

# Arterial Stiffness as Surrogate End Point Needed Clinical Trials

Stéphane Laurent, Marie Briet, Pierre Boutouyrie

Classic risk scores may underestimate the risk of cardiovascular (CV) events in specific risk groups suitable for primary prevention, such as asymptomatic hypertensive subjects.<sup>1</sup> Particularly, those considered as at intermediate risk may benefit the most from a reassessment of their CV risk using novel biomarkers.<sup>2</sup> In primary prevention, some imaging biomarkers, such as arterial stiffness, enhance risk prediction to a higher extent than circulating biomarkers.<sup>3</sup> Whether novel biomarkers are ready for routine clinical use is a matter of controversy.<sup>1-4</sup> Particularly, whether an imaging biomarker can be substituted to clinical events in outcome trials and be considered as surrogate end point has rarely been demonstrated.<sup>1-4</sup> The aims of the present Brief Review are to address the concepts of “imaging biomarker” and “surrogate end point”; to focus on arterial stiffness as putative surrogate end point for future CV events; and to suggest additional studies to demonstrate its value as surrogate end point. Particularly, we will discuss experimental designs of randomized clinical trials demonstrating that a therapeutic strategy that normalizes arterial stiffness is more effective in preventing CV events than usual care.

## “Circulating” Biomarkers Versus “Tissue” or “Imaging” Biomarkers

Although classic risk scores, such as the Framingham risk score<sup>5</sup> and the European Systematic Coronary Risk Evaluation,<sup>6</sup> detect patients at high risk of CV events, they are largely influenced by aging, leading to undermanagement of CV risk in other risk groups, particularly those considered as at intermediate risk. A very large number of newer biomarkers have been proposed in the literature<sup>2,4</sup> to increase risk prediction beyond classic risk scores. According to the Biomarkers Definition Working Group of the National Institutes of Health,<sup>7</sup> a biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.” Thus, biomarkers could be either circulating ones, that is, requiring blood sampling and specific dosage, or imaging ones, that is, requiring measurements with either ultrasounds (eg, left ventricular mass index or carotid intima-media thickness) or any imaging technology (eg, aortic stiffness).<sup>2-4</sup>

The use of sophisticated circulating biomarkers has been suggested for increasing the individual prediction of CV risk, beyond the established CV risk factors, such as age, systolic blood pressure (BP), antihypertensive treatment, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering treatment, diabetes mellitus, smoking status, and body mass index. Results were contrasted. For instance, in the Framingham cohort, using high-sensitivity C-reactive protein, plasma renin, brain natriuretic peptide, homocysteine, and urinary albumin/creatinine ratio did not improve the prediction of outcome.<sup>8</sup> However, in a community-based cohort of elderly men, a combination of circulating biomarkers reflecting myocardial cell damage, left ventricular dysfunction, renal failure, and inflammation (eg, troponin I, N-terminal pro-brain natriuretic peptide, cystatin C, and C-reactive protein, respectively) improved the risk assessment beyond established CV risk factors and increased the C statistics.<sup>9</sup>

As an alternative to using circulating biomarkers in hypertensive patients, estimation of CV risk can investigate target organ damage, such as left ventricular hypertrophy, carotid wall thickening, or aortic stiffening.<sup>1</sup> Thus, target organ damage could play the role of an imaging biomarker<sup>2,10</sup> and may help to identify patients at high risk of developing CV disease. This strategy has a strong background, because target organ damage, which integrates the long-lasting cumulative effects of all identified and nonidentified CV risk factors, can be detected before clinical events occur, at a stage when intervention may reverse damage.<sup>1</sup> By contrast, circulating biomarkers may fail to adequately predict the risk of CV events because of their instantaneous fluctuations, as many “snapshots” of the complex deleterious situation.<sup>10</sup> To underline the structural changes of target organs either directly observed (eg, left ventricular hypertrophy) or associated with a functional alteration (eg, aortic stiffening), we added in this review the wording “tissue” for this category of biomarkers. Among tissue/imaging biomarkers, arterial stiffness in general and aortic stiffness in particular can be considered as measures of the cumulative influence of CV risk factors with aging on the arterial tree, having limited acute variability (mainly depending on BP) and enough inertia to

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From the Department of Pharmacology, European Georges Pompidou Hospital, Assistance Publique Hôpitaux de Paris, Institut National de la Santé et de la Recherche Médicale U970 and University Paris Descartes, Paris, France.

Correspondence to Stéphane Laurent, Department of Pharmacology and INSERM U970, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Université Paris Descartes, 20 rue Leblanc, 75015 Paris, France. E-mail stephane.laurent@egp.aphp.fr

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**Table. Phases to be Completed Before Aortic Stiffness Could be Considered as a Surrogate End Point of CV Events**

Phase	Aortic Stiffness
1. Proof of concept	Yes (3, 10–13)
2. Prospective validation	Yes (15–20)
3. Incremental value	Yes (16–18)
4. Clinical use	Yes (17–20)
5. Clinical outcomes	Weak indirect evidence (21)
6. Cost-effectiveness	No

See Reference 12. References (original studies, meta-analyses, and reviews) related to each phase are indicated in brackets.

reflect the integrated damage of the arterial wall.<sup>3,10</sup> Recent studies showed the potentiating effect of the “large/small artery cross-talk”<sup>11</sup> on heart, brain, retina, and kidney damage.

“Surrogate end points” are a subset of biomarkers. According to the Biomarkers Definition Working Group of the National Institutes of Health,<sup>7</sup> a surrogate end point is “a biomarker that is intended to substitute for a clinical end point. A surrogate end point is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiological, therapeutic, pathophysiologic, or other scientific evidence . . .”<sup>7</sup> To avoid confusion with the substitution for a marker, although it is really a substitution for a clinical end point, the term “surrogate marker” has been discouraged.<sup>7</sup> The next paragraph details how arterial stiffness has demonstrated its usefulness as an imaging biomarker and what should be demonstrated before considering that arterial stiffness is a true surrogate end point, that is, whether the reduction in arterial stiffness translates into a reduction in CV events.

### Arterial Stiffness as a Surrogate End Point

Several review articles<sup>2,4,12</sup> have recently analyzed the various methods for estimating the clinical use of a biomarker. Particularly, a statement from the American Heart Association recommended that several steps should be completed for evaluating a novel risk marker and ultimately concluding that the novel risk marker could be used as surrogate end point of CV events.<sup>12</sup> Six phases of increasing stringency are described below and in the Table.

#### Phase 1: Proof of Concept—Do Novel Marker Levels Differ Between Subjects With and Without Outcome?

This is clearly the case for arterial stiffness, because a large number of pathophysiological conditions are associated with it, as reported in several reviews.<sup>3,13</sup> In addition to aging, they included several physiological conditions, the genetic background, classic CV risk factors, and established CV disease. Importantly, arterial stiffness is also increased in several diseases of non-CV origin, although it is complicated by CV events, such as end-stage renal disease, moderate chronic kidney disease, and disease characterized by chronic low-grade inflammation, such as rheumatoid arthritis, systemic vasculitis, systemic lupus erythematosus, AIDS, and inflammatory bowel disease.<sup>3,14</sup>

#### Phase 2: Prospective Validation—Does the Novel Marker Predict Development of Future Outcomes in a Prospective Cohort or Nested Case-Cohort Study?

Aortic stiffness has predictive value for all-cause and CV mortality, as well as total CV events. This was reported initially in the late 1990s to early 2000s. Currently, as many as 19 studies consistently showed the predictive value of aortic stiffness for fatal and nonfatal CV events in various populations having different levels of CV risk, including a general population, hypertensive patients, elderly subjects, type 2 diabetic patients, and patients with end-stage renal disease. Seventeen longitudinal studies totaling 15 877 subjects with a mean follow-up of 7.7 years were included in a recent meta-analysis,<sup>15</sup> which showed, for 1-SD increase in pulse wave velocity (PWV), a risk ratio of 1.47 (95% CI, 1.31 to 1.64) for total mortality, 1.47 (95% CI, 1.29 to 1.66) for CV mortality, and 1.42 (95% CI, 1.29 to 1.58) for all-cause mortality.

#### Phase 3: Incremental Value—Does the Novel Marker Add Predictive Information to Established, Standard Risk Markers?

The predictive value of aortic stiffness for CV events has been demonstrated after adjustment for classic CV risk factors, including brachial pulse pressure. According to this definition, all of the studies described above showed predictive value of aortic stiffness for CV events independent of classic CV risk factors. The additive value of pulse wave velocity (PWV) above and beyond traditional risk factors has been quantified by 3 separate studies.<sup>16–18</sup> The first was performed in 1045 hypertensive patients, with a longitudinal follow-up of 5.9 years for coronary heart disease events.<sup>16</sup> The increase in coronary heart disease with tertiles of PWV was steeper for patients belonging to the first and second tertiles of the Framingham risk score. The C statistic (quantifying the area under the curve of the receiver operating characteristic, ie, sensitivity versus [1–specificity] curve) is useful for quantifying discrimination, that is, the ability of PWV to distinguish patients in whom CV events will occur from those who will remain free of CV complications. In the group of low-to-medium-risk patients, the C statistics showed that Framingham risk score and PWV had similar predictive value (area under the curve,  $0.65 \pm 0.07$  and  $0.63 \pm 0.08$ , respectively), and, when combined, the predictive value increased because the area under the curve significantly rose to  $0.76 \pm 0.09$ , indicating that PWV improved the prediction of CV events beyond Framingham risk score. This improved ability of aortic stiffness to predict CV mortality was confirmed by Mattace-Raso et al<sup>17</sup> in the elderly subjects from a general population and by Sehestedt et al<sup>18</sup> in middle-aged subjects from a general population. The various mechanisms by which an increase in aortic stiffness generates higher risk of cardiac and cerebrovascular events have been described in details in several reviews.<sup>3,11,13</sup>

#### Phase 4: Clinical Use—Does the Novel Risk Marker Change Predicted Risk Sufficiently to Change Recommended Therapy?

In other words, does the addition of PWV result in a substantial proportion of individuals being reclassified across

a predefined treatment threshold? The answer is yes, because several studies showed that a substantial amount of patients at intermediate risk could be reclassified into a higher or a lower CV risk, when arterial stiffness was measured.<sup>17–19</sup> For instance, in the Framingham study, 15.7% of patients at intermediate risk could be reclassified into a higher (14.3%) or lower (1.4%) risk.<sup>19</sup> In a recent unpublished meta-analysis, 19% and 22% of intermediate risk individuals were reclassified into higher or lower quartiles of risk for coronary heart disease and stroke outcomes, respectively.<sup>20</sup>

### **Phase 5: The Clinical Outcomes—Does Use of the Novel Risk Marker Improve Clinical Outcomes, Especially When Tested in a Randomized Clinical Trial?**

An important issue here is whether the reduction in arterial stiffness translates into a reduction in CV events. There is only very little indirect evidence. To our knowledge, only 1 study reported CV outcomes in patients having repeated measurements of PWV along several years<sup>21</sup>: 150 patients (aged  $52 \pm 16$  years) with end-stage renal disease were monitored for  $51 \pm 38$  months for BP and PWV. Fifty-nine deaths occurred, including 40 CV and 19 non-CV events. Cox analyses demonstrated that the lack of PWV decrease in response to BP reduction was a strong independent predictor of all-cause (relative risk, 2.59 [95% CI, 1.51–4.43]) and CV mortality (relative risk, 2.35 [95% CI, 1.23–4.41]). However, this study experiences several limitations: this was not a randomized clinical trial, rather a post hoc retrospective analysis; baseline PWV was different in the 2 groups and there is no mention that statistical analysis was adjusted to it; finally, this study included patients at very high risk, and results cannot be extrapolated to other (milder) clinical situations, as discussed thereafter.

### **Phase 6: Cost-Effectiveness—Does Use of the Novel Risk Marker Improve Clinical Outcomes Sufficiently to Justify the Additional Costs?**

The cost-effectiveness issue describes the balance between the additional cost associated with the measurement of aortic stiffness and the subtracted cost because of less CV complications when patients are managed according to aortic stiffness measurement. Cost-effectiveness is a complex public health issue, particularly regarding the quantification of avoided or delayed clinical complication and improved quality of life. This issue is far from solved, even for well-established tests in other medical specialties (eg, mammography in breast cancer).

### **Needed Clinical Studies**

One of the most important issues for assessing the usefulness of arterial stiffness as a surrogate end point is whether the reduction in arterial stiffness translates into a reduction in CV events. To solve this issue, large intervention trials conducted either by the pharmaceutical industry or national research institutes should include the measurement of aortic stiffness. This should be done in all participants of the main study rather than as an ancillary study, to be related to the largest number of CV events.

An alternative strategy is to determine whether the change in patient management according to aortic stiffness can improve the outcome. We describe here the experimental design of a

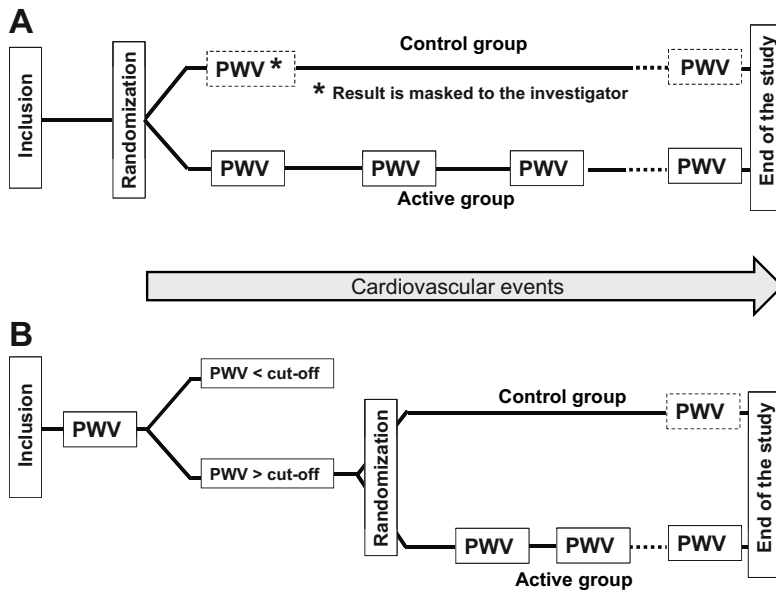
randomized clinical trial, funded by the French Ministry of Health and the French Federation for Hypertension Research, which is planned for launch in 2012 in 40 French centers. Alternative experimental designs will be then discussed.

The aim of the Stratégie de Prévention Cardiovasculaire Basée sur la Rigidité Artérielle Study (SPARTE) is to test the hypothesis that a therapeutic strategy that targets the normalization of arterial stiffness is more effective in preventing CV events than usual care. In a Prospective Randomized Open Blinded End Point parallel group study, we will assign 3000 hypertensive patients, aged 55 to 75 years, who are at medium to very high risk for cardiorenal events to receive either a treatment according to international guidelines for the management of BP (control group) or an additional therapeutic strategy aiming at normalizing PWV values (active group) during 4 years. The primary end point is composite (death from CV causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, coronary revascularization, hospitalization for congestive heart failure, angioplasty for peripheral artery disease, amputation of lower limb, aortic dissection, doubling of serum creatinine, dialysis, and resuscitation after sudden cardiac arrest). We calculated that 1500 patients at medium to very high risk are needed in each group to detect a 20% reduction in combined end points in the active group after 4 years of follow-up, with a 90% power.

In this study, the control group is treated according to the 2007 European Society of Hypertension international guidelines for the management of BP,<sup>1,22</sup> and the active group is treated according to these guidelines and specific treatment aiming at normalizing PWV values. In the control group, the target is BP, with the aim of normalizing it to  $<140$  mm Hg systolic BP and 90 mm Hg diastolic BP. In the active group, the target is aortic stiffness with the aim of normalizing it to  $<10$  m/s. This value corresponds with the threshold of 12 m/s, determined by the 2007 European Society of Hypertension Guidelines for the Management of Hypertension,<sup>1,22</sup> reduced recently by a factor of 0.8 at 10 m/s according to a recent expert consensus statement.<sup>23</sup> In both groups, aortic stiffness is measured after randomization at baseline, and results are masked to the investigator in the control group. Aortic stiffness is measured at the end of the study in the control group to compare the changes from baseline in both groups. Aortic stiffness is repeatedly measured in the active group to adapt treatment.

Aortic stiffness will be normalized first through the strict normalization of BP and then with additional therapeutic strategies. Normalization of BP is a prerequisite, because the fall in BP passively unloads the stiff components of the aortic wall and, thus, reduces aortic stiffness.<sup>3,24</sup> In addition, long-term arterial remodeling, which may need several months<sup>25</sup> or even years<sup>26</sup> to develop, contributes to the normalization of aortic stiffness beyond BP lowering. Specific therapeutic strategies aiming at reducing arterial stiffness beyond BP reduction will be used, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers at high recommended dosages, that is, the maximum dosages recommended by the manufacturer,<sup>24</sup> excluding their combination. The addition of spironolactone will also be considered. Indeed, our group and others have shown, using dedicated long-term randomized, controlled trials, that the angiotensin-





**Figure.** Experimental design of randomized clinical trials aiming at determining whether a therapeutic strategy aiming at normalizing aortic stiffness (active group) is more effective in preventing cardiovascular (CV) events than usual care (control group). **A**, Patients are randomly allocated either to control group (the target is blood pressure) or active group (the target is aortic stiffness) before pulse wave velocity (PWV) measurement. Baseline PWV can be measured in the control group (the result will be masked to the investigator) and at the end of the study to compare PWV changes in the control and active groups. **B**, PWV is measured during the inclusion phase and only patients in whom PWV is above a given cutoff value are randomized to the control group vs the active group.

converting enzyme inhibitors perindopril<sup>27</sup> and trandolapril<sup>28</sup> and the aldosterone-antagonist spironolactone<sup>29</sup> reduced PWV partly independently of BP changes.  $\beta$ -Blockers will be avoided in the absence of compelling indication, such as coronary heart disease, atrial fibrillation, or congestive heart failure,<sup>1,24</sup> because they can limit the destiffening of the arterial wall or increase its stiffness in some populations.<sup>11,24,30</sup>

A multifactorial approach aiming at reducing classic CV risk factors will be associated, including physical exercise, reduction of weight, salt and alcohol, and smoking cessation, all known for being able to decrease aortic stiffness.<sup>3</sup> In addition, antiplatelet agents, lipid-lowering agents, and antidiabetic drugs will be prescribed according to international recommendations, although their effects on aortic stiffness have been less often investigated and consistently demonstrated.<sup>3</sup> This multifactorial approach, already included in the European Society of Hypertension Guidelines,<sup>1,22</sup> will be applied in both groups but intensified in the active group.

Finally, because elevated PWV is sometimes accompanied by aortic calcification, the question may arise as to whether decalcifying measure should be prescribed along with a destiffening approach. However, to our knowledge there is currently no evidence-based treatment regimen that can reduce calcification of large arteries,<sup>31</sup> and the effect of treating CV risk factors on the progression of large artery calcification has not yet been evaluated.<sup>31</sup>

The timing of randomization is a critical issue (Figure). If randomization occurs before PWV measurement, as in the Statégie de Prévention Cardiovasculaire Basée sur la Rigidité Arterielle Study, patients are randomly allocated to 1 of 2 predetermined therapeutic strategies: one is adapted to baseline and subsequent PWV values in the active group; the other is fully independent of baseline PWV value in the control group. An important requirement is that PWV value should be masked to the investigator in the control group. Another possibility is that patients are randomized to either control or active group only if PWV is measured above a given cutoff value. An advantage of this experimental design

is to select patients with PWV sufficiently high to be effectively reduced by treatment, such as in the Losartan Intervention For Endpoint Reduction in Hypertension Study,<sup>32</sup> in which only patients with ECG-left ventricular hypertrophy were selected. A drawback is that a “regression to the mean” effect can limit the interpretation of the results. Repeated PWV measurements before randomization could limit the regression to the mean phenomenon but likely reduce feasibility and recruitment in such an “academic” environment. Whether aortic stiffness should be measured also in the control group, mainly at baseline, has to be discussed: this is the only means to prove that PWV values do not differ between groups. However, a strict procedure should be applied so that the physicians in charge of patients in the control group are truly blinded to the value of PWV. An additional measure of PWV at the end of study in the control group would warrant that the reduction in PWV differs between groups after intervention.

The confounding effect of BP reduction may limit the interpretation of the data. Because antihypertensive treatment is intensified in the active group, as well as the treatment of other CV risk factors, one may ask whether the benefit in terms of CV events, if it occurs, can be attributed to the reduction in PWV, the control of CV risk factors, or both. The specific influence of PWV reduction can be analyzed through multivariate analysis, accounting for BP reduction, low-density lipoprotein lowering, and changes in other CV risk factors. However, this issue is more an academic one than a practical problem. Indeed, participants to the active group and their physicians will be aware of the usefulness of aortic stiffness as subclinical organ damage. There are several mechanisms by which biomarker measurement can improve health outcome,<sup>4</sup> including better patient understanding of the disease, healthier patient behaviors, and better clinical decisions. Finally, additional “nested” studies should take advantage of the main protocol, to integrate the financial cost linked to the use of aortic stiffness as a novel imaging biomarker into its overall cost/benefit analysis.

## Conclusion

Aortic stiffness proved to complete a number of criteria for being considered as a true surrogate end point for CV events, although not all. There is a need for studies comparing aortic stiffness-guided therapeutic strategies with classic guidelines-guided strategies for preventing CV events.

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## Disclosures

None.

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