INVITED PAPER

Is arterial stiffness a surrogate end-point for cardiovascular complications? A tentative answer given by the SPARTE Study

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Concept and objectives

Very few studies have tested whether reducing hypertension-mediated organ damage (HMOD) translated into a reduction of cardiovascular (CV) and renal complications beyond blood pressure (BP) reduction. This was the case for left ventricular hypertrophy and urinary albumin excretion¹⁻² which, thus, qualified as surrogate endpoints³. Arterial stiffness, measured through pulse wave velocity (PWV, is the most characteristic clinical feature of vascular aging in response to both classical CV risk factors and poorly identified risk factors⁴⁻⁵; whether arterial stiffness is a surrogate end-point for CV disease has never been directly demonstrated by a controlled clinical trial. We set up the SPARTE trial as a Strategy for Preventing Cardiovascular and Renal Events Based on ARterial Stiffness (ClinicalTrials.gov number, NCT02617238)⁶⁻⁷. We hypothesized that a therapeutic strategy targeting the normalisation of arterial stiffness in addition to the implementation of the 2007 ESC – ESH (European Society of Cardiology and European Society of Hypertension) guidelines for the management of hypertension⁸ would reduce more CV and renal events compared to the unique implementation of the 2007 ESC-ESH guidelines (current guidelines at the time of the beginning of the study). Our secondary objectives were to demonstrate that monitoring vascular aging through repeated PWV measurements would result in better intensification of treatment, better prevention of vascular aging and better control of blood pressure.

Design and methods

All data have been previously published in detail⁶⁻⁷. SPARTE is a multicenter, prospective, open-label randomized controlled trial with blinded endpoint evaluation (PROBE

design), undertaken at 25 French hypertension centers in university hospitals, and lasting 4 years. Patients were adults with primary hypertension, aged 55 to 75 years at inclusion, at medium-to-very high cardiovascular risk, according to the 2007 ESH-ESC guidelines for the management of hypertension⁸. Participants were randomly assigned (1:1) to two groups: an intervention group aiming at normalisation of PWV through a pre-specified therapeutic strategy (PWV group) and a control group where ESH-ESC Guidelines were applied, without reference to PWV (conventional group).

In both groups, attended seated office BP was measured during each visit, using validated semi-automatic oscillometric medical devices. Ambulatory BP monitoring (ABPM) was performed at baseline and at 6 and 48 months. Carotid-femoral PWV, central BP and augmentation index (AIx) were measured by applanation tonometry using the Sphygmocor device (Atcor Medical, Sydney, Australia)⁴. The follow-up study duration was 4 years, during which 2 scheduled clinical visits were performed per year for both groups. In the intervention PWV group, both patients and investigators were aware of PWV values, and treatments were adjusted to target a PWV of less than 10 m/s. For that purpose, non-pharmacological measures and antihypertensive treatment were adjusted and CV risk factors corrected until normalisation of PWV. Combination therapy using a RAS blocker (ACEI or ARB) and a CCB was recommended as first step. If BP was not controlled despite a triple combination (ACEI/ARB+CCB+Diuretic, second step), or side effects occurred, the third step was to go to the highest recommended doses of ACEI or ARB within the combination⁹⁻¹⁰. In the conventional group, the objective was to bring office BP below 140/90 mmHg. Both investigators and patients were strictly blinded for PWV. Thus, PWV was not used for adapting therapeutic strategy and only served for comparing groups afterwards.

Because SPARTE was an open-label study, blinding applied for the adjudicated endpoints in both groups (PWV and conventional groups).

The primary outcome was a combined endpoint including stroke and coronary events (myocardial infarction-MI, angioplasty, bypass), fatal or not, peripheral artery disease (angioplasty, bypass, amputation), hospitalization for heart failure, aortic dissection, chronic kidney disease (doubling of creatinine, dialysis), and sudden death. The endpoint adjudication committee⁶ adjudicated all components of the primary outcomes of the study in a blinded fashion (allocation group and PWV value). Secondary outcomes, planned for a pre-specified statistical analysis⁶⁻⁷, included all individual components participating to the combined endpoint; the time-course changes in brachial office and ambulatory BP, PWV and central BP; and the time-course changes in treatments, in terms of pharmacological class, dosage and number of medications.

Results

A total of 536 participants were enrolled in the study (264 in the PWV group and 272 in the conventional group) between July 2013 and January 2016, with a median follow-up of 48.3 months. Patients were young elderly (65 years old), 2/3 were males, most of them were at high to very high risk. All were hypertensive with good BP control at entry (134/77 mmHg at office, similar at ABPM) with 2.5 antihypertensive drugs. More than 80% had dyslipidemia, 1/3 were diabetics, 1/4 had previously known CVD. Baseline characteristics were well balanced between groups, without significant difference.

Forty-one participants qualified for a primary outcome event: 17 (1.6% per year) in the PWV group and 24 (2.2% per year) in the conventional group. The hazard ratio was HR=0.74, however not significant (95% confidence interval [CI], 0.40 to 1.38; P=0.35) (Figure 1). Results were similar when adjusted on CV risk. Patients at medium+high CV risk had a significantly lower risk of presenting the primary outcome than very-high CV risk patients. In patients at very high CV risk, 6 events (2.0% per year) were observed in the PWV group and 12 events (4.0% per year) were observed in the conventional group (HR=0.49; 95% CI 0.19 to 1.32; P=0.16). Thus, despite continuing efforts, the SPARTE trial lacked sufficient statistical power to demonstrate a greater reduction in CV events in the PWV-based compared to the conventional treatment arm. Indeed, the SPARTE study included about three times less patients than initially planned (536 instead of 1500), due to competing protocols in study centers and insufficient financial support. The yearly incidence of the primary end-point was lower than

initially estimated (10%). In addition, the number of CV deaths which occurred during the SPARTE study was twice lower than predicted from individual SCORE risks¹¹.

However, we observed a significant treatment intensification, reduction in office and ambulatory SBP and DBP, and prevention of vascular aging in the PWV group. Indeed, the number of BP-lowering drugs and the treatment intensity score significantly increased over time in the PWV-based group but not in the conventional group. The trajectories of office and 24h SBP and DBP over time were significantly different between groups, with a greater reduction rate in the PWV group than in the conventional group. And PWV trajectories over time were significantly different between groups, with no increase in PWV in the PWV group (Figure 2). These good results in the PWV group were obtained without increasing adverse events.

Consideration for clinical practice

An important finding of the SPARTE study is that it is possible to further lower BP in patients that were considered, for most of them, as having controlled BP. The lack of SBP reduction and the limited DBP reduction in the conventional group demonstrate that targeting the normalization of office BP within the 130-139/80-85 mmHg range is not effective enough in clinical practice, as lately suggested by the SPRINT trial¹². At variance with, and beyond SPRINT, SPARTE study adds as an original contribution the importance of maximizing doses of “de-stiffening” drugs (such as RAS-blockers and CCBs), targeting the normalization of arterial stiffness through repeated PWV measurements and using these measurements as a tool for therapeutic education and sensitization of patients and physicians to treatment intensification.

Another important finding is that the intensification of antihypertensive treatment could reduce arterial stiffness and prevent arterial aging not only through BP lowering, but also independently of BP reduction, i.e., likely through long-term arterial remodeling⁹⁻¹⁰. Thus, the prevention of CV complications may require not only a good BP control, but also an effective prevention of arterial aging through adequate therapeutic measures including lifestyle changes and intensification of de-stiffening drugs, such as RAS-blockers and CCBs.

Finally, the SPARTE study, which has been underpowered for clinical events, should be replicated with a larger number of patients

Figure 1: Primary outcome events. A primary outcome was confirmed in 41 participants: 17 (1.6% per year) in the PWV group and 24 (2.2% per year) in the conventional group (HR=0.75; 95% confidence interval [CI], 0.40 to 1.38; P=0.35) (With permission from Laurent et al. 2021, ref 7)

Figure 2: Trajectories of pulse wave velocity (PWV) in the conventional (in blue) and in the PWV-based (in red) treatment arm. In the conventional arm, PWV increased with a rate of 0.20 m/s/year (P=0.001). In the PWV arm, the PWV increase rate was not significant (0.06 m/s/year, P=0.140). Whereas PWV was similar at inclusion in the two treatment arms, PWV trajectories over time were significantly different (P=0.012). Dots indicate mean values. Lines indicate fitting smoothing spline curves with 95% confidence intervals in grey. Trajectories over time have been obtained with latent variable analysis. (With permission from Laurent et al. 2021, ref 7)

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