Journal of Human Hypertension (2016), 1–7

www.nature.com/jhh

REVIEW

Management of resistant hypertension: expert consensus statement from the French Society of Hypertension, an affiliate of the French Society of Cardiology

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To improve the management of resistant hypertension, the French Society of Hypertension, an affiliate of the French Society of Cardiology, has published a set of eleven recommendations. The primary objective is to provide the most up-to-date information based on the strongest scientific rationale and that is easily applicable to daily clinical practice. Resistant hypertension is defined as uncontrolled blood pressure on office measurements and confirmed by out-of-office measurements despite a therapeutic strategy comprising appropriate lifestyle and dietary measures and the concurrent use of three antihypertensive agents including a thiazide diuretic, a renin-angiotensin system blocker (ARB or ACEI) and a calcium channel blocker, for at least 4 weeks, at optimal doses. Treatment compliance must be closely monitored, as must factors that are likely to affect treatment resistance (excessive dietary salt intake, alcohol, depression, drug interactions and vasopressor drugs). If the diagnosis of resistant hypertension is confirmed, the patient should be referred to a hypertension specialist to screen for potential target organ damage and secondary causes of hypertension. The recommended treatment regimen is a combination therapy comprising four treatment classes, including spironolactone (12.5–25 mg per day). In the event of a contraindication or a non-response to spironolactone, or if adverse effects occur, a β-blocker, an α-blocker, or a centrally acting antihypertensive drug should be prescribed. Because renal denervation is still undergoing assessment for the treatment of hypertension, this technique should only be prescribed by a specialist hypertension clinic.

Journal of Human Hypertension advance online publication, 28 January 2016; doi:10.1038/jhh.2015.122

INTRODUCTION

According to the World Health Organisation Report on cardiovascular risk factors, high blood pressure (BP) accounts for 18% of deaths in high-income countries and 45% of cardiovascular deaths;[1] it also causes severe disability as a result of stroke, dementia, heart failure and chronic renal disease. In 2008, cardiovascular deaths accounted for 30% of all deaths in France.[2]

Of the estimated 12–14 million patients in France who are on antihypertensive therapy[3] ~50% do not achieve adequate BP control, that is, their office BP levels are not at the target level. Among patients with uncontrolled hypertension, there are a large number of individuals whose high BP is resistant to conventional management. Seeking to improve the management of resistant hypertension can be justified by the documented ~50% higher prevalence of target organ damage and incidence of stroke among these patients over a period of 3.8 years as compared with patients with well controlled hypertension.

To improve the management of resistant hypertension, the French Society of Hypertension, an affiliate of the French Society of Cardiology, has published a set of eleven recommendations. The primary objective is to provide the most up-to-date information based on the strongest scientific rationale and that is easily applicable to daily clinical practice. The number of recommendations has intentionally been restricted so that the final document is clear and concise. In addition, to ensure the recommendations are easy to use for both general practitioners and hypertension specialists, the different treatment steps are summarised in Figures 1 and 2. For the purposes of easy reading, the rationale behind the recommendations has intentionally been kept to a minimum; the full text in French can however be accessed on www.sfhta.eu.

METHODOLOGY

The following rules were applied in the preparation of these recommendations:

- Data search was conducted using the following key words: resistant hypertension, treatment-resistant hypertension, resistant hypertension review.
- Articles identified by the data search to be used to answer the following questions: definition of resistant hypertension, prevalence among treated hypertensive patients, healthcare circuit describing the role of the general practitioner and the hypertension specialist, role of BP measurements outside the doctor's office, assessment of treatment compliance, non-pharmacological measures, work-up to screen for secondary hypertension, assessment of target organ damage, hypertension induced by exogenous substances, use of

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Received 25 August 2015; revised 2 November 2015; accepted 16 November 2015

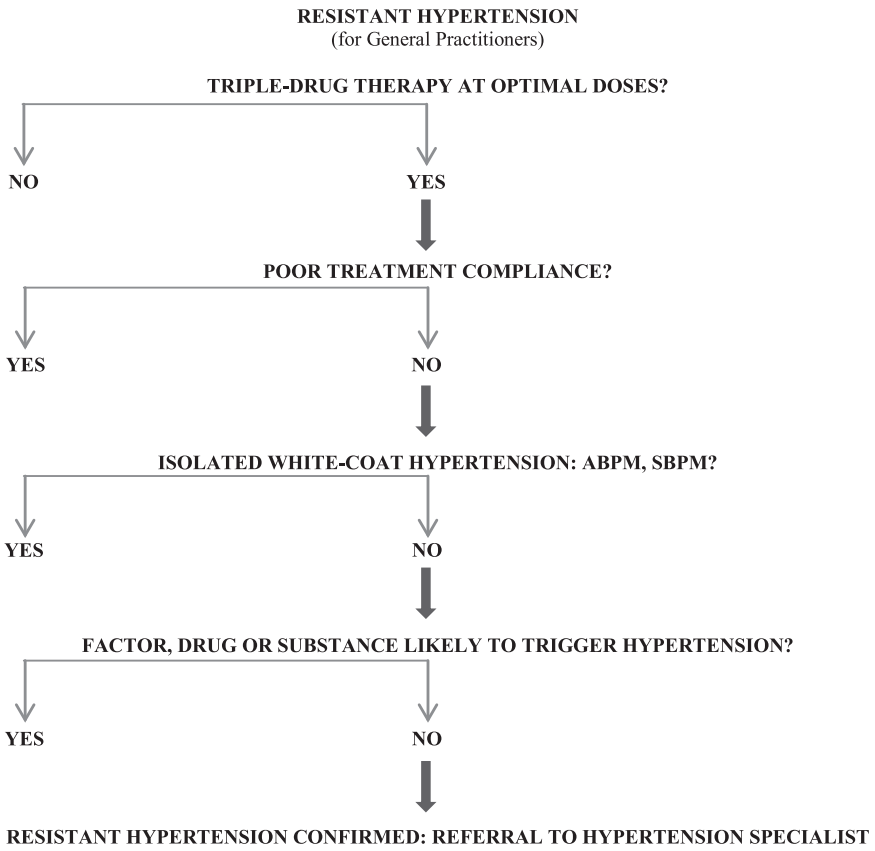

Figure 1. Treatment steps for the management of resistant hypertension for general practitioners.

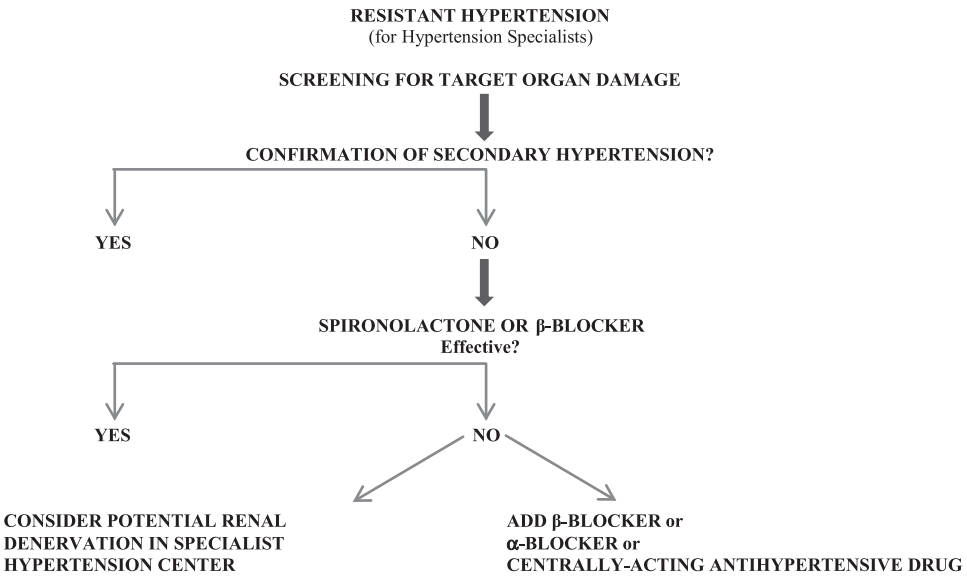

Figure 2. Treatment steps for the management of resistant hypertension for hypertension specialists.

combination therapy comprising several antihypertensive drugs, usefulness of renal denervation, follow-up once BP has been controlled.

- Rationale to be written and used as a basis for each recommendation.
- Recommendations to be ranked by the working group according to the GRADE method that ranks the overall quality of the scientific evidence (number and quality of the studies) and the strength of the recommendations produced (weight of evidence for/against the recommendation). The recommendations are Class 1 (is recommended), Class 2 (is suggested), Class 3 (is not recommended) and Level A (strong scientific evidence), Level B (moderate scientific evidence), Level C (weak scientific evidence).
- Assessment of each recommendation by the working-group experts according to the DELPHI method, which quantifies the

level of agreement relating to each recommendation using a Grade from + (weak majority) to ++++ (total consensus).
- Recommendations to be submitted to a review panel made up of hospital practitioners, physicians in private practice, general practitioners and specialists. For each recommendation, the following criteria are to be assessed: accuracy, relevance, applicability, suitability with clinical practice and usefulness; a mark is then to be given using a scale from 1 to 9.
- The review panel give their final assessment and the final draft of the recommendations is then written.

RECOMMENDATION AND RATIONALE

Recommendation No. 1:

It is recommended that resistant hypertension should be defined as uncontrolled hypertension both on office measurements (BP $\geqslant$ 140/90 mm Hg in individuals $<$ 80 years, or SBP $\geqslant$ 150 mm Hg in individuals $>$80 years) and confirmed by out-of-office measurements (home (HBPM) or ambulatory (ABPM) BP measurement) despite a therapeutic strategy comprising appropriate lifestyle and dietary measures and the concurrent use of a triple-drug antihypertensive treatment, including a thiazide diuretic, for at least 4 weeks, at optimal doses.

Class 1, Level C, Grade +++

International learned societies and organisations known for publishing professional recommendations have already produced guidelines for the management of resistant hypertension. The target population for these guidelines is traditionally defined as treated hypertensive patients whose BP as measured in the clinician's office is higher than the target level despite optimal doses of three antihypertensive agents (AHA recommendation 2013),[4] or those whose BP is higher than 140/90 mm Hg despite a therapeutic strategy comprising appropriate lifestyle and dietary measures and the concurrent use of three antihypertensive agents including a diuretic and appropriate doses of two other antihypertensive agents from different classes (ESC/ESH recommendation 2013).[5]

The first step in patient care is to ensure adequate assessment of office BP: this means using a standardized device, using an appropriate cuff-size for the patient's arm circumference, and eliminating white-coat hypertension (elevated office BP but normal BP as measured by ABPM and/or HBPM). One study conducted in general practice by the French Health Insurance system showed that 27% of hypertensive patients classed as 'uncontrolled' by triple therapy on three consecutive consultations, actually had normal clinic BP levels when measured with an automatic device and an appropriate cuff-size, and that a white-coat effect was confirmed in a further 6% of patients whose BP was in fact on target.[6]

Before confirming the diagnosis of uncontrolled hypertension, ABPM is a useful tool for detecting a potential white-coat effect, leading to a subsequent 38% reduction in the prevalence of uncontrolled hypertension. The efficacy of HBPM and ABPM has been compared in the context of uncontrolled hypertension; although the two methods have been shown to be generally equivalent, the comparison did highlight the importance, in certain patients, of measuring nocturnal BP and of an accurate assessment of the circadian pattern. In patients with resistant hypertension, ABPM has been shown to be necessary to confirm BP levels and to analyse the specific characteristics.

Interpretation of HBPM and ABPM is based on the following thresholds for uncontrolled hypertension:

HBPM $\geqslant$ 135/85 mm Hg
24-h ABPM $\geqslant$ 130/80 mm Hg
Day-time ABPM $\geqslant$ 135/85 mm Hg
Night-time ABPM $\geqslant$ 120/70 mm Hg

The second step in the management of non-controlled hypertension is the prescription of an appropriate triple-drug combination. This decision is based on documented improvements of BP control following the addition of a third pharmacological class. Randomized trials have assessed the efficacy of triple-drug regimens to reduce BP in patients with hypertension that was not controlled by a two-drug combination.[7,8] These studies have demonstrated the benefits of triple-drug regimens over two-drug combinations at reducing SBP/DBP.

Depending on the actual definition of the number and the dosage of antihypertensive agents used, one recent study has shown that in a given population, the prevalence of resistant hypertension is either 30.9% (failure to achieve BP control with a triple-drug regimen or BP control with a four-drug regimen) or 3.4% (failure to achieve BP control despite maximum doses of three antihypertensive agents including a diuretic).[9]

Recommendation No. 2:

2-A: In addition to a thiazide diuretic, triple-drug antihypertensive therapy should include a renin-angiotensin system blocker (ARB or ACEI) and a calcium channel blocker. Other pharmacological classes should be used in the event of adverse effects or specific indications.

2-B: Resistant hypertension should be treated with a thiazide diuretic: chlorthalidone 12.5–50 mg per day, hydrochlorothiazide $\geqslant$ 25 mg per day or indapamide 2.5 or 1.5 mg SR per day.

2-C: In patients with chronic kidney disease stage 4 or 5 (eGFR $<$ 30 ml min^{-1} 1.73 m^{-2}), the thiazide diuretic should be replaced by a loop diuretic, such as furosemide, torasemide or bumetanide, at a dosage adapted to the patient's renal function.

Class 1, Level A, Grade +++

No randomized trial to date has conducted an assessment of the different antihypertensive agents available for triple-drug combinations to treat resistant hypertension. The 2013 American Heart Association recommendations[4] highlight the fact that the choice of a triple-drug combination is largely empiric and is based on the clinical context and the mechanism of action of the different pharmacological classes of antihypertensive drugs. The 2013 ESC/ESH European recommendations[5] stipulate that when a triple-drug combination is used, the choice of antihypertensive agents can be made from four pharmacological classes: thiazide diuretics, renin-angiotensin system blockers (ACEI or ARB), β-blockers and calcium channel blockers. In France, data from the French League Against Hypertension Survey (FLAHS) on prescriptions of antihypertensive drugs show that for the 15% of hypertensive patients treated with a triple-drug regimen,[10] only 33% of them had a prescription for the combination of a thiazide diuretic plus an RAS blocker (ARB or ACEI) and a calcium channel blocker; another 33% had prescriptions for the combination of an RAS blocker, a diuretic and a β-blocker, and last, 21% of prescriptions were for the combination of a β-blocker with two other drug classes. According to data from the French Health Insurance system, 88% of hypertensive patients on triple-drug therapy and recognised as having ALD status (Affection de Longue Durée (long-standing disease)) have a prescription including a diuretic,[6] whereas a study conducted in the USA showed that despite treatment including at least three different drugs, only 50% of patients with uncontrolled hypertension actually receive optimal doses of the antihypertensive agents.[11]

Before confirming the diagnosis of resistant hypertension, treatment of uncontrolled hypertension should be based on a

triple-drug regimen including a thiazide diuretic, an RAS blocker (ARB or ACEI) and a calcium channel blocker. Other pharmacological classes should be used in the event of adverse effects or specific indications. The following recommendations concerning the choice of diuretic should be adhered to: thiazide diuretic (chlorthalidone 12.5–50 mg per day, hydrochlorothiazide $\geqslant$ 25 mg per day, or indapamide 2.5 or 1.5 mg SR per day). In patients with chronic kidney disease stage 4 or 5 (eGFR < 30 ml min^{-1} 1.73 m^{-2}), the thiazide diuretic should be replaced by a loop diuretic, such as furosemide, torasemide or bumetanide.

Recommendation No. 3:
It is recommended that poor treatment compliance should be identified using a questionnaire, urine drug analysis and/or pill-count.

Class 1, Level C, Grade +++

Recommendation No. 4:
It is suggested that patient information, therapeutic education for patients and HBPM are likely to improve BP control.

Class 2, Level B, Grade ++

The 2013 ESC/ESH European recommendations[5] highlight the importance of identifying poor treatment compliance in patients with resistant hypertension, but also stipulate that detecting poor compliance by questioning the patient can be misleading. Although poor treatment compliance can be demonstrated by direct methods in clinical trials (pill counts, electronic pill dispensers and toxicological urine screening), these are not always applicable to everyday clinical practice. Direct observation of drug administration on a given day during hospitalisation may prove useful. A specific questionnaire that was developed and assessed in clinical practice has been shown to be useful for identifying poor compliance and improving patient care in cases of non-controlled hypertension.[12]

Assessing treatment compliance in patients with resistant hypertension will frequently provide useful information as demonstrated by a study conducted in Germany. Using toxicological urine analysis the investigators demonstrated poor treatment compliance in 53% of patients, 30% of whom were not taking any of the drugs prescribed.[13]

Analysis of prescription databases relating to antihypertensive drugs has shown that the number of patients who discontinue antihypertensive therapy is highest within 1 year of treatment initiation. One study that used the French Health Insurance database to assess treatment compliance[14] showed that 12 months after the initial prescription of an antihypertensive drug, 35% of patients had stopped taking their treatment and 63% had already stopped taking it at least once and for longer than 14 days. Certain factors are more likely to be associated with good treatment compliance (persistence with treatment): elderly patients, diabetes or a history of cardiovascular disease, a limited number of pills, fixed-dose combinations.

With a view to improving compliance to antihypertensive treatment, a number of intervention studies have assessed the impact of different approaches including patient information, therapeutic education for patients, HBPM, use of weekly pill organisers or close cooperation with pharmacists. The results of these studies are rarely conclusive.

Recommendation No. 5:
It is suggested that patients should be screened for factors likely to influence treatment resistance (excessive dietary salt intake, alcohol, depression and drug interactions) or vasopressor drugs and substances (Table 1).

Class 2, Level B, Grade ++

Specific advice concerning lifestyle measures for patients with resistant hypertension is similar to that for patients with well controlled hypertension, and is as follows:

- overweight (BMI $>$ 25 kg m^{-2}) or obese (BMI $>$ 30 kg m^{-2}) patients should lose weight;
- excessive dietary salt intake should be reduced;
- alcohol consumption should be limited;
- patients should undertake regular physical activity;
- the vegetable content of their diet should be increased and the consumption of animal fats reduced.

Sodium intake can be measured on natriuresis using 24-h urine collection. If natriuresis exceeds 12 g per day (200 mmol), salt consumption can be considered excessive. The patient will be advised to target a 24-h excretion rate of ~6 g NaCl (100 mmol). Questioning the patient about dietary habits will reveal intake of food substances with a high hidden-salt content (cheese, bread, cured meats, pizza, stock cubes and so on.).

Depression or chronic pain will need to be authenticated; subsequently, appropriate management of these conditions is likely to improve control of treatment-resistant hypertension.[15]

Table 1. Drugs and substances known to have a vasopressor activity or to affect the metabolism and/or activity of antihypertensive drugs

Drugs and substances known to have a vasopressor activity (non-exhaustive list):
Anti-angiogenic agents
Cyclosporine, tacrolimus
Corticosteroids
Erythropoietin
Synthetic forms of oestrogen (oral contraceptive)
Sympathomimetics
SNRIs
Alcohol
Cocaine, amphetamines
Herbal supplements (ephedra or ma huang)
Licorice (glycyrrhizic acid)
Drugs and substances with the capacity to affect the metabolism and/or activity of antihypertensive drugs (non-exhaustive list):
Non-steroidal anti-inflammatory drugs
Anti-retroviral drugs
CYP17A1 inhibitors: grapefruit juice, macrolides and azole antifungal drugs

Abbreviation: SNRIs, serotonin and noradrenaline reuptake inhibitors.

Recommendation No. 6:
If resistant hypertension is confirmed, it is recommended that the patient be referred to a hypertension specialist to screen for secondary hypertension or target organ damage, and to determine the future treatment strategy.

Class 2, Level B, Grade ++

Recommendation No. 7:
Investigative techniques to identify secondary hypertension or any potential triggering factors will be conducted according to the clinical context, access to the techniques and the experience of the hypertension specialist. They are as follows:

- Blood electrolytes and 2-h natriuresis, serum creatinine, 24-h urine creatinine and proteinuria
- Abdominal angiogram
- Doppler ultrasound of renal arteries
- Plasma aldosterone and renin levels to calculate the plasma aldosterone/renin ratio
- 24-h urinary metanephrine and normetanephrine
- 24-h urinary free cortisol measurements, dexamethasone suppression test 1 mg

Nocturnal oximetry, ventilation polygraph and polysomnography.

Class 2, Level B, Grade ++

Both European and American recommendations[4,5] highlight the importance of screening for secondary hypertension in patients with resistant hypertension. Although a secondary cause of hypertension is rare among the general population of hypertensive patients, it is considerably more frequent in patients presenting resistant hypertension. One trial published in 2011[16] studied the prevalence of the different causes of secondary hypertension in a population of patients with resistant hypertension in Brazil. Primary hyperaldosteronism was diagnosed in 5.6%, renal artery stenosis in 2.4%, renal parenchymal disease in 1.6%, whereas obstructive sleep apnoea was diagnosed in 64% of patients.

Several critical factors have led to the proposal that screening for secondary hypertension should be conducted by a hypertension specialist. The reasoning behind this decision is the lack of a screening strategy that has been approved for use in primary care, and the fact that it is difficult, and in some cases, impossible to conduct a number of these examinations in optimal conditions.

The assessment will include the prevalence of each aetiology depending on patient characteristics. This requires detailed questioning of the patient, a physical examination and further specifically oriented examinations. Although it is clearly not always necessary to carry out all the investigations proposed in recommendation n°7, a step-by-step process can be established from this list by individual centres. Investigative techniques to identify secondary hypertension or any potential triggering factors must to be conducted according to the clinical context, access to the techniques and the experience of the hypertension specialist.

Recommendation No. 8:
Suggested examinations to screen for target organ damage are as follows:

- serum creatinine, urine creatinine, microalbuminuria and/or proteinuria
- resting electrocardiogram and echocardiogram

Class 2, Level B, Grade ++

The search for target organ damage should be carried out during the work-up for resistant hypertension. Electrical or echocardiographic evidence of left ventricular hypertrophy, the presence of microalbuminuria, proteinuria, impaired renal function or vascular disease will confirm the diagnosis of resistant hypertension and are sufficient arguments to support increasing the antihypertensive treatment.

In addition, regression of left ventricular hypertrophy and proteinuria have been shown to be correlated with improved cardiovascular outcomes.[17,18]

Depending on the clinical context, the availability of investigation techniques and the experience of the specialist, a vascular assessment will be performed. The cardiovascular benefit of regression of intima-media thickness has not been clearly established.

Recommendation No. 9:
In the absence of a curable aetiology in patients < 80 years, it is recommended that a four-drug combination therapy should be initiated, including first-line spironolactone (12.5–25 mg per day) once the absence of any contraindication has been confirmed. Serum potassium and creatine levels require monitoring. A β-blocker may well be the preferred choice of drug depending on the clinical situation.

Class 1, Level A, Grade ++++

Recommendation No. 10:
In the event of a contraindication or a non-response to spironolactone, or if adverse effects occur, it is suggested that a β-blocker, an α-blocker, or a centrally acting antihypertensive drug should be prescribed.

Class 2, Level C, Grade ++

If a triple-drug combination therapy fails to achieve the target BP level, a four-drug combination should be proposed. Although no randomized study to date has identified the optimal therapeutic regimen after failure of a three-drug combination, increasing the diuretic therapy is suggested when a sodium overload is suspected.[19]

The strategy that has been the most widely assessed is that of combining spironolactone with a triple-drug therapy. Several studies have reported the beneficial effects on BP levels of adding spironolactone to create a four-drug combination.[20] The benefits of a combination of several diuretics for certain resistant hypertensive patients are possibly related to the specific hormone profile of these patients (low renin levels with or without detectable hyperaldosteronism). If spironolactone proves effective but a patient encounters difficulties with tolerability, substitution with amiloride or eplerenone (when authorised by national health authorities) should be proposed.

In the event of a contraindication or a non-response to treatment with spironolactone, or if adverse effects occur, it is suggested that a β-blocker, an α-blocker, or a centrally acting antihypertensive drug should be prescribed.

Recommendation No. 11:
Because renal denervation is still undergoing assessment for the treatment of hypertension, it is suggested this technique should only be proposed by a multidisciplinary team in a specialist hypertension clinic.

Class 1, Level C, Grade +++

The purpose of endovascular renal denervation is ablation of certain afferent and efferent sympathetic nerve fibres within the adventitia of renal arteries; this procedure is known to reduce BP. Early clinical trials showed significant reductions in office BP in

patients with resistant hypertension; the effect was seen to persist 36 months post-surgery (−27/ − 17 mm Hg). The reduction in BP levels is not immediate and must therefore be assessed at least 3 months after the intervention. No cases of severe complications or orthostatic hypotension have been reported. Renal function was stable at 6 months.[21,22] Nevertheless, a few cases of renal artery stenosis following denervation have been reported. The results of one randomized study comparing denervation with an incomplete (sham) endovascular procedure, but with well-standardized use of antihypertensive medication, only reported a non-significant, small BP reduction that was attributable to the denervation procedure, when BP was measured by ABPM at 6 months.[23] Although the technique has been criticised since the publication of the Symplicity 3 trial[24] and a recent prospective, randomized controlled trial with blinded endpoint evaluation of patients with resistant hypertension, conducted in 15 French tertiary care centres specialized in hypertension management, reported a significantly greater reduction in ABPM levels with renal denervation than with standardized stepped-care antihypertensive treatment.[25] Until the results of further trials giving a clearer definition of the indications of this technique for treating hypertension become available, several consensus and international recommendations have been published.[26,27] The French consensus is the most restrictive recommendation; renal denervation is only proposed after consideration by a multidisciplinary team including a hypertension specialist. It is also recommended that the procedure should be restricted to patients with essential hypertension that is resistant to a four-drug combination including a diuretic and 25 mg per day of spironolactone, who have clinic SBP > 160 mm Hg and/or clinic DBP > 100 mm Hg, HBPM or diurnal ABPM > 135/85 mm Hg, and whose renal artery anatomy is compatible with the technique.[28]

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CONFLICT OF INTEREST

The authors of these guidelines have several links of interest with manufacturers who sell health products. The authors declare that these recommendations have been developed independently of any commercial entity.

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