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Blood Pressure. New targets?

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Abstract

Arterial hypertension is one of the principal risk factors for the development of cardiovascular (CV) and chronic renal (CRD) diseases. Is responsible for 10% of all healthcare spending . High blood pressure, specially high systolic pressure, has a high prevalence worldwide and is a key risk factor of attributable disability-adjusted life-years DAILYs In the last two years, several new guidelines, in special, American College of Cardiology and American Heart AssociationACC/AHA guidelines, the European Society of Cardiology and the European Society of Hypertension ESC/ESH guidelines, create new challenges including new targets sometimes not coincident even in special groups. Also ESC/ESH introduces the concept of boundaries limits But can we realistically compare the results of trials that are open and with results from blind, controlled studies ? Blood pressure acts by a effect and by is irregular variability . Shouldn't we carefully examine the importance of variability? Should we be required to give importance to "absolute risk" factors when making decisions? Isn't the need for precocity of the beginning of the treatment a serious point ?

Keywords: Arterial hypertension, blood pressure, DALY, myocardial infarction, stroke

Arterial hypertension is one of the principal risk factors for the development of cardiovascular (CV) and chronic renal (CRD) diseases [1,2]. Is responsible for 10% of all healthcare spending [3]. High blood pressure, specialy high systolic pressure, has a high prevalence worldwide and is a key risk factor of attributable disability-adjusted life-years DAILYs [4]. In fact, the Global Burden of Diseases (GBD), Injuries, and Risk Factors Study [4] identified high systolic blood pressure as the leading cause of level 3 of the GBD (at this level the GBD takes in account 50 of a total of 84 risks) [4]. Blood pressure control is mandatory for the maintenance of good health and has an impressive impact on the reduction of CV-associated morbidity and mortality. However, despite a range of antihypertensive drugs, which are well tolerated, less expensive, associated with more effective campaigns than previous ones and despite the public being more informed regarding the problem; in our modern world we only have only been able treat 30% of patients with high blood pressure adequately[5]. This phenomenon is what Chobanain coined the “hypertension paradox” [5].

In the majority of cases, arterial hypertension does not present alone, but instead is linked to other health-associated risk factors [6]. The effects of blood pressure are: mechanical per se, by is irregular variability [7]. especially with respect to

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very-short-term (beat-by-beat), short term (within the 24-h circadian cycle) and long-term (day-by-day) variability [7,8]. Also, when medical professionals analyze data in order to make decisions regarding when and to whom blood pressure issues should be addressed, other risk factors associated with high blood pressure must be taken into account. Instead of treating patients at the blood pressure level, the decision to treat is often be based on "absolute risk", which means the likelihood of a patient having a stroke, a myocardial infarction, or acute coronary syndrome in 5–10 years is assessed and treatment is only administered when the absolute risk of associated issues indicates a need for treatment [9]. This concept is outlined, in part, in the American College of Cardiology and American Heart Association ACC/AHA guidelines [10]. This decision treat patients in this manner has advantages, but excludes, for instance, many young people and other hypertensive patients without other risk factors that will have, according to these guidelines, insufficient risk to justify treatment with medication [9]. This has the potential to make patients feel like they are left behind, a phenomenon that has been called the legacy effect, but does not necessarily mean that the approach is wrong in terms of overall patient outcomes [9].

In the last two years, new guidelines for the treatment of blood pressure have been created, which include new target values for blood pressure levels [5,10–13]. USA guidelines now suggest that blood pressure is considered elevated when systolic blood pressure is above 120-129 mmHg and diastolic blood pressure < 80 mmHg. Further, define arterial hypertension as having systolic/diastolic blood pressure values of 130–139 mmHg/80–89 mmHg. Patients with blood pressure values falling within this range may require medical treatment if CV risk estimates for the next 10 y are above 10%. Medical treatment is suggested for all individuals with stage I hypertension, in which systolic and diastolic values are above 140mmHg and 90 mmHg, respectively [10]. The European Guidelines of Hypertension of European Society of Cardiology and the European Society of Hypertension (ESC/ESH) [12] have designated levels of hypertension according to the same categories, and have described grade I hypertension as having a systolic pressure above than 140 mmHg and a diastolic pressure above 90 mmHg, similar to ESC/ESH guidelines established in 2013 [14]. In regard to treatment, USA guidelines advocate for the application of treatment with the aim of reducing systolic/diastolic blood pressure to less than 130 mmHg/80 mmHg, even for those who are greater than 65 years old [10]. The ESC/ESH 2018 recommends that those under 65 years old reduce systolic blood pressure to values between 120–129 mmHg while those over 65 years must maintain systolic levels under 130–139 mmHg. Diastolic values, according to ESC/ESH guidelines recommend that treatments be administered to achieve levels less than 80 mmHg for all hypertensive patients of all ages [12].

ESC/ESH 2018 guidelines introduce the concept of "safety boundaries" which can be described lower blood pressure boundaries that define the range of blood pressure levels that are considered safe. In practice, those less than 65 years old should not have systolic or diastolic pressure values that are less than 120 mmHg and 70 mmHg, respectively. For those greater than 65 years old, systolic pressure should be under 130 mmHg [12]. This concept was introduced based on the evidence showing that below certain target pressures there are, potentially, serious adverse events that can outweigh the benefit of reducing of blood pressure to below levels defined here [15]. ACC/AHA guidelines of 2017 were mainly based on the SPRINT study [16]. ESC/ESH guidelines and criteria were based in two meta-analyses [17,18], one of which included the SPRINT study [18].

The SPRINT Study was an open study that compared two types of treatment strategies. The first was an intensive type of treatment in which target systolic values were below 120 mmHg, versus the second, standard treatment in which target systolic values were kept below 140 mmHg. The treatments implemented with the goal of preventing CV events throughout a five-year period in which patient health was monitored. The study was interrupted after 3.26 years because the primary composite outcome of the study showed a reduction in the occurrence of CV-related events in the intensive group by 25% compared with patients undergoing the standard treatment [16].

However, the SPRINT study should be examined carefully because it has some particularities. The blood pressure of the patients were assessed

using the unattended method, which is not common in this type of trial. Use of the unattended method requires that the patient sit in a silent room while an automated device measures blood pressure three separate times without warning [16]. This methodology eliminates white coat effects observed when measuring office blood pressure in an office setting. Further, the individual effects associated with differences between measurements taken by different practitioners are minimised. These can account for differences of 5–15 mmHg in systolic blood pressure measurements according to some authors [12]. In other studies [19] comparing unattended method with attended method, systolic measurements produced variation of up to 13.8 mmHg lower in unattended method in the first measure of attended measure and 7.3 mmHg lower in unattended method when compared with the second attended measure.

Unattended measurements were more consistent for diastolic values, measurements were only 3.9 mmHg and 2.9 mmHg lower for first and the second attended diastolic measurements, respectively [19]. In relation to ambulatory blood pressure (ABPM), the authors obtained that in non-diabetic patients the unattended, values were similar to the 24H of ABPM values and in diabetic patients unattended values were similar to Daytime ABPM values [19]. However, some systematic reviews and metanalysis haven't supported similar conclusions, even when operating under the assumption that there is heterogeneity in the studies analysed [20]. In general we can accept that the unattended method excludes the alert effects "going to measure", "being measure in a doctor behaviour" and is not surprise that the maiority of the studies had found inferior values of blood pressure with unattended method[12,19,21–24].

The SPRINT study did not include diabetic patients or those with a history of stroke. Those who were able to achieve systolic blood pressure values of 121 mmHg compared with those who achieve 136,2 mmHg, were 25% less likely to experience major CV events and were 27% less likely to die overall. However, there was no significant reduction observed in the occurrence of myocardial infarction (AMI) or stroke [16]. Improved outcomes observed in the study were due to reductions in the occurrence of heart failure (0.41%/y vs. 0.61%/y; hazard ratio 0.89 (0.63–1.25)] while the occurrence of stroke did not produce significant results (0.41%/y vs 0.47%/year; hazard ratio 0.89 (0.63– 1.25)] [16]. Interestingly, the intensive treatment group received more thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers and aldosterone receptor antagonists then the standard group treated to a standard level [25]. Also in the group of intensive treatment there 25% of more visits to adjust the medication in relation to standard treatment group [26].

In our view, results and the conclusions of the SPRINT study should be interpreted carefully, while considering the limitations and biases that could affect overall conclusions. Further, there are several several questions regarding the study that remain unanswered. In practice, the Sprint study was unable to show that intensive reductions of systolic blood pressure to less than 120 mmHg decreased the incidence of stroke or the incidence of AMI [16].

The ESC/ESH 2018 guidelines for blood pressure indicate that a target systolic blood pressure of 130 mmHg or less can be tolerated in individuals who are less than 65 years old, while systolic values of 139 mmHg or less are tolerated in individuals older than 65 years old. Both age groups, however, should maintain systolic pressure values of at least 120 mmHg. Regarding diastolic blood pressure measurements, values should be less than 80 mmHg, but never under 70 mmHg [12]. This acceptable range has been based on the results of two meta analyses [17,18], and ESC/ ESH guidelines concluded that according to the scientific evidence available at the time, some benefits associated with maintenance of low blood pressure values could be lost due to the appearance of an increasing number of adverse effects associated with intensive treatment. These findings suggested that when considering the costs and benefits of treatment, outcomes would suffer when attempting to maintain systolic values of less than 120 mmHg or diastolic values of less than 70 mmHg [12].

The American Guidelines predict that if the new guidelines are implemented, and goals are both achieved and maintained (maintenance is important, since prognosis worsens with a lack of consistency [27], that in the next ten years 3 million additional CV events may be prevented than if the old guidelines were followed. However, we have

to acknowledge [5] that there are serious potential risks associated with overtreatment [5]. As a result, implementation of the new guidelines may promote 3 million new adverse events related to aggressive treatment [5]. Rueda-Ochoa et al. assed the impact of cumulative SBP and SAEs using a cumulative joint model (cJM) to analyse the SPRINT study and concluded that the initial benefit throughout the follow-up period could be lost in general population, especially within special groups such as CKD chronic disease, CVD permanent, women, young people, black persons, and those with initial systolic blood pressure values greater than 132 mmHg [27]

The European Guidelines have introduced the concept of "safety boundaries" to try to avoid downfalls associated with aggressive treatment. These guidelines aim to balance treatment intensity with safety measures. In the following paragraphs risks to particular groups have been discussed in detail.

Patients with chronic renal disease

Arterial hypertension is one of the major risk factors for the development and progression of renal disease [12]. The studies examining this group are not homogenous [11,12,28,29] , there are studies that found that drastically lowering blood pressure may benefit patients with CKD, but benefits of treatment were only observed in patients with micro albuminuria in relation to CKD but did not reduce the occurrence of CV events [29]. The Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, that compared the effect of benazepril plus amlodipine versus benazepril plus hydrochlorothiazide in patients with hypertension, with age above 55 years and with high risk for CV events[28] being the chronic kidney disease one of the objectives' ,on the other hand, was able to show that the treatment of arterial hypertension resulted in the reduction of CV events [28]. As a result, ESC/ESH guidelines propose treating CKD patients with sodium restriction, and suggest that systolic blood pressure should be reduced to less than 140 mmHg, while targets for diastolic should be less than 90 mmHg. A final target systolic pressure of 130 mmHg accompanied by diastolic targets of 70–79 mmHg may be pursued if treatment proceeds without incident. Further, individuals > 65 years old who are tolerating treatment well were given systolic targets of 130–139 mmHg and diastolic targets of 70–79 mmHg. The reduction of albuminuria should be also a concern if present [12].

The Kidney Disease Outcomes Quality Initiative KDOQI work group commentary of 2017 [11] states that screening for CKD in hypertensive patients is cost effective, but is not proven that the same is for most of the general population [11]. Treating those who have high blood pressure and are in CHD stages 1 to 3 so that they maintain systolic blood pressure levels of less than 130 mmHg is beneficial, especially if they have albuminuria [11]. For those who have had a previous stroke, systolic pressure should be reduced in patients with systolic value greater than 140 mmHg to a target of 130 mmHg if tolerated. There is a lack of data for diastolic targets. There are also no large, conclusive randomised controlled trials (RCT) for those who are dialysis dependent or are in non-dialysis dependent stage 5 CKD [11].

Patients with Diabetes

Hypertensive patients with diabetes comprise a special hypertensive group. They have two types of complications which include increased risk for both macrovascular (MI, acute coronary syndrome not resulting in MI, stroke, acute decompensated HF, death from cardiovascular) and microvascular (retinopathy, albuminuria, neuropathy) events. All key studies and metanalyses published thus far have failed to produce conclusive results for the group [30–31]. The ESC/ESH guidelines suggest that blood pressure should be reduced when systolic values are greater than 140 mmHg and diastolic values are over 90 mmHg. Target values for such patients are systolic values of 130 mmHg or less if tolerated, but never systolic pressure should never be pushed below 120 mmHg. In older persons greater than 65 years old, guidelines suggest reducing systolic values to 130–139 mmHg. Diastolic value should be reduced to less than 80 mmHg, but never be pushed below 70 mmHg.

Older patients

When we talk about older individuals, we are referring to people who are 65 years old or greater.

Within this group we must remember that here is a wide range of ages which also include very elderly individuals that are greater than 80 or 90 years old. And for the same age groups, there are also individuals that can be categorised as very independent and very healthy, while there are others that are very dependent and are experiencing deteriorating health. Therefore, for this stage of life we have to consider the frailty and the disability of each patient [32]. Also, blood pressure decreases in old age approximately 20 years before death [33] and especially within the 24 months before the end [34]. Therefore, it is not surprising that ESC/ESH guidelines advises taking into account comorbidities, other medications taken, the frailty of the patient when considering treating blood pressure. In general, the treatment of elderly persons should be directed at reaching systolic blood pressure targets between 130–139 mmHg and diastolic value targets that are less than 80 mmHg. Any systolic targets less than 130 mmHg should be avoided.

The importance of precocity in achieving targets

Beginning treatment in a timely manner also appears to be important. In a nice editorial comment, Brent M Egan [35] discussed the problem tardiness with respect to initiating treatment. He specifically discussed a study by Martinz-Fernandez et al, that examined a set of 18,721 newly-diagnosed, hypertensive patients from 45 primary care facilities. The authors found that delaying treatment was associated with an increase in the incidence of all causes of mortality [36]. Other studies had previously pointed in a similar direction and could be explained by the principle, "the sooner the better" [37,38].

In conclusion, I would to submit some questions for discussion. First, can we realistically compare the results of trials that are open with results from blind, controlled studies? Second, is it possible to compare blood pressure values obtained using two different methodologies? Should we be required to give importance to "absolute risk" factors when making decisions regarding the treatment of patients and the creation of guidelines for care? Should we carefully examine the importance of variability in the origin of hypertensive disease? Isn't the need for precocity of the beginning of the treatment a serious point that should be emphasized?

Limitations

This article has some limitations. The majority of questions and criticisms posed here can not be tested in a blind study aimed at proving or disproving a hypothesis. Instead, this article was written to probe studies in a way can be also provocative but also largely inconclusive.

Conflict of intereset

The author declare no conflict of interest.

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