

Debate on Blood Pressure Lowering Targets after the SPRINT Trial

Debate sobre objetivos de descenso de la presión arterial luego de Sprint

Agonist

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Hypertension has been for a long time defined as blood pressure $\geq 140/90$ mmHg, partly based on the results of actuarial studies of insurance companies showing that blood pressures above 140/90 mmHg were associated with a significant increase in cardiovascular events. Different multicenter randomized studies have confirmed the benefit of lowering the blood pressure of hypertensive patients below 140/90 mmHg [Systolic Hypertension in the Elderly Program or SHEP (1) and The Systolic Hypertension in Europe or Syst-Eur Trial (2)], or below 150/90 mmHg for subjects over 80 years of age (Hypertension in the Very Elderly Trial or HYVET) (3)

There have been no studies trying to achieve greater blood pressure lowering except the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study in diabetic patients, which showed no benefit in decreasing blood pressure to $< 120/80$ compared with $< 140/90$ mmHg. (4)

Consequently, most of the therapeutic guidelines recommend lowering blood pressure below 140/90 mmHg in hypertensive patients (5-8) except for the JNC8 guideline (9) which proposes blood pressure $< 150/90$ mmHg for persons ≥ 60 years, or for elderly people aged ≥ 80 years in the case of the ASH/ISH (7) and CHEP (8) guidelines based on the HYVET (5) guideline.

According to observational studies, we know that the risk of mortality due to coronary artery events or stroke starts at 115/75 mmHg and doubles at each increase of 20/10 mmHg (10).

One of the questions that has stopped investigating blood pressures $< 140/90$ mmHg has been whether there is a J curve, as demonstrated in the secondary analysis of high blood pressure treatment clinical studies (11). For these reasons, the NHLBI sponsored the SPRINT trial (12) in subjects at high cardiovascular risk with treated or untreated hypertension, older than 50 years of age, with SBP between 130 and 180 mmHg,

clinical or subclinical cardiovascular disease (excluding stroke), chronic renal failure (CRF), 10-year Framingham cardiovascular disease risk score $\geq 15\%$, or age ≥ 75 years. Exclusion criteria were: stroke, diabetes mellitus, polycystic kidney disease, congestive heart failure, proteinuria $> 1\text{g/d}$, CRF, adherence to treatment issues, dementia or nursing home residence. A total of 9,361 subjects were recruited, half to intensive treatment with a target systolic blood pressure (SBP) < 120 mmHg and the rest to standard treatment with SBP < 140 mmHg. In the SPRINT trial, blood pressure was measured 3 times with an Omron 907XL oscillometric automatic device, and the mean estimated after 5 minutes of rest, without the presence of health staff. The study was discontinued after an average of 3.26 years for the obvious benefit of the intensive treatment group.

At the end of the study, SBP was 136.4 mmHg in the standard treatment group and 121.5 mmHg in the intensive treatment group. To achieve this SBP, patients in the intensive treatment group used an average of 2.8 antihypertensive drugs vs. 2 in the standard treatment group, including diuretics 68% vs. 40%, renin-angiotensin system inhibitors 75% vs. 55%, and calcium channel blockers 58% vs. 36%, respectively.

There was 25% relative risk reduction (RRR) of the cardiovascular primary composite endpoint in favor of intensive treatment, 38% RRR for heart failure and 43% RRR for cardiovascular death, surprising for a hypertension treatment study, with no RRR for myocardial infarction, acute coronary syndrome without infarction, or stroke. Regarding the secondary endpoint of all-cause mortality, which was rarely affected in previous studies, revealed 27% RRR with intensive treatment. These results were consistent across all the pre-specified groups ($>$ or < 75 years, CRF or non-CRF, men/women, black race or not, previous or no cardiovascular disease, and SBP upon entering the study < 132 , 132-145, or > 145). Among elderly par-

REV ARGENT CARDIOL 2017;85:357-365. <http://dx.doi.org/10.7775/RAC.v85.i3.9817>

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ticipants, the RRR of the primary endpoint showed similar benefit in the intensive treatment group compared with the entire patient cohort (13), whether the subjects were in good physical condition or not.

Regarding renal function the results were similar whether the patients had CRF or not. The side effects of intensive and standard treatment were similar and infrequent. Syncope and hypotension, electrolyte disorders and acute renal injury were rare but more frequent in the intensively treated group.

Intensive treatment, therefore, reduces cardiovascular disease and all-cause mortality, with no major differences in adverse effects and with infrequent serious secondary effects. These results are in agreement with meta-analyses of randomized clinical trials (14-15), including a recent network meta-analysis (16).

Based on the SPRINT results, some organizations have already adapted their therapeutic guidelines for the treatment of hypertension. Hypertension Canada in the 2016 edition of its therapeutic guidelines adopted the recommendation to intensively treat hypertensive patients that meet the inclusion criteria of the SPRINT trial and that fall outside the exclusion criteria (12, 17). However, it must be remembered that Hypertension Canada recommends blood pressure to be measured as in the SPRINT study.

It is also recommended that these SBP targets are applied with caution in patients who do not strictly respond to the SPRINT criteria. For example, for diabetic patients, a target blood pressure <130/80 mmHg is still recommended, based on the benefits regarding stroke observed in the ACCORD study (4) and the absence of benefit when SBP decreased below 120 mmHg in this study.

The reason why the ACCORD study afforded no positive result compared with the SPRINT trial has been much debated, without firm conclusions. Could it be attributed to the factorial design or to an insufficient number of subjects? Was it that the diabetic patients recruited had very advanced atherosclerosis? Because there is no doubt that diabetic patients are even at greater cardiovascular risk than those recruited for the SPRINT trial. In addition, cardiovascular disease in diabetes is unlikely to be different from that in non-diabetic patients at high cardiovascular risk. Perhaps different blood pressure measurement in the ACCORD and SPRINT studies is related to the difference in results, although it should be noted that the direction of results was the same in both studies but reached statistical significance only in the SPRINT trial.

As in the SPRINT trial blood pressure was measured in the absence of the health professional, the same level obtained in the ACCORD study (4) may have been more aggressive than in the SPRINT trial, and resulted according to the J-curve in an excess of morbidity that diminished the benefits of intensive treatment. (see below). These results and the new recommendations suggest that perhaps the time has

come to redefine hypertension.

Should we have definitions and goals of blood pressure depending on cardiovascular risk and how blood pressure is measured?

This last point is crucial. Blood pressure measured manually with a research technique is lower than that measured in the clinic during usual medical activity. (18) In addition, blood pressure measured automatically in the absence of the professional and with an average of 3-5 readings, after a 5-minute rest, is even lower than daytime ambulatory blood pressure or blood pressure measured at home. There is recent evidence that an unobserved automatically measured SBP between 110 and 120 mmHg in 6,183 residents of Ontario, Canada, aged ≥ 66 years and with mean follow-up of 4.6 years under antihypertensive treatment, is accompanied by minimal cardiovascular events compared with SBP above or below these levels (19). This result is in accordance with the SPRINT study, extending its results and the target SBP <120 mmHg to routine clinical practice, provided that blood pressure is measured unobserved and automatically. Automatic blood pressure measurement is more accurate, partially eliminating the effect of white-coat hypertension, and allows applying SPRINT results. If blood pressure is not measured as in the SPRINT trial, it is necessary to apply a correction that can be 10-15 mmHg or more. This is extremely important because if SBP is lowered <120 mmHg with the manual or even automatic technique but in the presence of the professional, these values can actually be much lower than the SBP of 110 mmHg measured with the unobserved automatic or SPRINT technique, and result in hypotension, falls and hip fractures for example, or acute renal failure.

Therefore, it is essential to clarify how blood pressure is measured. It is also necessary to consider the patients' preference. The decision to attempt an intensive treatment of blood pressure must be in agreement with the patient, who must understand the benefits and risks, the need for more visits and more medication, and the possibility of more side effects. The lack of human resources and medicines in countries of medium or scarce resources may render intensive treatment impossible. Thus the International Society of Hypertension has concluded that since automatic blood pressure measurement is not widely available at present, treatment target should be to approach a SBP <130 mmHg, without necessarily aiming at <120 mmHg. (20) But there is already evidence (in other populations not included in the SPRINT trial) that even with manual measurement of blood pressure, the intensification of the hypertension treatment can improve the prognosis. In the case of stroke, the China Stroke Primary Prevention Trial with 17,720 patients and 4.5-year follow-up (21) showed that the nadir of the SBP at which stroke is minimal is 120-130 mmHg, which is equivalent to 110-120 mmHg with automatic blood pressure measurement. This result is in agree-

ment with stroke in the ACCORD study (4) and with SPS3 (22), a study on the prevention of recurrent lacunar stroke, which showed, although not reaching statistical significance ($p=0.08$), the probable benefit of SBP <130 mmHg.

It is important to take into account the subgroups of patients who obtained benefit from intensive treatment, including those over 75 years of age. Of course, not only all the precautionary recommendations mentioned above, and the exclusions that are part of the SPRINT trial are applicable, but it must also be remembered to proceed with caution with these patients, reaching the desired targets in a slow and gentle way. Frailty does not seem to be an obstacle for the intensification of treatment, provided caution is exercised.

Faced with all these considerations, we believe that it is necessary to redefine hypertension after the SPRINT trial. Since the automatic measurement of blood pressure is not widely available, the definition of hypertension should continue to be $\geq 140/90$ mmHg, and the target pressure in most patients should be <140/90 mmHg. In individuals at high cardiovascular risk, including CRF, the elderly, those with a Framingham Risk Score $\geq 15\%$, and perhaps also diabetic subjects, the target pressure should be <130/80 mmHg. These blood pressure levels are those corresponding to blood pressure measured manually following instructions. Any mention of blood pressure must include a detailed identification of the measurement method. However, when measurements are performed unobserved, in the absence of the professional, with an automatic instrument that obtains several blood pressure readings after a 5-minute rest as in the SPRINT trial, hypertension in subjects at high cardiovascular risk should be defined as blood pressure $\geq 130/80$ mmHg with a 130/80 mmHg threshold for treatment, and a SBP target ≤ 120 mmHg. (23)

There are aspects of the SPRINT trial that are subject of concern: the measurement of blood pressure, which is not broadly available, the absence of benefit with respect to stroke and coronary heart disease, the greater benefit of subjects with SBP <130 mmHg, the fact that black people and women seem to benefit less, that white elderly men are those who benefited the most, and how to interpret the differences with the ACCORD study. What to do with populations at high risk with SBP ≥ 120 -130 mmHg? And with populations with less current cardiovascular risk but with higher cardiovascular risk throughout their entire lifetime? And in diabetes?

The global prevalence of high blood pressure (SBP ≥ 140 mmHg) is estimated at around 1 billion people, added to those at high cardiovascular risk with lower pressures. (24) If the SPRINT study is to be applied, knowing that it requires the use of more medication, and more medical visits and utilization of the health system, this implies a considerable increase in the cost of the system. However, Richman et al. (25)

in a recent study of the cost/benefit ratio of intensive blood pressure treatment demonstrated that intensive treatment compared to standard treatment provides excellent value in years of life gained adjusted for quality (QALYs).

The most important conclusions for the treatment of hypertension after the SPRINT trial are the following: lower SBP is better; it should be aimed at high risk patients, there are important aspects related to the implementation of intensive treatment such as patient selection, risk evaluation and treatment benefits, shared decision, follow-up, adverse effects, and methodology for blood pressure measurement. We believe that the increase in the popularity of automatic measurement will increase the accuracy of blood pressure measurement. Furthermore, beyond target SBP, considering that the intensive management of hypertension as in the SPRINT trial is not possible in many situations due to the cost and lack of resources, the mere idea of intensifying the treatment of blood pressure will improve the prognosis of patients in general, including the elderly.

Conflicts of interest:

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material)

REFERENCES

1. SHEP Cooperative Research Group. Prevention of stroke by anti-hypertensive drug treatment in older persons with isolated systolic hypertension: final results of the systolic hypertension in the elderly program (SHEP). *JAMA*. 1991;265:3255-64. <http://doi.org/c2gpz4>
2. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet*. 1997;350:757-64. <http://doi.org/d4kbbds>
3. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:1887-98. <http://doi.org/dw2snx>
4. ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575-85. <http://doi.org/dgx2qw>
5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al and the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206-52. <http://doi.org/cjszcd>
6. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281-357. <http://doi.org/wmq>
7. Weber MA, Schiffrin EL, Mann S, Lindholm LH, Kenerson JG, Flack JM, Carter BL, et al. Clinical Practice Guidelines for the Management of Hypertension in the Community: A Statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens*. 2014;32:3-15. <http://doi.org/f24pt6>
8. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K, et al; CHEP Guidelines Task Force. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can J Cardiol*. 2016;32:569-88. <http://doi.org/cd4z>

9. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-20. <http://doi.org/3pp>
10. Lewington, S, Clarke, R, Qizilbash, N, Peto, R, Collins, R, and the Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-13. <http://doi.org/bzsqj>
11. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, et al. Secondary Observational Analysis of the INVEST Study. *Ann Intern Med*. 2006;144:884-93. <http://doi.org/cd42>
12. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103-16. <http://doi.org/bbxid>
13. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥ 75 years: a randomized clinical trial. *JAMA*. 2016;315:2673-82. <http://doi.org/cd43>
14. Etehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957-67. <http://doi.org/f8schs>
15. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet*. 2016;387:435-43. <http://doi.org/bdx6>
16. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, He H, Chen J, Whelton PK, He J. Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis. *JAMA Cardiol*. Published online May 31, 2017.
17. Padwal R, Rabi DM, Schiffrin EL. Recommendations for Intensive Blood Pressure Lowering in High-Risk Patients, the Canadian Viewpoint. *Hypertension*. 2016;68:3-5. <http://doi.org/cd44>
18. Myers MG, Kaczorowski J, Paterson JM, Dolovich L, Tu K. Thresholds for diagnosing hypertension based on automatic office blood pressure measurements and cardiovascular risk. *Hypertension*. 2015;66:489-95. <http://doi.org/f7m7mc>
19. Myers MG, Kaczorowski J, Dolovich L, Tu K, Paterson JM. Cardiovascular Risk in Hypertension in Relation to Achieved Blood Pressure Using Automatic Office Blood Pressure Measurement. *Hypertension*. 2016;68:866-72. <http://doi.org/f88kkz>
20. Weber MA, Poulter NR, Schutte AE, Burrell L, Horiuchi M, Prabhakaran D, et al. Is it time to reappraise blood pressure thresholds and targets? Statement from the International Society of Hypertension – a global perspective. *Hypertension*. 2016;68:266-8. <http://doi.org/cd45>
21. Fan F, Yuan Z, Qin X, Li J1, Zhang Y, Li Y, et al. Optimal Systolic Blood Pressure Levels for Primary Prevention of Stroke in General Hypertensive Adults: Findings From the CSPPT (China Stroke Primary Prevention Trial). *Hypertension*. 2017;69:704. <http://doi.org/f93dzv>
22. The SPS3 Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet*. 2013;382:507-15. <http://doi.org/f2fznp>
23. Schiffrin EL, Calhoun DA, Flack JM. Do we need a new definition of hypertension after SPRINT? *Amer J Hyperten*. 2016;29:1127-9. <http://doi.org/cd46>
24. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marcak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 15 mmHg. *JAMA*. 2017;317:165-82. <http://doi.org/cdxw>
25. Richman IB, Fairley M, Jorgensen E, Schuler A, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of intensive blood pressure management. *JAMA Cardiol*. 2016;1:872-9. <http://doi.org/cd47>

Antagonist

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There is a linear relationship between blood pressure (BP) levels and the risk of mortality due to cardiovascular and cerebrovascular disease. Although this relationship is present starting from optimal BP levels (115/75 mmHg.), hypertension (HT) is defined as the value above which its detection and treatment correlates with an improvement in cardiovascular morbidity and mortality. This value of 140/90 mmHg was obtained in a conventional manner and so far the evidence showed no benefit in treating patients with antihypertensive drugs in the intermediate range between 115/75 mmHg and 140/90 mmHg. (1)

Before entering the core of the discussion, I would like to point out that, despite the high prevalence and damage caused by HT, the most important problem at least in our country is the lack of diagnosis, the high percentage of people that do not know they are hypertensive and in treated hypertensive patients, the scarce degree of its control. (2)

One of the daily questions in front of the hypertensive patient is, how much should we lower BP values and how long should we take to reach this therapeutic

target. There is a general consensus to reduce BP in the hypertensive population to values below 140/90 mmHg. However, in special populations, such as diabetics, chronic kidney disease patients or the elderly, there are discrepancies among the different guidelines in relation to therapeutic targets. The most striking fact is that these differences arise from evidence-based expert consensus derived from the same epidemiological studies or from the retrospective analysis of randomized clinical trials (RCT).

In the early 2000s, both the American guidelines (JNC7) and the European guidelines recommended BP therapeutic values below 130/80 mmHg in diabetic patients or with chronic kidney disease and 125/75 mmHg if they also had proteinuria. These recommendations were based more on epidemiological observations than on RCT and were supported by the criterion of “the lower the BP the better” (3-4).

The rationale of this recommendation is that a greater blood pressure decrease could reduce the high residual risk of these patients. However, post hoc analysis of several studies showed that lowering BP below certain values paradoxically could increase the risk of cardiovascular events, resulting in a J-curve (paradoxical increase in cardiovascular mortality). Therefore, establishing the therapeutic targets began

to be the subject of debate, controversy, and growing uncertainty.

This changing scenario was understandable given the lack of RCT designed to answer these questions, especially in certain clinical situations.

As an example, it suffices to evaluate the recommendations in the diabetic hypertensive patient, undoubtedly a patient at a higher cardiovascular risk. For many years there was agreement among the main guidelines to reduce BP to values below 130/80mmHg. In 2009, the European Society of Hypertension reevaluated the RCT performed so far, observing that the benefits of antihypertensive treatment in diabetic patients were more marked in those clinical trials with higher levels of initial BP (5).

For example, in the SYST-EUR study the systolic blood pressure (SBP) in the control group was 162 mmHg and in the active group 153 mmHg. This decrease meant 31% reduction of cardiovascular events (CVE) (6). In the UKPDS, the SBP in the control group was 155 mmHg and in the active group 144 mmHg, a decrease which reduced CVE by 34% (7). In the ABCD HTA study the control group achieved a SBP of 138 mmHg and the active group of 132 mmHg with no reduction in CVE (8). To sum up, the lower the initial BP, the lower the benefit of the antihypertensive treatment.

The ACCORD study was the first one conducted in diabetic hypertensive patients designed to assess whether a more intensive target (SBP <120 mmHg) conferred a greater reduction in CVE than a standard target (SBP <140 mmHg). After a 5-year follow-up period, no significant differences were found in the hard endpoints, cardiovascular mortality and myocardial infarction; but there was a significant reduction of stroke in the group with lower BP. It should be noted that the group with more intensive treatment had more than twice as many adverse events (hypotension, syncope, hyperkalemia, and renal failure). (9)

However, despite these evidences, there was no coincidence in BP levels as therapeutic targets in diabetic hypertensive patients in the different guidelines published in recent years. As an example four scientific societies established four different therapeutic targets for hypertensive diabetic patients (10-13). These discrepancies in the recommendations create confusion among primary care physicians.

In this context, the results of the SPRINT trial were published in advance at the end of 2015. Performed in 100 medical centers of the United States, 9,361 high-risk hypertensive patients, over 50 years of age, with no history of diabetes or stroke were included. They were randomized to two therapeutic targets: one group with intensive treatment (SBP <120 mmHg) and the other group with standard treatment (SBP <140 mmHg). At the beginning of the study, the SBP average value was 139 mmHg. An average of three antihypertensive drugs was used for the intensive treatment and two for the standard treatment.

The study was discontinued at 3.2 years, due to 25% reduction in the primary endpoint (cardiovascular composite) in patients with intensive treatment compared with standard treatment ($p \leq 0.001$). The intensive treatment group also showed 27% reduction in total mortality risk ($p=0.003$). The final values of SBP were 121 and 136 mmHg, respectively. (14)

These results, which contrast with other studies, have generated more uncertainty in the medical community and a series of communications, editorials, criticisms and controversies. (15-17)

There are several considerations and questions regarding the results of the SPRINT trial, some difficult to explain and one, undoubtedly the most important, related with the methodology of BP measurement.

The result of the primary composite endpoint was determined by a significant decrease in the rate of heart failure in the intensive treatment group, and certainly related to the greater use of diuretics; however, there was no significant benefit in decreasing the rate of myocardial infarction or stroke with the lower BP levels. This finding is inexplicable since stroke is the only event that continues to be prevented with SBP goals below 130 mmHg. (18)

Patients older than 75 years of age benefited more than those under that age. But a recent Irish study showed that people older than 75 years who met the criteria to enter the SPRINT trial had five times more falls and syncope than those registered in the SPRINT study. (19) This raises caution at the moment of generalizing the results of clinical trials to the patients of the "real world," with greater number of comorbidities and drugs, and with a less strict clinical follow-up. The question then arises: What were the characteristics of patients over 75 years of age who entered the study?

Another striking finding was that patients who were admitted with lower BP (SBP <132 mmHg) benefited more than hypertensive patients who were admitted with SBP levels >145 mmHg; whereas most clinical trials have shown that antihypertensive treatment produces a significant decrease in cardiovascular events when the initial BP is higher. (18) A probable explanation may be given by the fact that patients who were assigned to the standard group had to withdraw part of the medication to maintain that therapeutic target, especially the dose of diuretics.

An important result was the occurrence of serious adverse events in the group of the most intensive treatment. Although there was less orthostatic hypotension in this group, probably due to lower pressures, there was a significant increase in hospitalizations due to syncope, sustained hypotension, electrolyte abnormalities such as hyponatremia and hypokalemia, and acute renal damage, even more noticeable in patients with good previous renal function.

Again, these events could be related to the greater use of diuretics and higher doses of renin angiotensin system blockers. These adverse events have an im-

pact, at least in the real world, on adherence to treatment (20) and should be taken into account in the cost-benefit ratio of reaching lower BP targets.

Finally, the most important aspect to take into account in the results of the SPRINT trial is, in my opinion, the methodology used to measure BP. In order to eliminate the effect of white-coat HT, BP measurement was made with a fully automatic and programmable device (OMRON 907), without the presence of an observer (doctor or nurse). After remaining for 5 minutes under resting conditions, the device measured BP on three occasions, with intervals of one minute and an average of three readings. This way of measuring BP is essential to understand the results of the study. In principle, there are no previous clinical trials that have used this methodology, and therefore it is not possible to compare results. For example, in studies where different therapeutic targets were assessed, such as the ACCORD, SPS3 and HOT studies, although BP was measured with automatic devices, measurements were always performed in the presence of the observer. (9, 21-22)

The first reflection would then be that these results are only applicable for those patients who meet the inclusion and exclusion criteria of the SPRINT trial and if BP measurements are performed in the same way as in this study.

For more than a century, the conventional method for measuring office BP was the mercury sphygmomanometer with auscultatory technique. The main studies that defined HT were performed based on this conventional technique, demonstrating its risks and the benefit of antihypertensive treatment. Although in terms of population, BP measured in a conventional manner is a strong predictor of risk, in the individual patient it has a lower prognostic value. This conventional technique may be subject to several errors: single measurements, rounding, and the presence of the observer, being more marked before the doctor than before the nurse. With the advent of new technology in recent years, BP measurement with automatic devices by oscillometric method is an increasing practice. (23, 24)

However, BP measurement in the office with automatic devices remains an unresolved issue. There are different types of devices and different protocols; for example, there are automatic programmable devices that take BP 3 or 5 times, some discard the first reading and others average all, and fundamentally in some protocols, such as the one used in the SPRINT trial, the measurement takes place without the presence of the observer and in others this aspect is not considered.

The truth is that they are not universally accepted and recommended practices. These automatic devices are used in Canada and in some centers in the United States, and in these cases the thresholds for the diagnosis and treatment of HT are 5 mmHg lower than those used with the practice of conventional measure-

ment: 135/85 mmHg. vs. 140/90 mmHg, respectively. (25)

It is worth mentioning that, to date, we have five ways to assess BP: in the office with an observer and with an automatic oscillometric device (preferential for many), in the office with an observer and with an auscultatory method (mercury or aneroid sphygmomanometer), in the office without an observer with automatic device (SPRINT method) and outside the office: ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM)

Several studies were carried out with the purpose of comparing BP values measured with the SPRINT method with measurements made by the conventional method, or by ABPM or HBPM. Thus, in a study with a small number of patients, BP levels with the SPRINT method were similar to the 24-hour ambulatory SBP or even lower, and another study reported a 15 mmHg difference in SBP compared with the conventional auscultatory technique and 10 mmHg compared with the SBP measured by HBPM. (26) Assuming that the degree of concordance of BP is maintained in its different levels, an aspect that has not been studied, it could be inferred that if we measured BP with a conventional method, between 10 and 15 mmHg should be added to the therapeutic targets of the SPRINT study. This means that if the SPRINT trial had been performed with this technique, finally, we would be comparing a population with lower BP of (121+15) 136 mmHg vs. another population with uncontrolled HT of (136+15) 151 mmHg. In other words, we would compare a controlled hypertensive population vs. an uncontrolled hypertensive population and the results would be obvious. Thus, it is clear that we cannot extrapolate BP values from the SPRINT study to our daily practice. To determine what is the best therapeutic target is, in my view, still unclear. Intra-arterial pressure varies from beat to beat and is different depending on the distance from the measurement site to the heart. Blood pressure measurement with a non-invasive technique involves a series of difficulties and we also have two important components in blood perfusion: SBP and diastolic BP (DBP). The marked decrease in BP increases the risk of cardiovascular events, the J-or U curve in the graphs that relate BP levels with cardiovascular mortality. Surely there is no point of inflection, but a range of BP where above and below that range there is greater risk.

To date, many questions remain unanswered; surely the therapeutic targets of SBP and DBP should be different for different populations (diabetic, renal, coronary artery disease, frail and non-frail elderly patients). In addition, there should be an agreement to carry out interventional studies with the same methodology applicable to daily practice. Perhaps it is time to conduct studies with more universally accepted practices such as ABPM.

As a final reflection, some messages: 1. In HT the most important thing is to improve its awareness and

control. 2. The threshold for diagnosis and treatment in the general population is still 140/90 mmHg. 3. There are new methods to measure BP in the office. 4. The values of office BP with different methods are not comparable among them.

Conflicts of interest:

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material)

REFERENCES

- Lonn EM, Bosch J, López-Jaramillo J, Zhu J, Liu L, Pais P, et al. HOPE-3 Investigators. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Engl J Med*. 2016;374:2009-20. <http://doi.org/bjht>
- Marín MJ, Fabregues G, Rodríguez PD, Díaz D, Paez O, Alfie J, y col. Registro Nacional de Hipertensión Arterial. Conocimiento, tratamiento y control de la hipertensión arterial. Estudio RENATA. *Rev Argent Cardiol*. 2012;80:121-9.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-72. <http://doi.org/b67bsv>
- 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21:1011-53. <http://doi.org/dckh8n>
- Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009; 27:2121-58. <http://doi.org/chmkxz>
- Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhäger WH, et al, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; 350:757-64. <http://doi.org/d4kbds>
- UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703-13. <http://doi.org/dtrxj5>
- Savage S, Johnson Nagel N, Estacio RO, Feig PU, MacCarthy EP, Lukken NJ, et al. The ABCD (Appropriate Blood Pressure Control in Diabetes) trial. Rationale and design of a trial of hypertension control (moderate or intensive) in type II diabetes. *Online J Curr Clin Trials*. 1993:104.
- The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85. <http://doi.org/dgx2qw>
- James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 1:507-20. <http://doi.org/3pp>
- Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281-357. <http://doi.org/wmq>
- Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens*. 2014;32:3-15. <http://doi.org/f24pt6>
- American Diabetes Association. Standards of medical care in diabetes-2013. *Diabetes Care*. 2013;36(suppl 1):S11-S66. <http://doi.org/qp6>
- The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103-16. <http://doi.org/bbxd>
- Schiffrin EL, Calhoun DA, Flack JM. SPRINT proves that lower is better for non-diabetic high-risk patients, but at a price. *Am J Hypertens*. 2016;29:2-4. <http://doi.org/cfjz>
- Kjeldsen SE, Mancia G. Unobserved automated office blood pressure measurement in the Systolic Blood Pressure Intervention Trial (SPRINT): systolic blood pressure treatment target remains below 140 mmHg. *Eur Heart J Cardiovasc Pharmacother*. 2016;2:79-80. <http://doi.org/cfj2>
- Parati GF, Ochoa JE, Bilo G, Zanchetti A. SPRINT Blood Pressure Sprinting Back to Smirk's Basal Blood Pressure? *Hypertension*. 2017;69:15-9. <http://doi.org/cfj3>
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels—overview and meta-analyses of randomized trials. *J Hypertens*. 2014;32:2296-304. <http://doi.org/f6pzm9>
- Sexton DJ, Canney M, O'Connell MD, Moore P, Little MA, Seaghdha CM, et al. Injurious Falls and Syncope in Older Community Dwelling Adults Meeting Inclusion Criteria for SPRINT. *JAMA Intern Med* 2017;177:1385-7. <http://doi.org/cfj4>
- Thomopoulos, Parati G, Zanchetti A. Effects of blood pressure lowering treatment in hypertension: 8. Outcome reductions vs. discontinuations because of adverse drug events – meta-analyses of randomized trials. *J of Hypertension*: 2016;34:1451-63. <http://doi.org/f8t6sr>
- The SPS3 Study Group. Effects of blood pressure targets in patients with recent lacunar strokes. *Lancet*. 2013;382:507-15. <http://doi.org/f2fznp>
- Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998;351:1755-62. <http://doi.org/dxwzck>
- Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. Measurement of blood pressure in the office: recognizing the problem and proposing the solution. *Hypertension*. 2010;55:195-200. <http://doi.org/cgvrv>
- Myers MG, Kaczorowski J, Paterson JM, Dolovich L, Tu K. Thresholds for diagnosing hypertension based on automated office blood pressure measurements and cardiovascular risk. *Hypertension* 2015; 66:489-95. <http://doi.org/f7m7mc>
- Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K, et al. CHEP Guidelines Task Force. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for
- Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *Can J Cardiol*. 2016;32:569-88. <http://doi.org/cd4z>
- Filipovský J, Seidlerová J, Kratochvíl Z, Karnosová P, Hronová M, Mayer O Jr. Automated compared to manual office blood pressure and to home blood pressure in hypertensive patients. *Blood Press*. 2016;4:228-34. <http://doi.org/cfmp>

AGONIST'S REPLY

Dr. Marín opposes to the intensive treatment of blood pressure based on:

- 1) The differences between the various hypertension treatment guidelines
- 2) The method of measuring blood pressure
- 3) The adverse effects of intensive treatment in both ACCORD and SPRINT studies
- 4) The cost of intensive treatment, using more medications and more visits to the doctor.

Undoubtedly there are different treatment goals in the different therapeutic guidelines, but they precede the SPRINT trial, and only the recommendations of Hypertension Canada (1-2) take the SPRINT trial

into account for the moment. There will soon be other therapeutic guidelines that will follow the example of Hypertension Canada incorporating recommendations based, at least in part, on the SPRINT trial. The American College of Cardiology and the American Heart Association are about to publish a recommendation, and we will see what they propose as therapeutic targets. It is likely that the European Society of Hypertension will continue to ignore the SPRINT trial based on the method of measuring blood pressure. (3-5)

This second point mentioned by Dr. Marín, but already discussed by me, means that targets for intensive treatment should be adapted to the different methods of measuring blood pressure in different settings. It is probable that there is a difference of around 10 mmHg between blood pressure measured as in the SPRINT trial and the classical technique, provided that the latter is obtained rigorously. Unfortunately, blood pressure is usually measured defectively, and the results are sometimes 15 to 20 mmHg higher than with the automatic electronic measurement with 3-5 readings and in the absence of the professional. For these reasons, we propose the SPRINT trial intensive targets for those that have devices such as those used in this study, which occurs in at least 40% of family doctor practices in Canada, and blood pressures <130/80 mmHg when it is measured in the classical way.

The question is whether these goals are only for SPRINT-type patients. I believe that in principle yes, but that with the agreement of the patient and with caution, they can be extended to other populations of hypertensive patients, including diabetic individuals. This last recommendation is based on the fact that the results of the ACCORD study resemble those of the SPRINT trial, but the ACCORD study did not recruit enough patients and the factorial design may also have contributed to the negative result. In addition, the benefit of stroke in the ACCORD study should be taken into account, even if it were in a few patients treated intensively.

The argument of adverse effects does not take into account that they were infrequent, and generally of a minor nature. For this reason, as long as the follow-up of the patients is adequate, and the treatment intensity reduced if undesirable effects appear, these should not be a problem.

The last point is that there may be an increase in cost. But the benefits are dramatic with intensive treatment, and the reduction in heart failure and mortality largely outweigh the higher costs, as has already been demonstrated.

Ernesto L. Schiffrin

REFERENCES

1. Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, et al.; HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374:2009-20. <http://doi.org/bjht>

2. Redon J, Lurbe E. Ambulatory Blood Pressure Monitoring Is Ready to Replace Clinic Blood Pressure in the Diagnosis of Hypertension: Con Side of the Argument. *Hypertension*. 2014;64:1169-74. <http://doi.org/cfmq>
3. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels - updated overview and meta-analyses of randomized trials. *J Hypertens*. 2016; 34:613-22. <http://doi.org/f8dp23>
4. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens*. 2017; 35:922-44. <http://doi.org/cfmr>

ANTAGONIST'S REPLY

To make a controversy about whether it is better to lower systolic blood pressure (SBP) to values below 120 or 140 mmHg, is at least striking, when in our country more than 75% of hypertensive patients do not reach traditional therapeutic values below 140/90 mmHg.

Dr. Schiffrin suggests redefining arterial hypertension depending on cardiovascular risk and how to measure blood pressure (BP). Regarding the first point, no one doubts the benefit of antihypertensive treatment in level 2 and 3 hypertensive patients. In the recent HOPE 3 study performed in patients at intermediate risk and with borderline BP levels and level 1 HT; only those patients in the highest tertile of BP benefited from antihypertensive treatment (>143.5 mmHg, mean 154.1 mmHg) (1). Once again, there is no evidence of starting pharmacological treatment with SBP values below 140 mmHg.

Concerning the way to measure BP, as indicated in my initial argument, we have at least five ways to perform it; most of the clinical trials used the conventional method, and only the SPRINT study used an automatic device without an observer.

In this sense, if the observer in the SPRINT study had included a measurement of conventional BP before leaving the office, it would have been very useful, and even if the treatment adjustment criteria were based on the automatic method, this measurement would have allowed comparing BP values with both methods.

The mainstay for HT diagnosis and monitoring continues to be BP measurement in the office. Its main limitation is its low reproducibility; due to the small number of measurements, the great variability, failures in the accuracy of an indirect measurement, and the presence of the observer which is the principal source of inaccuracy.

Hence the importance of taking measurements outside the office. Ambulatory BP monitoring has come to clarify this problem. Ambulatory BP correlates better with white organ damage, predicts cardiovascular events and there are studies suggesting that guiding treatment with ABPM is better than guid-

ing it through office BP (2). The SPRINT trial is the first study that proposes a new way to measure BP. We should propose a study to evaluate if this way of measuring BP is more convenient than the traditional one, ABPM or HBPM.

In a recent meta-analysis that included 16 clinical trials comparing more aggressive vs. less aggressive BP targets, it was observed that the more intensive treatment reduced in the same proportion the relative risk of all endpoints in both treatment approaches; while the reduction in absolute risk decreased in the lower strata of SBP (3).

It is very likely that the hypothesis “the lower the better” is opposed to the “J-curve” hypothesis. The current challenge is to individualize the target BP. Intermediate objectives of 130 mmHg could be reasonable. The reduction in SBP below 130 mmHg reduces the relative risk of major cardiovascular events, but the absolute reduction in cardiovascular risk is significantly lower and the occurrence of serious adverse effects such as hypotension, syncope, electrolyte dis-

turbances and impaired renal function increases the risk of treatment discontinuation. (4).

Dr. Marcos Marín

REFERENCES

1. Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, et al., HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2009-20. <http://doi.org/bjht>
2. Redon J, Lurbe E. Ambulatory Blood Pressure Monitoring Is Ready to Replace Clinic Blood Pressure in the Diagnosis of Hypertension: Con Side of the Argument. *Hypertension* 2014;64:1169-74. <http://doi.org/cfmq>
3. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels - updated overview and meta-analyses of randomized trials. *J Hypertens* 2016; 34:613-22. <http://doi.org/f8dp23>
4. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens* 2017; 35:922-44. <http://doi.org/cfmr>