Editorial

Target blood pressure and cardiovascular risk

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An article recently published in the *Lancet* (1) concerned a meta-analysis of two therapeutic trials ONTARGET (2) and TRANSCEND (3). They were both designed to compare angiotensin receptor blocker (ARB) to angiotensin-converting enzyme (ACE) inhibitors (or their combination) or placebo respectively, to reduce the rate of a composite of cardiovascular death, myocardial infarction (MI), stroke and hospital admission for heart failure, among patients at high risk for cardiovascular events.

The aim of this analysis, performed in 30,937 patients with a median follow-up of 56 months, was to evaluate the relation of different cardiovascular outcomes (composite outcome of cardiovascular death, MI, hospital admission for heart failure and stroke; individual components of the composite outcome; and all-cause death), with mean systolic blood pressure (SBP) or diastolic blood pressure (DBP) achieved on treatment; prerandomization baseline blood pressure (BP); or time-updated BP (last on-treatment value before an event). It appeared throughout the trials that the most predictive BP component was the mean achieved SBP. Moreover, SBP less than 130 mmHg during treatment was associated with increased risk of cardiovascular outcomes except for MI and stroke. Similar results were observed for DBP less than 75 mmHg, except for stroke. A J-curve was also observed for cardiovascular death and all-cause death in patients with mean achieved SBP/DBP below 120/70 mmHg.

Finally, they conclude that concerning treatment-achieved BP, the lower was not necessarily the better for high risk patients, without being able to rule out totally some effect of reverse causality because of the post-hoc design, although the authors performed sub-groups analysis according to presence of comorbidities, baseline low BP or only active study drugs. They believe that a 120–130 mmHg SBP goal should be safe for most and result in improved outcomes. Their findings suggest that in some patient at low SBP on treatment, BP "medication might have to be reduced to avoid adverse outcomes because treat to target does not mean treat under target".

This new post-hoc analysis is of major interest and answers but also asks several questions.

First of all, it emerged from this study that the best value of BP to predict the composite outcome of cardiovascular death, MI, stroke and hospital admission for heart failure was the mean achieved BP on treatment, in comparison with the prerandomization baseline BP and the time-updated BP (last on-treatment value before an event). Superiority of mean achieved SBP on treatment over prerandomization baseline SBP is important to consider from a clinical point of view. Indeed, such results are complementary to those demonstrating a cardiovascular risk reduction in high-risk patients when SBP is "normalized". In a meta-analysis on 44,989 patients from 19 trials, there was a significant reduction in events in high-risk patients when BP was reduced to 133/76 mmHg compared to 140/81 mmHg (4).

Otherwise, we observed that BP targets were different when taking into account the different cardiovascular outcomes. Such results could mean that we need new biomarkers that can predict cardiovascular diseases to improve both individual diagnosis and therapeutic

strategies. This article based all analysis on SBP and DBP. However, other hemodynamic biomarkers increased cardiovascular risk evaluation accuracy such as pulse pressure (PP), a peripheral marker of central arterial stiffness. Indeed, PP provided valuable prognostic information in specific populations. In many studies, effect of PP persisted after adjusting for medication use and was present in normotensive patients, in hypertensives, in the elderly and in patients with end-stage renal disease to predict the risk of MI, stroke, cardiovascular mortality, or the risk of heart failure (5). In the REACH Registry, authors studied whether PP was associated with major cardiovascular outcomes, independently of mean arterial BP. PP was determined in 45,087 patients and its association with all cardiovascular outcomes was analyzed. After adjusting for all known interfering factors, PP was still associated with cardiovascular outcomes except stroke and cardiovascular death (6). Other studies highlighted the role of other arterial biomarkers as intima-media thickness or resistive index of the internal carotid artery (7), or carotid-femoral pulse wave velocity (5). Consideration of such biomarkers in risk assessment or/and risk reduction strategies needs further research. Concerning cardiovascular risk assessment, the Framingham scale is a well-known tool, function of traditional cardiovascular risk factors. Anyhow, several nontraditional risk factors have been suggested to improve risk stratification to provide a new algorithm for predicting coronary heart disease. In the review article of Patel and Budoff (8), two factors with the most available data: C-reactive protein (CRP) and coronary artery calcification (CAC) were comparatively analyzed. Current review of the literature available suggested CAC to be more relevant in evaluating coronary heart disease in a clinical setting. This article emphasized the need of adding predictive value, for a new biomarker, over and above traditional cardiovascular risk factors. Furthermore, given the higher cost of CAC scanning compared with CRP measurement, cost-effectiveness studies are still needed (8).

In this analysis (1), the optimal target SBP was superior to 130 mmHg for all cardiovascular events except for stroke and MI and the target DBP was superior to 75 mmHg except for stroke. Those goals, in particular the systolic-one, are in contradiction with the results of the recent SPRINT trial (9). Indeed, despite significant adverse effects, this trial highlighted that cardiovascular risk decreased when SBP was less than 120 mmHg in comparison with SBP less than 140 mmHg. In ONTARGET and TRANSCEND trials, SBP and DBP values were measured in the doctor's office, in the presence of the physician. Importantly, the BP measurement method used in SPRINT differed from previous clinical trials, namely from ONTARGET and TRANSCEND; it was performed by averaging several values obtained via a semiautomatic measuring device in individuals left alone in a room for several minutes, a procedure shown to be unaffected by the alerting response and the rise that characterize BP when measured by or in the presence of healthcare staff. Although, believed to amount to only a few mmHg by some investigators (10), it seems possible that larger differences divide these measuring approaches. Intra-arterial ambulatory BP monitoring studies, for example, have shown that during a doctor's visit mean arterial pressure increased by an average of about 17 mmHg (11). Furthermore, in a recent study, a 15 mmHg difference between attended manual and unattended semiautomatic SBP measurements has been reported (12). This suggests that the unattended semiautomatic office BP of 120 mmHg, as measured in the SPRINT trial, could be similar to the conventional office BP of 130–135 mmHg, as measured in the ONTARGET and TRANSCEND trials. Indeed, major correction factors need to be applied to the unattended semiautomatic office BP to make them confrontable with the target BP recommended by guidelines, and raised the issue of whether a more accurate method should be used in clinical trials and if such method would be feasible in clinical practice.

This study gave optimal BP targets proposals for patients with high cardiovascular risk, but we had to notice that these proposed optimal targets differ for stroke and for MI. For example, considering a DBP inferior to 75 mmHg further decreased the risk of stroke, but was associated with an increased risk of MI. It would be valuable to distinguish patients more likely exposed to stroke or to MI. A DBP goal inferior to 75 mmHg could be proposed to the former, superior to 75 mmHg to the latter. Independently of the severity of coronary artery disease, ischemia signs on ECG were observed in patient with DBP below 75 mmHg (13), those were related with anomalies of coronary perfusion during diastolic phase that could be an explanation of worst cardiovascular prognosis (14). Some studies tried to develop individual prediction models to tailor the intensity of BP control based on the projected risk and benefit for each unique patient (15). Currently, new studies proposed to personalize the BP target. One study developed a clinical tool which provided updated risk estimates based on evidence from high-quality systematic reviews and meta-analyses of the ABCS (aspirin therapy in appropriate

patients, BP control, cholesterol management, and smoking cessation) therapies: the Million Hearts Initiative. It had a goal of preventing 1 million heart attacks and strokes. The Cardiovascular Risk Reduction Model was developed as a strategy to assess a value-based payment approach toward reduction in 10-year predicted risk of atherosclerotic cardiovascular disease by implementing cardiovascular preventive strategies to manage the "ABCS" (16).

Moreover, considering the necessity to move from risk assessment to risk reduction strategies, several studies have shown close relations between arterial stiffness and cardiovascular risk, independent of achieved BP (17). Arterial stiffness could be assessed non-invasively by measuring pressure waveforms in order to calculate aortic pulse wave velocity (5). Some studies demonstrated that patients treated and controlled for their arterial hypertension remained at high cardiovascular risk (18). It could be explained in part by the pulse wave velocity which remained elevated in some patients, even under effective antihypertensive treatments (19). Low DBP is also a major component of PP as marker of arterial stiffness. Thereby, the lower achieved DBP group could have selected individuals with higher PP i.e. higher arterial stiffness associated with worst prognosis (5). Those findings might support the use of arterial stiffness, in addition to BP, to further evaluate and refine cardiovascular risk in order to adapt and individualize risk reduction strategies.

Finally, despite the existence of several tools to assess the cardiovascular risk of individuals, universal BP targets are difficult to recommend since different BP levels are associated to different cardiovascular diseases. One size does not fit all, and, ideally, BP goals should be defined according to the risks of all possible cardiovascular diseases. In the hypothesis of an elevated stroke risk (because of personal or familial history or because of the level of a given biomarker for example), a SBP goal inferior to 120 mmHg could be proposed. Such strategies should of course be validated by dedicated therapeutic trials. In this respect, further research is urgently needed.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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