Blood pressure target values: the saga continues

Alan H. Gradman*

Department of Medicine, Temple University School of Medicine, Philadelphia, PA, USA

Online publish-ahead-of-print 18 December 2015

This editorial refers to ‘Cardiovascular outcomes at different on-treatment blood pressures in the hypertensive patients of the VALUE trial’, by G. Mancia et al., on page 955.

Blood pressure (BP) targets are practical objectives which aid clinicians in delivering rational and consistent treatment to patients with hypertension. The goal is to select targets which minimize overall cardiovascular risk when applied prospectively to hypertensive populations. Following critical reviews highlighting the inadequate evidence base of existing guidelines, investigators worldwide have focused attention on establishing optimal BP targets based on the results of clinical trials. The study by Mancia and colleagues which appears in this issue of the journal is an important continuation of these efforts. It is a retrospective analysis of on-treatment blood pressure data from VALUE, a clinical trial which randomized high-risk hypertensives to receive therapy initiated with valsartan or amlodipine. As occurrence of the primary endpoint did not differ between treatment groups, a pooled analysis was conducted to determine the relationship between on-treatment BP and cardiovascular outcomes, and compare the utility of <140/90 and <130/80 mmHg as treatment targets.

The BP target set by the VALUE protocol was <140/90 mmHg for all participants. A lower incidence of cardiovascular events was observed in direct proportion to the percentage of patients in which BP <140/90 mmHg was recorded; the lowest event rates occurred in patients at or below target BP >75% of the time. When the data were analysed as if BP <130/80 mmHg had been the treatment target, the results suggest to the authors that consistent achievement of BPs below this cut-off did not improve overall outcomes and attenuated some of the beneficial effects of BP reduction. When mean on-treatment BPs were examined, the lowest risk for most events was seen with mean systolic BPs in the 130–139 mmHg range compared with those with means <130 mmHg, the exception being stroke incidence which continued to decline with decreasing average BP. The authors conclude that a target BP of <140/90 mmHg rather than <130/80 mmHg is appropriate for most high-risk hypertensive patients, with the possible exception of populations or individuals at demonstrated increased risk of stroke.

As the authors acknowledge, the effects of randomization are lost when on-treatment BP data are examined. There is always concern that pre-existing differences in populations may bias any observations made. If the VALUE cohort is divided according to the percentage of visits in which BP <140/90 mmHg was documented (their table 1), striking disparities in baseline characteristics are evident. The reference group (patients achieving BP <140/90 mmHg at <25% of visits) had mean baseline BP of 165/90 mmHg despite the fact that most were receiving antihypertensive treatment at the time of enrolment. As a group, they apparently consisted of patients who were poor responders to previous drug therapy or had significant untreated hypertension. In all probability, these patients had been exposed to years of poorly controlled hypertension. In contrast, the group that achieved BP <140/90 >75% of the time had a mean baseline BP of 146/86 mmHg. Many had BPs <140/90 mmHg on their prior regimen and were responders to drug treatment. These are different patient populations and it is doubtful whether the statistical methods utilized could compensate for all the factors—known and unknown—which contributed to the high risk seen in this subgroup.

The distinctive characteristics of the reference subgroup may explain both the magnitude of the overall effects attributed to BP control and the observation that most of these effects were seen in patients with BP <140/90 mmHg only 25–49% of the time. The reduction in cardiovascular events (57%), stroke (58%), myocardial infarction (50%), and all-cause mortality (32%) between the reference population and lowest risk category was significantly greater than that seen in most hypertension trials. The steep reduction in event rates between the reference population and patients achieving BP <140/90 mmHg 25–49% of the time reflects a qualitative difference between the 27% of patients in this subgroup and the remainder of the VALUE population. This distinction is also seen in the response of the four BP control categories to administered antihypertensive therapy. Patients in the high-risk reference group exhibited the poorest response to drug treatment compared with the three other response categories. This result is in contrast to...
the usual observation that BP reduction with drug therapy is greater in patients with higher initial BPs. BP reductions in the three categories of patients who achieved BP <140/90 mmHg on at least 25% of visits were similar to each other and to the overall BP treatment effect seen in VALUE. It is likely that general lack of responsiveness to pharmacological treatment contributed to the very high event rates in the reference population and exaggerated the benefits of even variable achievement of target BP.

Nonetheless, as an evaluation of the <140/90 mmHg target, the study is valid and yields information of interest. It is valid because <140/90 mmHg was the target BP actually used in VALUE. If the usefulness of a BP target depends upon overall risk reduction in a population treated according to that target, the treated population must be examined in its entirety, and the authors did so. The results are useful to clinicians because they give guidance in conducting office practice. The authors have documented, by comparing the three subgroups of responders, that what drives endpoint reduction is not only the achievement of target BP but also the consistency with which it is maintained. To minimize risk using a low-cost but sophisticated approach and a target <140/90 mmHg, BP should be measured accurately preferably using automated devices, reduced to goal within a few months, and therapy adjusted to maintain BP below target on a continuous and consistent basis.

A further test of the utility of the <140/90 mmHg BP target would involve intensively treating a population of relatively resistant hypertensives similar to the 27% of patients in VALUE who achieved BP <140/90 mmHg on <25% of visits. Recent studies document that a large fraction of patients with apparently resistant hypertension can achieve their BP targets through the use of additional drugs and other measures. This study indicates that hypertensive patients who reach a BP target <140/90 mmHg quickly and maintain it smoothly over time have a favourable prognosis. It is unknown, however, if patients who require more intensive treatment share the same beneficial outcomes if they achieve the same degree of BP control. Also unknown is whether these distinct populations should be treated according to the same BP target.

The utility of this study as an evaluation of the lower target BP <130/80 mmHg is subject to interpretation. This target was not used in VALUE and its achievement could be viewed as an unintended consequence of treatment aimed at reducing BP to <140/90 mmHg. If the test of a BP target is the overall effect of its application to a hypertensive population, this test was not applied as the lower target was not used to make the treatment decisions which resulted in the observed distribution of on-treatment BPs. Another concern relates to differences in the reference groups used to calculate endpoint reductions. The on-treatment BP in the <130/80 mmHg reference population was 144/82 mmHg. A significant percentage of this group had mean BPs in the systolic BP 130–139 mmHg range—identified by the authors as the on-treatment stratum at lowest risk. The risk of mortality and all major cardiovascular events was quite different—16% mortality and 22% total cardiovascular events in the group used to calculate risk reductions accompanying achievement of the <140/90 mmHg goal, and 11% and 14% in the group used for the <130/80 mmHg analysis. These differences in the populations used as standards for comparison make it difficult to draw definitive conclusions regarding the benefit or harm that might have resulted if the lower target had been used in VALUE.

Another recent publication from the VALUE investigators indicating no increase in cardiovascular event rates in patients on-treatment BPs <130/70 mmHg (i.e. no J-curve) is further evidence of uncertainty regarding optimal on-treatment BP in this population.

Unfortunately, the controversy over appropriate BP targets for high-risk individuals with hypertension will not be resolved by this or any one study. The difficulties in this study derive, in part, from its retrospective nature, the hazards of which are well known. However, it is by no means certain that prospective clinical trials will easily and definitively answer such questions. The recently reported results of SPRINT which randomized high-risk hypertensives to systolic BP targets of <140 and <120 mmHg contradict many of the findings of ACCORD which randomized a different population of high-risk hypertensives to the same BP targets. An important difference between these studies lies in their definition of ‘high risk’, and this may be the key to identifying the best BP targets going forward. In the study of Mancia et al., the distinctive characteristics of patients who entered the study with higher BPs and responded poorly to treatment differentiated them from others who met the inclusion criteria for VALUE. It is possible that patients such as this with long-standing, drug-resistant hypertension require different BP levels to optimize organ perfusion compared with lower risk patients. It will be necessary in the future specifically to examine well-defined subgroups and synthesize all available evidence—prospective, retrospective, and epidemiological—in order to continue to advance the enormous success story that is the treatment of hypertension.

Conflict of interest: The author was an investigator in the VALUE trial, and has been an investigator, consultant, and speaker for Novartis within the past 3 years.

References

Double inlet left ventricle with unrestricted pulmonary blood flow and survival into adulthood

Margarita Brida*, Gerhard-Paul Diller, Helmut Baumgartner, and Stefan Orwat

Division of Adult Congenital and Valvular Heart Disease, Department of Cardiovascular Medicine, University Hospital Muenster, Albert-Schweitzer-Campus 1, Muenster 48149, Germany

* Corresponding author. Tel: +49 251 83 46110, Fax: +49 251 83 46109, Email: margarita.brida@icloud.com

A 21-year-old male refugee from Syria with known but ill-defined congenital heart disease, presented with palpitations, no signs of heart failure, and near normal oxygen saturation. Chest radiography showed a globally enlarged heart with prominent hilar and pulmonary vessels (Panel A). Transthoracic echocardiography revealed a double-inlet-left-ventricle (DILV) with good systolic function (Panel B), malposition of the great arteries with the small aorta arising from an outflow chamber with non-restricted connection to the ventricle. Surprisingly, there was no subpulmonary or pulmonary stenosis (PS) and thus unrestricted flow to the markedly dilated pulmonary arteries (Panel C). This was confirmed by magnetic resonance imaging (MRI; Panels D–F). Cardiac catheterization revealed that systolic pulmonary arterial pressure was indeed systemic but pulmonary blood flow massively increased resulting in a low calculated pulmonary vascular resistance (84 dynes s cm⁻⁵) and near normal arterial oxygen saturations. Magnetic resonance imaging confirmed the massive left-to-right shunt by flow calculations in the aorta and pulmonary artery (Panel G).

Survival of patients with DILV is mainly determined by the degree of pulmonary blood flow. If there is no anatomic restriction to pulmonary blood flow most patients die in early childhood due to intractable heart failure. Those who survive unoperated normally develop severe pulmonary vascular disease. To our knowledge, this is a unique case of exceptional haemodynamics in an unoperated DILV patient without PS. Our patient in his 20s ‘defied the odds’, not only by reaching adulthood but also because of his good functional state with no signs of heart failure and near normal arterial oxygen saturation.

Ao, aorta; DILV, double-inlet-left-ventricle; LA, left atrium; PA, pulmonary artery; RA, right atrium.

Supplementary material is available at European Heart Journal online.