 80 years of age without frailty, SBP blood pressure levels <140 mmHg may be considered; in patients ≥ 80 years and SBP ≥ 160 mmHg, an initial SBP reduction of between 150 and 140 mmHg may be allowed".

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: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [3]

"The benefit of treatment outweighs the potential damage in the PA threshold ≥ 130/80 mmHg. For adults with confirmed hypertension and known CV event or risk of atherosclerotic cardiovascular disease ≥ 10% at 10 years, a BP target of 130/80 mmHg is recommended. Recommendations for the purpose of BP for patients with hypertension without additional markers of increased risk for CVD, a target lower than 130/80 mmHg may be reasonable. For *ASCVD Risk Estimator,* consult: [*http://tools.acc.org/ASCVD-Risk-Estimator*]".

2018 ESC/ESH Guidelines for management arterial hypertension[2]

"The first objective should be to lower BP to <140/90 mmHg in all patients. Provided treatment is well tolerated, SBP should be directed to 130/80 mmHg or lower in most patients. In patients <65 years receiving medications, it is recommended that SBP should be reduced to a pressure range of 120-129 mmHg in most patients. In elderly patients (> 65 years), SBP should be directed to a range between 130 and 139 and DBP <80 mmHg. SBP should not be directed to <120 and DBP <70 mmHg due to an increased incidence of CV events and death. Intensive BP reduction treatment (achieved SBP 121 vs. 136 mmHg) has been associated with a 25% reduction in cardiovascular events and a 21% reduction in all-cause mortality (but not reduction in myocardial infarction)".

"However, this randomized clinical trial (RCT) does not clarify the target of BP because the method used for office BP measurement (unattended automatic measurement) had not been used in any RCTs that provide the evidence base for the treatment of arterial hypertension. This is because unattended automated BP measurement results in lower BP values than in-office BP measurement due to the absence of the white coat effect. Thus, it has been suggested that BP values reported in Sprint may correspond to the systolic pressures of conventional IT 130–140 and 140–150 mmHg vs. ST respectively".

In future RCTs, will systemic blood pressure be measured using automatic, non-invasive digital electronic arm-monitor devices similar to the methodology used in the Sprint study? Have these devices replaced the well-established sphygmomanometers and auscultatory method that are traditional in our offices?

In conclusion, when using Sprint data in clinical practice, the physician should keep in mind the suggested correspondence cited in, "2018 ESC / ESH Guidelines for the management of arterial hypertension,"[2] between SBP obtained by self-measurement in the office, without supervision by any healthcare professional, by means of an automatic measuring device, and traditional auscultatory measurement. When reducing SBP to values below 130 mmHg, the physician should take into consideration the binomial of good medical practice: risk/benefit and, if orientated in the three pillars of the equilateral triangle of common sense: scientific evidence, clinical judgment and patient consent. (Figure 1)

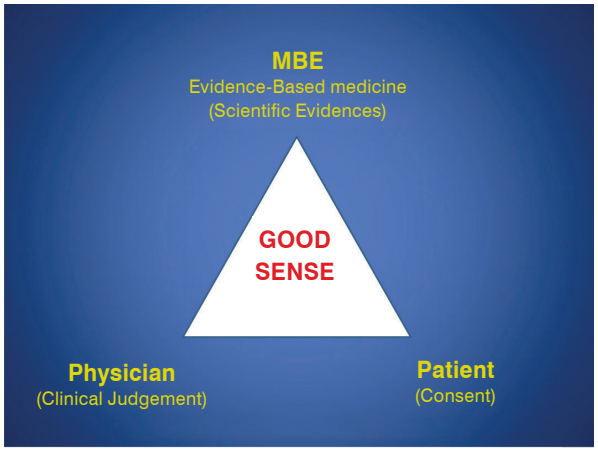


Figure 1. Good Sense Equilateral Triangle. Weverton Leite.

PATHWAY 2 STUDY

Resistant arterial hypertension (RAH) is defined when blood pressure (BP) remains above the recommended goals with the use of three antihypertensive drugs with synergistic actions at maximum recommended and tolerated doses, one of which is preferably a diuretic, or when in use of four or more antihypertensive drugs, even with controlled BP.[7] The prognosis is usually reserved because chronic exposure to above-target blood pressure levels most often leads to damage to target organs (heart, brain, kidneys and vessels), being associated with high cardiovascular risk. However, studies evaluating the prognosis of RAH are not uniform, especially in relation to the drugs used, the inclusion of pseudohypertension, insufficient follow-up time, and the non-inclusion of young people.[8] In RAH analysis, the following are importance factors: elevated blood pressure, the degree of hypertension, target organ damage, excess mineralocorticoids (aldosterone), and high sodium consumption.[9,10] Several studies have shown that aldosterone is an important marker of the severity of cardiovascular disease. [11]

Prevalence of RAH is estimated to be around 10% of treated hypertensive patients.[7] In genesis, as in non-resistant hypertension, it is a multifactorial phenomenon, involving genetic and environmental aspects, but salt plays an extremely important role.

In the treatment flowchart the three drugs indicated are a renin angiotensin aldosterone system inhibitor (RAASi) plus a calcium channel antagonist (CCA) plus a thiazide-like diuretic. However, the use of the fourth drug is totally empirical, reflecting the absence of controlled studies comparing the possible drugs candidates for the fourth drug.

PATHWAY-2 (*The Prevention And Treatment of Hypertension With Algorithm based therapY*) study believing that HAR is a heterogeneous state, predominantly caused by sodium retention, chose spironolactone (mineralocorticoid receptor blocker) as the additional diuretic. In addition, some studies using case series analysis have shown effectiveness in lowering blood pressure, but have never been compared with other drugs that are also used in RAH.[12]

It was a double-blind, placebo-controlled, crossover study involving patients aged 18 to 79 years with systolic blood pressure (SBP) ≥ 140 mmHg (or ≥135 mmHg for diabetics) with out-of-office evaluation (with 18 measurements in four days) with SBP ≥ 130 mmHg, and in treatment for more than three months with three antihypertensive drugs at maximum tolerated doses. Patients were randomized to use spironolactone (25-50 mg), bisoprolol (5-10 mg), doxazosin (4-8 mg) or placebo for 12 weeks. Drug doses were doubled after six weeks.

The primary goal was to evaluate the difference between out-of-office SBP (home assessment) between spironolactone and the other two drugs. The analysis was by intention to treat.

A total of 335 patients were included, and after exclusion of 21 patients, patients randomly received three drug and placebo cycles and 285 patients received spironolactone, 282 doxazosin, 285 bisoprolol and 274 placebo. Of the total, 230 patients completed the entire treatment cycle.

The mean reduction in systolic blood pressure in spironolactone group was -8.7 mmHg, higher than placebo (95% CI –9.72 to –7.69; p <0.0001), and higher than the average of the other two drugs. (doxazosin and bisoprolol; –4.26 [95% CI –5.13 to –3.38]; p <0.0001) and higher when compared individually. When compared with doxazosin the reduction was –4.03 mmHg [95% CI –5.04 to –3.02]; p <0.0001) and versus bisoprolol of -4.48 mmHg (95% CI, -5.50 to -3.46; p <0.0001). (Figure 2)

The use of spironolactone was well tolerated, and only in six patients did serum creatinine exceed 6.0 mmmol / L on one occasion.

PATHWAY-2 study was the first randomized, controlled, double-blind trial designed to compare different drugs for the treatment of RAH. It was the first comparison of a mineralocorticoid receptor blocker with other sympathetic blocking drugs commonly used to achieve targets in this group of resistant patients. The sample size was expressive with cross-sectional design and the use of spironolactone 25 to 50 mg/day was significantly (p <0.0001) higher than alpha or beta blocker when added to the renin angiotensin aldosterone blockade plus CCA and a diuretic. Residential systolic pressure was controlled in about 60% of patients.

Because plasma renin is significantly decreased despite treatment with three drugs that usually raise renin, the hypothesis of sodium retention in RAH is strengthened. In addition, there was an inverse correlation between plasma renin and blood pressure reduction by spironolactone. At the individual crossover, the data showed that in addition of the fourth drug, spironolactone was by far the most effective drug in most resistant patients.

This unambiguous superiority, with the safety shown by the data, indicates spironolactone as the fourth drug in RAH.

Another interesting aspect of the study was the use of home BP measurement, as it minimizes the placebo effect, which was quite evident in the study, and thus eliminated those patients whose pressure could be falsely elevated at baseline (white coat effect).

The use of spironolactone as a fourth drug was already routine and based on observations of daily practice and small studies.[13,14]

PATHWAY2 study consolidates the use of this mineralocorticoid receptor blocker as the fourth drug in the RAH treatment flowchart. The results were so striking that the European guideline on arterial hypertension substantially changed the orientation of the pharmacological sequence of treatment.[15]

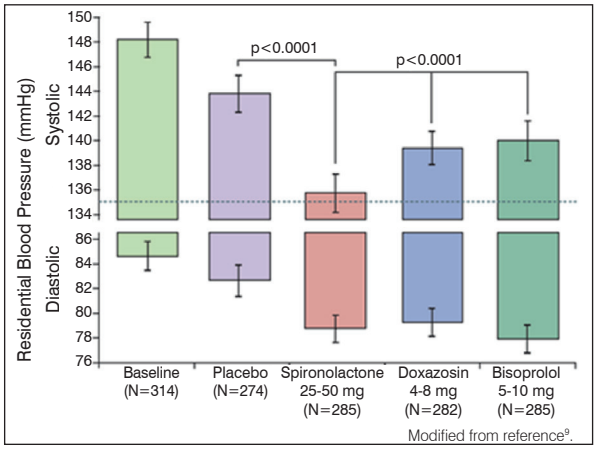


Figure 2. Systolic and diastolic residential blood pressure in resistant hypertension comparing spironolactone with doxazosin and bisoprolol.

Brazilian Resistant Hypertension Optimal Treatment (ReHOT) study compared spironolactone with clonidine, which was not superior, but with very similar results, however considering the secondary outcomes, spironolactone is still preferable as the fourth drug.[16]

According to the guidelines of the "*2018 ESC/ESH Guidelines for the management of arterial hypertension"* the algorithm should follow the following guidelines:

"Treatment start in most patients should be carried out by combining two drugs into a single pill to improve efficiency, speed and blood pressure control".

"Combinations of two preferred drugs are a RAAS inhibitor with a CCA or a diuretic if there is no specific indication for beta-blocker use (angina, infarction or heart failure)".

"The use of a single pill containing a RAAS inhibitor with CCA plus a diuretic if the pressure was not controlled with two drugs".

"The addition of spironolactone for the treatment of RAH unless contraindicated." (Figure 3)

This study evaluating the best drug in RAH was fundamental for the change of conduct in clinical practice, bringing robust data that convince the change of strategy in the treatment flow chart of hypertension. It profoundly influenced the European guideline in the pharmacological sequence.[15] However, some questions remain unanswered, mainly related to the mechanism by which the combination of a second diuretic acted extraordinarily in lowering blood pressure. In addition, the question still remained whether RAH is simply a state of excessive Na^+ retention, and whether the benefits of spironolactone could be replicated by another diuretic. Thus Williams B et al.[15] continued the study, resulting in "PATHWAY-2 mechanisms" where the effect of amiloride on the 10-20 mg dosage, another diuretic, in this group of resistant drugs was evaluated.[16] Results were similar to that of spironolactone. Thus, they concluded that RAH is predominantly a clinical situation of excessive sodium retention characterized by low plasma renin levels and inappropriately high aldosterone levels. The benefits of spironolactone and amiloride are primarily due to diuretic action. They found that a significant proportion of patients with inappropriate aldosterone secretion were probably due to aldosterone-producing micro adenomas (usually undetectable by conventional imaging methods), which would explain the superior therapeutic response of spironolactone or amiloride in these cases.

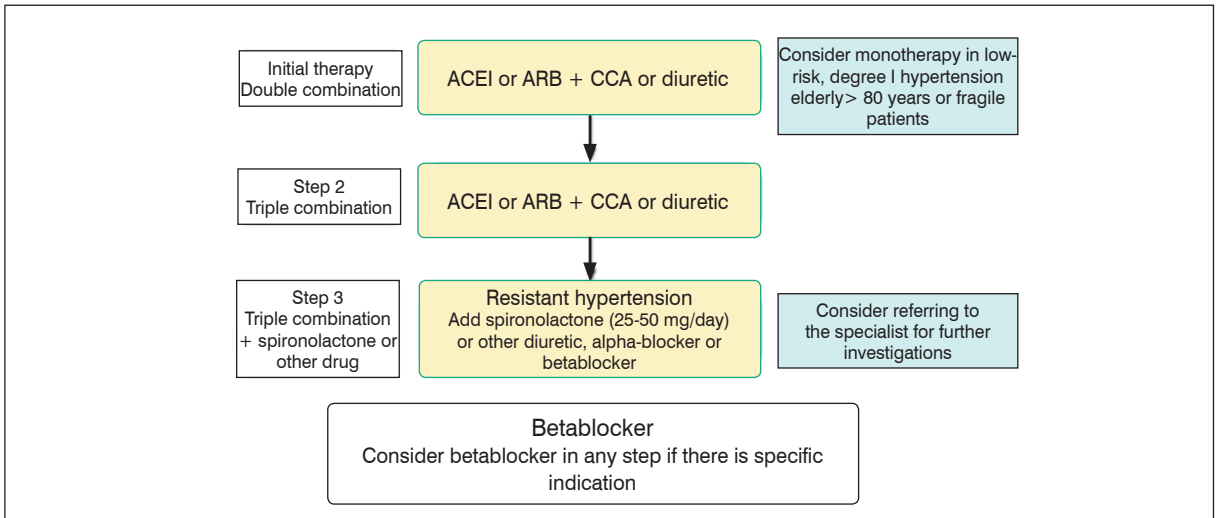
SIMPLICITY HTN-3 STUDY

Resistant Arterial Hypertension (RAH) is by definition a blood pressure that remains elevated for more than three months of treatment despite the use of three or more medications at optimal doses.[17] This clinical condition has been a challenge for those dealing with arterial hypertension. Renal sympathetic denervation (RSD) has come as a promise in solving this important clinical problem.

A number of studies and clinical records have emerged supporting the benefits of using this technique in the treatment of resistant arterial hypertension. SYMPLICITY HTN-1[18] and SYMPLICITY HTN-2 [19] studies demonstrated that RSD could significantly reduce the casual blood pressure obtained at the physician's office. These results led to the emergence of a range of successful case studies and reports with the new methodology, including comments on RAH treatment guidelines.[20]

Given the great euphoria for the method and the absence of control group studies, the Food and Drug Administration (FDA) demanded that for the registration of the method-specific catheter there was a better designed study with the inclusion of a control group. For this purpose, SYMPLICITY HTN-3.study was prepared.[21]

SYMPLICITY HTN-3 was designed as a prospective, randomized, single-blind, control group study. The study included 535 patients in order to compare in a 2:1 ratio (364 intervention group and 171 (control group) the effect of RSD with Symplicity catheter (Medtronic, Minneapolis, MN-USA) with control group of patients who underwent angiography, but without proceeding for renal denervation. Eighty-eight centers in the United States from October 2011 to May 2013 participated in the study.



ACEI Angiotensin-converting enzyme inhibitors; ARB Angiotensin receptor blocker; CCA Calcium channels antagonist. Modified from reference[12].

Figure 3. Flowchart of the uncomplicated hypertension treatment strategy.

Among the inclusion criteria, in addition to having high blood pressure in the office, there was also the need to prove 24-hour systolic blood pressure increase above 135 mmHg by ABPM (ambulatory blood pressure monitoring.

The study had two primary objectives; one of efficacy (change in casual systolic blood pressure and 24-hour mean ABPM by six months) and the other of safety was the composite of mortality from any cause, end-stage renal disease, embolic events, renal vascular complications or other areas, hypertensive crisis within 30 days after the procedure or renal artery stenosis at the denervation site within the next six months of follow-up.

The results of this study showed no statistically significant differences between blood pressure reductions with renal denervation and clinical treatment (14.1 ± 23 mmHg - denervation group vs. 11.7 ± 25 mmHg - clinical treatment group). Pressure measurements obtained by ABPM also did not show significant differences between groups. On the other hand, the study showed to be a very safe method with very low incidence of complications.

Initially this study was very disappointing for those researchers who worked with the method. A more detailed evaluation of the study observed several points that produced bias in the results. Firstly, several professionals who performed renal denervation did not have adequate training for this procedure. There was also no adequate control on the number of radiofrequency wave emissions in each case. The number of radiofrequency applications in each renal artery should be around 8; however, the average number of shots in the study was only four. In addition to the above it should be considered that within the study patients who were assigned to the control group may have had a better adherence to treatment, which also improved the results of this group in reducing blood pressure, and some of these patients could be those considered as pseudo-resistant, i.e., the sample may not have been ideal for an adequate evaluation of the procedure in a population of true resistant hypertensive patients.

Therefore, Simplicity HTN 3 study has modified clinical practice in the sense that all hypertension guidelines are unanimous in stating that such a procedure should currently be reserved for specific clinical research laboratories of the method and should not be employed as an established treatment option. We still need to answer who are the ideal candidates for this procedure and we do not have effective methods to measure how much denervation is obtained by this methodology.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

AUTHORS' CONTRIBUTIONS: The article was written by CA author and revised by RMSP, WFL who made important contributions in its final definition. As it is a review article, all contributed by adding aspects of their experience in the critical analysis of the selected articles. The articles were selected by the three authors.

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