Benefits and potential risks of intensive goals in the treatment of arterial hypertension – Systematic review and meta-analysis of clinical trials

Beneficios y riesgos potenciales de las metas intensivas en el tratamiento de la hipertensión arterial. Revisión sistemática y metaanálisis de ensayos clínicos

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Abstract

Introduction and objectives: There is controversy regarding the most appropriate goals for blood pressure (BP) control. We assess the benefits and risks of choosing different therapeutic thresholds. **Methods:** We perform a systematic review and meta-analysis of large clinical trials to assess the impact of different therapeutic strategies on the reduction of cardiovascular events and the development of serious adverse effects. **Results:** Four trials with 29,820 participants were included, with mean age of 65 ± 7.9 years; 42.2% were women and 22% were diabetic. Overall, intensive goals showed a non-significant trend toward reducing cardiovascular mortality (relative risk [RR]: 0.89; 95% confidence interval [CI]: 0.68-1.07; $p = 0.16$) with non-impact in total mortality ($p = 0.45$) and with moderate heterogeneity among the included trials (I^2 index [I] 2:44 and 59%, respectively). Nevertheless, intensive goals reduce non-fatal cardiovascular events (RR: 0.82; 95% CI: 0.70-0.91; $p = 0.0003$), being consistent in all the analyzed trials (I^2 : 0%). Regarding adverse effects, intensive goals caused more emergency consultations or hospitalization (RR: 1.98; 95% CI: 1.59-2.46; $p < 0.0001$; I^2 : 14%), with no clear increase in renal failure (RR: 1.65; 95% CI: 0.94-2.89) but with increase in falls and syncope (RR: 2.39; 95% CI: 1.56-3.67; $p < 0.0001$; I^2 : 28%). **Conclusion:** Intensive BP goals reduce non-fatal cardiovascular events, without reduction in mortality, and with an increase of risk of adverse events. These results suggest that individual goals should be set according to the risk of each patient. **Clinical trial registration:** PROSPERO (CRD42020149134).

Key words: Hypertension. Benefits. Risks. Intensive goals. Meta-analysis.

Resumen

Introducción y objetivos: Existe controversia respecto a las metas más adecuadas para el control de la presión arterial. Debido a ello nos propusimos valorar los beneficios y riesgos de adoptar distintos umbrales terapéuticos. **Métodos:** Revisión sistemática y metaanálisis de ensayos clínicos de grandes dimensiones a fin de valorar el impacto de las distintas estrategias

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terapéuticas en la reducción de eventos cardiovasculares y desarrollo de efectos adversos serios. **Resultados:** Se incluyeron cuatro ensayos con 29,820 participantes, con edad media de 65 ± 7.9 años. El 42.2% eran mujeres y el 22% eran diabéticos. Globalmente las metas intensivas mostraron una tendencia no significativa hacia la reducción de la mortalidad cardiovascular (riesgo relativo [RR]: 0.89; intervalo de confianza del 95% [IC 95%]: 0.68-1.07; $p=0.16$) sin impacto en la mortalidad total ($p=0.45$) y con moderada heterogeneidad entre los ensayos (índice I [I^2]: 44 y 59% respectivamente). En cambio, sí redujeron eventos cardiovasculares no fatales (RR: 0.82; IC 95%: 0.70-0.91; $p = 0.0003$), siendo esto consistente en los ensayos analizados (I^2 : 0%). Respecto a los efectos adversos, las metas intensivas generaron más consultas a guardia o internaciones (RR: 1.98; IC 95%: 1.59-2.46; $p<0.0001$; I^2 : 14%), sin claro incremento en la insuficiencia renal (RR: 1.65; IC95%: 0.94-2.89) y con aumento de las caídas y síncope (RR: 2.39; IC 95%: 1.56-3.67; $p<0.0001$; I^2 : 28%). **Conclusión:** Metas intensivas de presión arterial reducen eventos cardiovasculares no fatales, sin impacto en la mortalidad, y con un incremento en el riesgo de eventos adversos. Parecería razonable individualizar los objetivos terapéuticos de acuerdo con el riesgo de cada paciente. **Registro:** PROSPERO (CRD42020149134).

Palabras clave: Hipertensión arterial. Beneficios. Riesgos. Metas intensivas. Metaanálisis.

Introduction

Although the relationship between blood pressure (BP) and vascular events is positive and linear even at relatively low values, establishing a clear cutoff point for high BP (HBP) diagnosis and follow-up has its advantages, both for doctors and patients¹. For these reasons, since the end of the 1970s, the first consensus for the management of this entity have emerged^{2,3}. The 1988 Fourth Joint Declaration of the National Committee for detection, evaluation, and treatment of HBP (JNC IV) established the figures of $\geq 160/90$ mmHg for systolic BP (SBP) and diastolic (DBP), respectively, as cutoff points for HBP diagnosis and treatment⁴. In 1993, JNC V was published, which modified these values for the $\geq 140/90$ mmHg values⁵, which prevailed without questioning until recent years. In November 2017, the latest guidelines for diagnosis and treatment of HBP were published, which were developed by multiple scientific societies from different specialties of the USA⁶ and established a new cutoff point for HBP diagnosis, with said value being established at 130/80 mmHg. The element with the heaviest weight for driving the modification of the goals was the SBP Intervention Trial (SPRINT)⁷. This study received numerous practical⁸ and methodological⁹⁻¹¹ questionings, while the technique used to measure BP has been criticized¹²⁻¹⁵. The discussion regarding the new HBP goals led to a multiplication of meta-analyses trying to answer this question¹⁶⁻¹⁸. However, instead of settling the conflict, the new publications have contributed to perpetuate it, since the different analyses have shown opposing results. This is basically explained by the heterogeneity of the inclusion criteria used when selecting studies for meta-analysis. On the other hand, most these publications have focused on the benefits

of HBP intensive treatment, but without weighing the risks this intervention entails. Therefore, within the framework of the development of the of the National Clinical Practice Guidelines for HBP diagnosis and treatment of the Ministry of Health of the Argentine Nation, we decided to carry out a meta-analysis to weight the most appropriate therapeutic thresholds for the treatment of people with HBP.

Materials and methods

Inclusion criteria

Randomized clinical trials (RCTs) that aimed at comparing intensive and usual BP goals as their primary objective, with at least 1000 participants per group, and with a follow-up equal to or longer than 12 months were included in the study.

Intensive goals were defined as BP values that were equal to or lower than 130/80 mmHg, and usual goals, as values that were similar or lower than 140/90 mmHg. Studies with a non-randomized design and repeated reports of a single RCT were excluded if they did not add information to that provided by the original report of the study. Those RCTs where the control arm had BP means higher than 145/95 mmHg were also excluded from the study. PRISMA²⁰ recommendations were followed for the report on the methodology¹⁹ and results.

Literature search

A search for RCTs, without time restrictions and using the English, Portuguese, and Spanish languages, was performed. This process was carried out simultaneously by two experienced operators (S.G.Z. and

A.R.) who selected the studies to be included. Disagreements were resolved by consensus. Medline, LILACS, academic Google, and the Cochrane collaboration database were used as search engines.

Evaluated endpoints

Of the selected studies, data on total and cardiovascular mortality were collected, as well as on cardiovascular events occurrence: acute coronary syndromes (with acute myocardial infarction [AMI] with and without ST-segment elevation and unstable angina being grouped), ischemic and hemorrhagic cerebrovascular accidents (CVA), and transient ischemic attack. As for adverse effects, the following were assessed: falls, syncope, hypotension, acute kidney failure, and “serious” adverse effects, understood as all those events that led to an emergency room or on duty physician visit, or that required participants’ hospital admission, regardless of whether RCTs used another operational definition for these events. For identification of these end points, the definitions provided by the researchers of each trial were used.

Risk of bias assessment

Assessment of the risk of bias of included studies was carried out, according to the Cochrane Handbook recommendations^{21,22}. The evaluated domains were random sequence generation, allocation concealment, blinding of personnel and participants, blinding of evaluators, incomplete outcome data evaluation, selective reporting, and one last domain for other potential biases. Risk of bias was categorically evaluated as low risk, uncertain risk, and high risk, following the recommendations for this purpose²¹⁻²³.

Registry

The present meta-analysis was registered in PROSPERO with identification number CRD42020149134.

Statistical analysis

Since these were clinical trials, relative risks (RR) and their respective confidence intervals (CIs) were used as summary measure. To meta-analyze the data, and due to the differences in the selected studies, using a random effects model was decided, as described by DerSimonian and Laird²⁴. Heterogeneity of the studies was assessed by calculating between-study variance (square

tau) and the square I index (I^2)²⁵. Data analysis was carried out using Review Manager 5.3.

Results

Five-hundred and thirty potentially relevant articles were identified, out of which 246 were excluded because they were duplicated, five for not being RCTs and 275 for not meeting the inclusion criteria. Finally, four clinical trials were analyzed (Suppl. Fig. 1): SPRINT⁷, ACCORD (action to control cardiovascular risk in diabetes)²⁶, heart outcomes prevention evaluation-3 (HOPE-3)²⁷, and secondary prevention of small subcortical strokes (SPS3)²⁸, with a total of 29,820 participants. Study participants mean age was 65 ± 7.9 years; 42.2% were women and 22% were diabetics. The rest of the features of the included RCTs are summarized in Table 1. Some additional relevant characteristics of the individual clinical trials included in the review are specified in Table 2. Quality of the evidence of the studies was then assessed according to the aforementioned guidelines (Suppl. Fig. 2). The reasons why some domains of each trial were regarded as having an uncertain or high risk of bias are described in Appendix 1.

Supplementary figure 3 outlines evidence overall quality; the domain with the highest risk of bias is observed to be “Blinding of personnel and participants,” since three of the four trials were open label.

Globally analyzed, all four studies (SPRINT, HOPE-3, ACCORD, and SPS3) showed a non-significant trend toward a reduction in cardiovascular mortality with the use of intensive BP goals (RR: 0.89; 95% CI: 0.68-1.07; $p = 0.16$), with moderate heterogeneity (I^2 : 44%) (Fig. 1).

Intensive goals did not reduce overall mortality either (RR: 0.94; 95% CI: 0.8-1.1; $p = 0.45$) (Fig. 2).

When cardiovascular events were analyzed as a whole, intensive goals significantly reduced them (RR: 0.82; 95% CI: 0.70-0.91; $p = 0.0003$), with no evidence of heterogeneity (I^2 : 0%) (Fig. 3).

To accurately assess the risk-benefit ratio of the different BP control goals, adverse effects occurring in the different treatment arms were analyzed. One study (HOPE-3) did not report the need for unscheduled care by trial participants due to the employment of drug treatment and therefore could not be included for that purpose. In the remaining three studies, serious adverse events were more common in the intensive arm, with this being more noticeable in those RCTs that established lower BP targets (ACCORD and SPRINT). Overall, intensive

Table 1. Characteristics of included studies

Characteristics	ACCORD ACCORD study group, 2010 ²⁶	SPS3 SPS3 study group, 2013 ²⁸	SPRINT SPRINT research group, 2015 ⁷	HOPE-3 Lonn et al., 2016 ²⁷
Publication year	2010	2013	2015	2016
Participants (n)	4,733	3,020	9,361	12,705
Age (SD)	62.2 ± 6.9	63 ± 10.8	67.9 ± 9.5	65.8 ± 6.4
Admission BP (mmHg)	139/76	143/79	140/78	138/82
Females (%)	2,258 (47.7)	1,118 (37)	3,332 (35.6)	5,874 (46.2)
Diabetics (%)	4,733 (100)	1,106 (36.6)	0 (0)	731 (5.8)
Body mass index (kg/m ²)	32.1 ± 5.6	29.2 ± 6.8	29.9 ± 5.8	27.1 ± 4.8
Coronary artery disease (%)	33.7%*	11%	20.1%	0%
Cerebrovascular disease (%)		100%	0%	0%
BP goals in the study	SBP <120	SBP <130	SBP <120	Fixed drug dose
BP difference at follow-up end (mmHg)	14.2/6.1	11/- [†]	14.8/7.6	6/3
Average follow-up (years)	4.7	3.7	3.26 [‡]	5.6
Type of study	Open label	Open label	Open label	Double blind
Estimated cardiovascular risk of included patients	High	High	High	Intermediate

*Coronary artery disease and cerebrovascular disease not discriminated.

[†]DBP value not reported.[‡]Terminated prematurely for demonstrated benefit.

BP: blood pressure; SD: standard deviation; SBP: systolic blood pressure; ACCORD: Action to Control Cardiovascular Risk in Diabetes; SPS3: Secondary Prevention of Small Subcortical Strokes; SPRINT: Systolic Blood Pressure Intervention Trial; HOPE-3: Heart Outcomes Prevention Evaluation-3; DBP: diastolic blood pressure.

Table 2. Additional characteristics of included studies

Study	Details
ACCORD ACCORD study group 2010 ²⁶	– Participants' mean glycated hemoglobin: 8.3 ± 1.1% (with no differences between groups)
SPS3 SPS3 study group, 2013 ²⁸	– 98.6% of participants were enrolled due to an ischemic stroke and 1.4% to a transient ischemic accident
SPRINT SPRINT research group, 2015 ⁷	– Terminated early due to evidence of benefit – An unusual strategy was employed to measure BP – In the control arm, 87% of participants had their antihypertensive treatment reduced, with participants being found asymptomatic – There was a significantly higher proportion of diuretic use in the intensive arm
HOPE-3 Lonn et al., 2016 ²⁷	– Candesartan 16 mg fixed dose + hydrochlorothiazide 12.5 mg – A pre-specified subgroup analysis found benefits with BP reduction among participants with higher BP values (top third of the sample)

BP: blood pressure; ACCORD: Action to Control Cardiovascular Risk in Diabetes; SPS3: Secondary Prevention of Small Subcortical Strokes; SPRINT: Systolic Blood Pressure Intervention Trial; HOPE-3: Heart Outcomes Prevention Evaluation-3.

goals were associated with an increased risk of serious adverse events (RR: 1.98; 95% CI: 1.59-2.46; $p < 0.0001$; I^2 : 14%) (Fig. 4).

Given that kidney failure is a major concern when establishing more demanding BP control goals, it was

analyzed as an independent outcome. A non-significant trend was observed toward an increased risk of impaired kidney function episodes with intensive goals ($p = 0.08$), but with marked heterogeneity between the analyzed trials (Fig. 5).

Figura 1. Forest plot 1: overall mortality.

Figura 2. Forest plot 2: cardiovascular mortality.

Figura 3. Forest plot 3: cardiovascular events.

It should be noted that heterogeneity regarding the risk of kidney function impairment was not only statistical, but there were marked differences in clinical definitions. Thus, while in ACCORD, this was categorized as creatinine values higher than 3.3 mg/dL or need for

dialysis, in SPRINT, it was defined as the coding within the first three diagnoses at hospital discharge.

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Finally, pharmacological treatment-attributable occurrence of syncope and falls was compared, with an

Figure 4. Forest plot 4: serious adverse events.

Figure 5. Forest plot 5: acute kidney failure.

Figure 6. Forest plot 6: falls and syncope.

increased risk in the intensive goals group being observed (RR: 2.39; 95% CI: 1.56-3.67; $p < 0.0001$), with low heterogeneity ($I^2 = 28\%$) (Fig. 6).

As it was observed in the serious adverse effects analysis, it can be appreciated how the studies with

lower BP goals (ACCORD and SPRINT vs. HOPE-3 and SPS3) contributed the highest number of events for this outcome.

To assess the impact of diabetic patients on this results, a sensitivity analysis was performed excluding

the ACCORD study, without differences being found, except for the risk of kidney failure, which became significant (data not shown).

Although the assessment of publication bias has limitations in the context of meta-analyses with <10 studies^{21,22}, it was carried out, without important bias for the present review been suggested (Suppl. Fig. 4).

Discussion

Our meta-analysis suggests that intensive BP control goals reduce major cardiovascular events, with a non-significant trend toward cardiovascular and overall mortality reduction, and an increased risk for adverse effects. Although the benefits of antihypertensive treatment have been demonstrated for decades²⁹, in recent years, the SPRINT⁷ study results, and changes in BP values to diagnose HBP established by the last US multisociety guidelines for the management this pathology⁶, have generated marked controversy regarding the most beneficial treatment goals. Thus, some meta-analyses have supported the change of treatment goals, claiming that BP figures lower than 130 mmHg for SBP would have benefits in terms of cardiovascular events and reduce mortality in treated patients³⁰⁻³⁴. When analyzing the results of these meta-analyses, four aspects should be borne in mind: (1) they included studies with patients with a wide range of BP values (even above 180 mmHg) and with therapeutic goals that ranged from <120 mmHg to <160 mmHg for SBP; (2) they included studies of small dimensions (with even <250 participants); (3) some of the included studies had surrogate endpoints as primary goals (such as progression of renal dysfunction) without having assessed fatal outcomes; and (4) included studies that did not report treatment-related adverse effects or that limited themselves to reporting the percentage of patients who discontinued treatment for this reason. The only RCT that found a reduction in cardiovascular and overall mortality with BP intensive goals was SPRINT, but, notably, this occurred without differences in the occurrence of AMI and CVA being demonstrated⁹⁻¹⁵.

Given that drug adverse effects sometimes occur lately, and that RCTs sample size calculation is carried out to detect components of the primary endpoint, but not adverse effects, these are often underrepresented in most trials. Adding the failure to report adverse effects, there is a risk for the intervention to be overestimated, thus magnifying the benefits and omitting the undesirable consequences associated with it.

Two 2014 meta-analyses^{35,36} found that although BP reduction produced similar benefits in all groups of participants, those with higher baseline risk also experienced greater absolute event reduction. Another recent meta-analysis³⁷ found similar results: with equal BP decreases, patients at higher cardiovascular risk obtained greater benefits in absolute terms. Therefore, including studies where participants had very HBP values at admission, or where the control arm had less stringent treatment goals than those currently recommended (<140/90 mmHg) could be a potential source of bias when assessing the benefit of two BP goals. This motivated that, in the present meta-analysis, only RCTs where control group participants had mean SBP values with figures ranging from 140 to 145 mmHg were included. On the other hand, in highly prevalent pathologies, studies of small dimensions entail two risks (1) that they include particular subpopulations that do not adequately represent the universe of individuals with the disease and (2) the existence of publication bias for positive studies. To avoid these sources of error, only medium-sized or large studies with a mean follow-up of at least 12 months were included.

Three recent meta-analyses found similar results to ours^{16,38,39}. Saiz et al.¹⁶ included six studies with 9795 patients and reported that intensive goals reduced cardiovascular events, hospitalization, and death from heart failure, without overall or cardiovascular mortality being reduced. They did not find an increase in the rate of major adverse events in the group assigned to intensive treatment, but did find more medication discontinuation due to adverse effects in general. Xie et al.³⁸ included 19 studies with 44,989 participants and found that intensive BP goals would reduce cardiovascular events, albuminuria, and retinopathy progression, with no impact on overall mortality, cardiovascular mortality, heart failure, and progression to end-stage kidney disease. As regard adverse effects, they did not find a significant increase in serious adverse effects, but they did in the occurrence of serious hypotension. Brunström and Carlberg³⁹ included 74 studies with 306,273 participants. According to their results, the impact on event reduction would vary according to BP baseline levels: in those studies, where participants had SBP values higher than 160 mmHg, antihypertensive treatment reduced cardiovascular disease events and death, while in studies with baseline figures of between 140 and 159 mmHg, treatment only reduced cardiovascular events. Conversely, in studies where participants had BP baseline values lower than 140 mmHg, antihypertensive treatment only reduced cardiovascular events when

subjects had a history of coronary artery disease. The present study delved deeper into the occurrence of different adverse events, understanding that the choice of usual and intensive antihypertensive goals should be an individualized decision, weighing the benefits and potential risks, with results that support the European Society of Cardiology recommendations⁴⁰.

Some of the aforementioned meta-analyses included, among the cardiovascular events, the occurrence of heart failure with different BP goals. In fact, at SPRINT, heart failure was one of the components of the primary endpoint where a larger difference was observed between groups⁷. However, both in this study and in others, the groups with intensive treatment received a higher proportion of diuretics¹². Consequently, it is difficult to determine if intensive BP goals reduce heart failure occurrence *per se* or if this observation is confounded by pharmacological treatment.

In our meta-analysis, 22% of included patients (n = 6570) had diabetes. Of these, the largest proportion come from the ACCORD study, which was carried out exclusively among individuals with this condition. While ACCORD showed no benefits in the primary endpoint that was analyzed, neither did it provide evidence of a worse prognosis with intensive goals. When participants of this study were excluded from our analysis, we did not find substantial differences in the results. This suggests that our analysis overall results are most likely applicable to patients with this disease.

Finally, another debatable aspect is the inclusion of studies with patients at high and intermediate cardiovascular risk in the present meta-analysis. If we accept that BP is a continuous variable and, that its relationship with cardiovascular risk is, therefore, linear, one would expect for the impact on its reduction to be similar but of lower magnitude in individuals with lower risk. This is observed in our meta-analysis with HOPE-3 results. Although this might have diminished the global estimator of analyzed effects, it increases their external validity, since in daily practice, it is not always that easy to accurately estimate the future risk of each individual person.

Limitations

The first major limitation of this work is that the databases of the included studies were not available. Not performing a meta-analysis of individual data precludes the performance some sensitivity analyses, as a more detailed assessment of diabetic patients or for better delineating the characteristics of subjects that are most susceptible to the development of adverse effects with

intensive BP control goals. In the second place, although using rigorous inclusion criteria limits some of the aforementioned biases, this entails risk of incurring others, such as selection bias. In fact, our meta-analysis is the one that has fewer studies included among those that have been recently conducted. However, by having included large studies, it has a larger number of participants than that of other publications. In addition of the above, it should be borne in mind that these data are not applicable to octogenarian patients, given that this is a frankly underrepresented population in most clinical trials. In fact, the only study so far available in these patients established SBP goals of 150 mmHg. Given that clinical trials, time horizon is limited, it is not possible to determine the mid- or long-term impact opting for intensive or conservative BP goals might have. While it is reasonable to assume that non-fatal events reduction might have a beneficial impact on the decrease of long-term fatal events, supporting this inference with currently available data is not possible. On the other hand, this limitation is applicable both to the benefits and to the risk for the development of undesirable events during follow-up.

Conclusion

Our data suggest that BP intensive goals with systolic pressure values close to 130 mmHg reduce cardiovascular events, with no impact on short-term mortality, and with an increase in the risk of adverse events. Moreover, we did not find evidence suggesting the need for establishing different BP control goals in diabetic and non-diabetic individuals.

In view of the above, BP control should be reinforced for all hypertensive subjects, considering the use of intensive goals in those individuals who belong to subgroups of higher cardiovascular risk, with low risk of adverse effects.

New studies are needed to assess the mid- and long-term impact of different antihypertensive goals.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Supplementary material

Supplementary material is available at *Archivos de Cardiología de México* (<http://www.archivoscardiologia.com/>). This material is provided by the corresponding author and published online to the benefit of the reader. The content of the supplementary material is the responsibility of the authors.

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