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Vascular Aging

A Tale of EVA and ADAM in Cardiovascular Risk Assessment and Prevention

Peter M. Nilsson, Pierre Boutouyrie, Stéphane Laurent

Cardiovascular disease (CVD) manifestations still pose a substantial threat to public health, as summarized in a recent report from the American Heart Association Statistics Committee for an update in 2009.¹ Classic risk factors are of major importance to screen for, to evaluate, and to control with lifestyle advice or drug therapy. However, because the risk of CVD is still representing a challenge in spite of prevention and all treatment efforts, there is a need for new pathophysiological models for better understanding of cardiovascular risk and its treatment, based on new concepts.

It has been shown that target organ damage (TOD) represents a mediating step between risk factors and CVD events. Examples of well-established TOD categories include left ventricular hypertrophy and albumin excretion. In addition, substantial evidence has accumulated to show that arterial stiffness and increased pulse wave velocity (PWV), as well as central aortic pulse pressure, are important independent predictors of CVD events.² These are in fact not only examples of TOD but also of the underlying pathological process, because increased PWV might determine the degree of left ventricular hypertrophy through increased arterial pulse wave reflection, central pulse pressure, and postload.²

Because aging is a common denominator to many chronic disease manifestations, eg, CVD, type 2 diabetes mellitus, or cancer, we propose that early vascular aging (EVA) could be a useful concept to better guide clinical investigations in subjects at increased cardiovascular (CV) risk. This could be the case in individuals with marginal elevation of classic risk factors or with a strong family history of early CVD manifestations. There might also be a special link between adverse growth patterns in fetal or early postnatal life (the “mismatch” growth hypothesis) and the EVA syndrome, as summarized recently.³

Vascular aging in general, and EVA more specifically, can be investigated noninvasively through the measurement of arterial stiffness, central blood pressure (BP), carotid intima-media thickness, and endothelial dysfunction. These parameters, which can be considered as arterial “tissue biomarkers,” may be more predictive than “circulating” biomarkers,

like high-sensitivity C-reactive protein, and show a better additional prediction when coupled to classic CV risk scores.⁴ We, therefore, propose that clinical research should focus on the validation of tissue biomarkers as surrogate end points for CV risk reduction in large clinical trials. In addition, clinical research should also determine the respective predictive values of various available arterial tissue biomarkers.

What should be done to counteract the pathophysiological processes reflected in the EVA syndrome? To use a classical dichotomy, the answer is “ADAM,” which stands here for aggressive decrease of atherosclerosis modifiers, eg, risk factor control that will be further explored addressing new types of intervention under development.

“Circulating” Biomarkers or Tissue Biomarkers: Crucial Influence of Aging

Classic risk scores (ie, Framingham risk score [FRS]⁵ and European Systemic COronary Risk Evaluation [SCORE]⁶) are quite effective for predicting CV events in patients with several CV risk factors. However, they may fail to predict CV events in other risk groups suitable for early prevention. The use of sophisticated biomarkers was suggested for increasing the individual prediction of CV risk. A variety of biomarkers were proposed, the most popular being homocysteine or high-sensitivity C-reactive protein. However, this approach has generally been deceiving, even if homocysteine recently demonstrated a greater predictive value for CVD than classic risk factors in very old people, by shifting the receiver operating characteristic (ROC) curve relative to the Framingham risk score alone.⁷

In a recent article, Wang et al⁸ demonstrated that the added value of using multiple biomarkers was negligible, because their use, either individually or in any combination, did not improve the prediction of outcome in the Framingham study. Subsequently, popular but disputed biomarkers, eg, high-sensitivity C-reactive protein, were withdrawn from current European guidelines for the management of hypertension.⁹ It remains doubtful whether any other refinement of the biomar-

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ker approach will lead to a better individual prediction of CV risk, except in specific populations.⁴

The metabolic syndrome can be viewed as a combination of circulating and tissue biomarkers, because it is an association of 3 among 5 criteria, including either high-density lipoprotein cholesterol, triglycerides, blood glucose, BP, and waist circumference. In a subgroup of older participants from the Cardiovascular Health Study who were free of CVD at baseline, the metabolic syndrome, as defined by the Adult Treatment Panel III criteria, demonstrated an independent predictive value for coronary and cerebrovascular events, even after adjusting for traditional CV risk factors and the individual domains of the metabolic syndrome.¹⁰ The relationship between metabolic syndrome and tissue biomarkers is complex. Indeed, the metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness.¹¹ In offspring of diabetic subjects, endothelial function is blunted and aortic stiffness is increased, an association that is already present at a very young age, before any alteration in glycemic control or BP values can be detected, and is independent of the presence of the metabolic syndrome and its altered components.¹²

By contrast to the circulating biomarkers, TOD can be used as a tissue biomarker together with (or preferentially independently of) classic risk factors and may help to identify patients at high risk of developing CV disease. This strategy has a strong background, because TOD integrates the cumulative effects of CV risk factors with aging and can be detected before clinical events occur, at a stage when intervention may reverse damage. Numerous TOD categories have been identified, eg, the presence of left ventricular hypertrophy, microalbuminuria, reduction in glomerular filtration rate, and white matter cerebral lesions.

The damage of the arterial tree raises increasing interest: increased arterial stiffness, central pulse pressure, carotid intima-media thickness, and endothelial dysfunction.¹³ Recent studies showed a close relationship between microvascular damage in the heart, brain, retina, and kidney and arterial stiffness. Aortic stiffness is particularly associated with either silent cerebral small-vessel disease¹⁴ or decline in cognitive function¹⁵ in cross-sectional studies and is an independent predictor of loss in cognitive function in longitudinal studies.¹⁶

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 (Figure 1). Indeed, arterial stiffness reflects the true arterial wall damage, whereas BP, glycemia, and lipids, which are fluctuating along the follow-up of patients, may not. A temporal dissociation exists between the observed values of classic and sophisticated CV risk factors (ie, "circulating" biomarkers), which can be considered as "snapshots," and arterial stiffness, which integrates the long-lasting effects of all identified and nonidentified CV risk factors and, thus, may be considered as a tissue biomarker. Measurement of arterial stiffness may avoid patients being mistakenly classified as at low or moderate risk when they actually have an abnormally high arterial stiffness, placing them within a higher risk group.

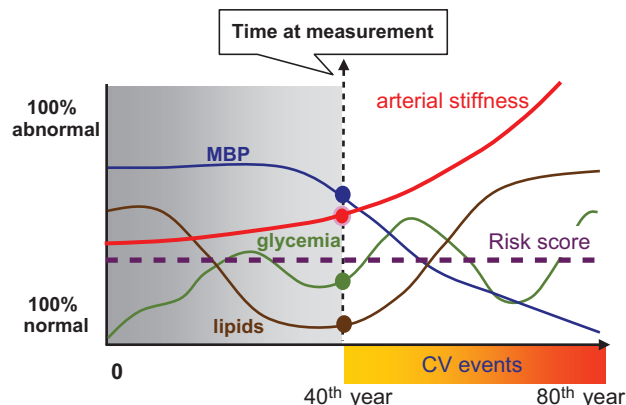


Figure 1. Arterial stiffness is a cumulative measure of the damaging effects of CV risk factors on the arterial wall with aging. Arterial stiffness, which reflects the true arterial wall damage of CV risk factors, increases with aging. By contrast, mean BP (MBP), glycemia, and lipids, which are fluctuating along the follow-up of patients, may give a constant value when combined into a CV risk score if their fluctuations occur in opposite directions, and their mean variation compensates for the effects of aging. Thus, measuring circulating biomarkers at a certain time may give only a snapshot and not the whole history of arterial wall damage. The gray zone before the time at measurement indicates that, most often, the physician does not know the amount of exposure to CV risk factors.

Additive Predictive Values of Arterial Stiffness and Classic Risk Scores

In a recent expert consensus document on arterial stiffness,² 11 longitudinal studies were listed, demonstrating that a simple measure of aortic stiffness through carotid-femoral (CF) PWV yielded prognostic values beyond and above traditional risk factors. Other arterial measurements can be used as surrogates for arterial stiffness. Among them, central pulse pressure is interesting, because it may be a better estimate of the true pressure acting on TOD.^{17,18} Augmentation index also gives information on wave reflection, which contributes to the increase in central BP.¹⁷ Under physiological conditions, the reflected pressure wave returns in diastole, explaining at least in part why systolic and pulse pressures measured close to the heart are lower than in the periphery. It may be interesting to substitute central BP for peripheral (brachial) BP, because it has been demonstrated that drugs may have a differential effect on central BP but not on peripheral BP.¹⁸ However, the level of evidence for the predictive values of central BP and augmentation index is lower than for aortic stiffness.^{2,17,18}

The additive value of CF-PWV above and beyond traditional risk factors has been demonstrated by 2 separate studies. The first was performed in 1045 hypertensive patients, with a longitudinal follow-up of 5.9 years for coronary heart disease (CHD) events.¹⁹ The increase in CHD with tertiles of CF-PWV was steeper for patients belonging to the first and second tertiles of the FRS. The area under the ROC curve (AUC) of CF-PWV decreased from the lowest to the highest tertile of FRS (from 0.65 ± 0.07 to 0.53 ± 0.04 ; $P=0.01$), indicating that the predictive value of CF-PWV was the highest in patients considered to be at low risk by the FRS. In the group of low-to-medium-risk patients, FRS and CF-PWV had similar predictive values (AUC: 0.65 ± 0.07 and

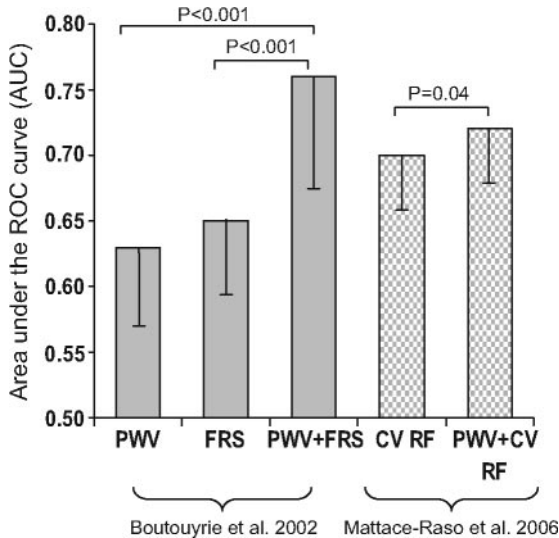


Figure 2. Additive predictive value of arterial stiffness and classic risk factors. In a group of low-to-medium-risk hypertensive patients¹⁹ with a longitudinal follow-up of 5.9 years, the predictive values of aortic stiffness (CF-PWV) and FRS for CHD events were assessed from the AUC. PWV and FRS had similar predictive values (AUC: 0.63 ± 0.08 and 0.65 ± 0.07 , respectively, mean \pm SD). When PWV and FRS were combined, the predictive value significantly increased (AUC: 0.76 ± 0.09 ; $P < 0.001$ vs each component), indicating that PWV improved the prediction of CHD events beyond FRS. Similarly, in a population of 2835 elderly subjects participating in the Rotterdam study,²⁰ the addition of aortic stiffness (PWV) significantly improved the predictive value of a combined criteria (classic CV risk factors+ankle-arm index+carotid intima-media thickness+brachial pulse pressure) for future CV events.

0.63 ± 0.08 , respectively), and, when combined, the predictive value increased, because the AUC rose to 0.76 ± 0.09 (unpublished data), indicating that CF-PWV improved the prediction of CV events beyond FRS (Figure 2).

This improved ability of aortic stiffness to predict CV mortality was more recently confirmed by Mattace-Raso et al²⁰ in the elderly subjects from a general population (Figure 2). By contrast, as seen above,⁸ the added value of multiple sophisticated circulating biomarkers was negligible, because their use, either individually or in any combination, did not improve the prediction of outcome in the Framingham study. Interestingly enough, for all of the published studies about the predictive value of aortic stiffness, patients were subsequently treated for their treatable risk factors. This means that the predictive value of arterial stiffness remains independent of common CV drug therapy. This may also explain why classic risk factors, once detected and treated, cease to have a strong influence on further events.

From these results, it can be concluded that, in patients considered as low risk by classic CV risk scores, aortic stiffness is a strong independent predictor of CV outcome, providing a level of information equal to classic CV risk factors, the value of which is additive to it. These patients are likely those with conditions such as high normal BP and a background of positive family history for early CVD or subjects with impaired glucose tolerance, metabolic syndrome, or endothelial dysfunction. These patients are known for often having an increased arterial stiffness, because these

Table. Pharmacological Tools for Reducing Vascular Aging

Modifiable CV Risk Factors and Classic Drug Targets	Current Alternatives to Classic Drugs, Under Evaluation	Future Alternatives to Classic Drugs
Obesity-related drugs	Sex hormones (estrogens)	Telomerase activators
Smoking-cessation drugs	Advanced-glycation end product breakers	Farnesyl transferase inhibitors
Antihypertensive agents	Selective treatments for osteoporosis	
Lipid-lowering agents		
Antidiabetic agents		
Antiplatelet agents		

conditions are correlated. However, the measurement of PWV and the finding of a higher value than expected from the number of CV risk factors would call attention to the excessive CV risk of these patients and the need for a multifactorial therapeutic approach.²¹ For that purpose, we currently need large, population-based data as to how the conventional CV risk factors shift the relationship between aging and arterial stiffness.

Telomere Biology and Vascular Aging

One new marker of aging is telomere length or the dynamics of telomere length change over time.^{22,23} Cross-sectional studies have illustrated the complex associations between telomere length and clusters of CV risk factors, including hypertension,²⁴ dyslipidemia,²⁵ and obesity and smoking,²⁶ as well as unhealthy lifestyle in general.²⁷ Furthermore, a recent report has shown that an increased telomere attrition rate is a predictor of CV mortality in elderly men.²⁸ It is, therefore, of great interest to further elucidate the interaction between genetic and environmental influences on the aging process in general and on EVA in particular. Cross-sectional studies have shown that subjects with increased arterial stiffness have shorter telomeres.²⁹ No study so far has investigated whether the telomeric change over time is also related to changes in vascular function or morphology. Finally, the effects of different pharmacological interventions are still only marginally known, even if it has been shown that statin therapy might reduce the risk of shorter telomeres for CHD in the West of Scotland Coronary Prevention Trial³⁰ and that lifestyle intervention improved telomerase activity in men with prostatic cancer.³¹

New Interventions to Halt the Process of Vascular Aging

Once EVA is defined and the different pathways investigated, it remains to be determined whether intervention could slow down the aging process. For this purpose, we review some of the elements through which the detrimental effect of aging could be neutralized (Table).

Lifestyle Changes and Conventional Drugs

As a first attempt, interventions designed to correct lifestyle and major CV risk factors, eg, hypertension, dyslipidemia,

and diabetes mellitus, are accompanied by a regression in arterial stiffness. A large number of publications and several reviews² reported the changes in arterial stiffness and wave reflections after various interventions, either lifestyle or pharmacological. Nonpharmacological treatments that are able to reduce arterial stiffness include exercise training and dietary changes (including weight loss,³² low-salt diet,³³ moderate alcohol consumption, garlic powder, α -linoleic acid, dark chocolate, and fish oil).

Pharmacological treatments that are able to reduce arterial stiffness include the following: (1) antihypertensive treatment, eg, diuretics, β -receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin II type 1 blockers, and calcium channel antagonists; (2) treatments of congestive heart failure, eg, angiotensin-converting enzyme inhibitors, nitrates, aldosterone antagonists, and β -blockers³⁴; (3) hypolipidemic agents, eg, statins; and (4) antidiabetic agents, eg, thiazolidinediones.

The cumulative effect of lifestyle changes and pharmacotherapy for CV risk factors has not been documented in a single clinical trial. However, Guerin et al³⁵ have shown that, even in a population at extremely high risk, end-stage renal disease patients, intensive BP lowering, together with optimized management, could induce a reduction in aortic stiffness and that this reduction in aortic stiffness was associated with less CV events. Large clinical trials with multiple target interventions have shown a benefit in reduction in CV events during long-term follow-up.³⁶ Hopefully, combined lifestyle changes in young people,³⁷ associated with multiple drug combinations in adults, will demonstrate such effectiveness on EVA and premature CV events.

Preventing Vascular Aging Beyond BP Reduction

Whether the reduction in arterial stiffness after antihypertensive treatment is only attributable to BP lowering or whether additional BP-independent effects are involved is still debated. Most of the trials performed to demonstrate this so-called "BP-independent" effect were performed in animals treated with low-dose medication or in humans by comparing drug A with drug B, with no real emphasis on the quality of BP control. Thus, the arteries may have remained exposed to high BP. Through the unloading of fibrous components of the arterial wall in response to BP reduction, many antihypertensive drugs have proven their ability to reduce arterial stiffness. However, significant differences were observed between classes of antihypertensive drugs, eg, drugs interfering in the renin-angiotensin system are often more effective at reducing arterial stiffness than other drugs. The Conduit Artery Functional Endpoint Study,¹³ an ancillary study from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm, confirmed that, other than the lack of bradycardia, vasodilatation and long-term arterial remodeling in response to angiotensin-converting enzyme inhibitor and calcium antagonists were accompanied by a larger decrease in central BP compared with nonvasodilating β -receptor blocker plus thiazide treatment for a similar decrease in brachial BP. Unfortunately, aortic stiffness was not measured simultaneously, and central BP was not measured at baseline, both elements preventing the generalization of these results.

We have shown³⁸ a direct BP-independent effect of an angiotensin-converting enzyme inhibitor (perindopril) on carotid stiffness in patients with type 2 diabetes mellitus. Recently, similar results have also been reported for the reduction of aortic stiffness with an angiotensin II receptor antagonist (valsartan) in patients with type 2 diabetes mellitus.³⁹

Current Alternatives to Classic Drugs

Novel therapeutic approaches could also contribute to reduce vascular aging and CV events. Several years ago it was demonstrated that EVA was frequently associated with age-associated (sex) hormonal decline. After menopause, women with reduced levels of estrogen experience a disproportionate increase in pulse pressure,⁴⁰ a surrogate for aortic stiffness. In the Baltimore Longitudinal Study of Aging, postmenopausal women taking hormonal replacement therapy have a smaller increase in systolic BP over time than those not taking hormonal replacement therapy, a difference that is intensified at older ages.⁴¹ In postmenopausal women not receiving estrogen, the increase in systolic BP may involve inhibition of NO bioavailability, thus, endothelial dysfunction in response to a high-salt diet.⁴² Many publications have documented that arterial stiffness was increased disproportionately after menopause (either postsurgery or chronological). It was, therefore, tempting to determine whether hormonal replacement therapy after menopause was accompanied by a slower progression of arterial stiffness. This has been addressed by some clinical trials. For instance, Rajkumar et al⁴³ compared postmenopausal women either treated or not treated with sex hormones with younger nonmenopausal women. They showed that treatment by sex hormones was accompanied by a lower aortic stiffness and systemic arterial compliance than those found in untreated women. In addition, in a large randomized control trial, Hodis et al⁴⁴ showed that treatment with unopposed 17 β -estradiol slowed the rate of intima-media thickness progression.⁴⁵ Since this publication, however, many articles of randomized, double-blind studies have provided conflicting results about the clinical effect of sex hormones on arterial stiffness,⁴⁶ coronary atherosclerosis,⁴⁷ or endothelial function.⁴⁸ Together with the persistent doubt about the benefit/risk of sex hormones, this therapeutic pathway still waits for the ideal drug.

Osteoporosis is an increasingly common condition, not only in postmenopausal women, but also in elderly men, and one that is related both to increased CV risk and to EVA, as evidenced by increases in arterial stiffness.⁴⁹ Osteoprotegerin, which could represent the molecular link between bone resorption and vascular calcification, is an independent predictor of PWV in osteoporotic postmenopausal women.⁵⁰ Selective treatments for osteoporosis⁵¹ may lead to a decrease in arterial stiffness and, thus, a decrease in CV events. It is important that patients with osteoporosis have their classic CV risk factors assessed, together with the measurement of arterial stiffness.

The role of advanced glycation end products in the age-associated increase in arterial stiffness has been underlined, especially in patients with altered glucose metabolism or overt diabetes mellitus.⁵² Collagen fibers and other structural

proteins with long half-lives undergo nonenzymatic glycation caused by the Maillard reaction.⁵³ These cross-links tighten collagen fibers together with strong connections, limiting the sliding and unwrapping of fibers during distension, leading to increased stiffness of both large arteries⁵⁴ and the left ventricle.⁵⁵ This phenomenon is thought to be of key importance for the age-induced stiffening. This concept has been validated by several pharmacological experiments. Compounds such as aminoguanidine (pimagedine), which are able to inhibit the production of advanced glycation end products in various animal models,⁵⁶ however, failed to prevent the progression of nephropathy in type 1 diabetic patients.⁵⁷ Other molecules under development that are able to reverse the Maillard reaction may be more effective. Until now, only ALT711 (alagebrium) has undergone clinical trials with positive results. Alagebrium improved aortic stiffness in elderly hypertensive patients⁵⁸ without any change in BP and improved endothelial function in patients with systolic hypertension.⁵⁹ In the latter study, interestingly, improvement in endothelial function and collagen turnover were proportional. The effects of alagebrium have not been reported in larger-scale trials, and further evidence for clinical benefits is needed.

Other Possible Alternatives to Classic Drugs

Telomerase inhibitors have been developed for the treatment of cancer, although their effect on tissue aging is unknown.⁶⁰ Targeting telomerase activity for slowing aging is an active domain, and many patents are taken on telomerase activators, some of them having potential antiaging properties. That telomerase residual activity is present in a limited number of tissues and that the activation of telomerase occurs in 90% of human tumors may be some warnings about the safety of this approach.⁶¹

Lamin A has been implicated in physiological aging,⁶² leading to the concept that targeting the Lamin A maturation pathway may be an effective antiaging pharmacotherapy. Progeria (or Hutchinson-Gilford syndrome), which is associated with an abnormal Lamin A, is probably the most severe syndrome of early aging.⁶³ Affected patients exhibit a physical aspect of elderly patients and die before age 17 years. The major cause of death in progeria is CVD with ischemic heart disease and stroke. This autosomal-dominant disease has

been associated recently with the mutation of prelamin A, lacking a cleavage site for the removal of a farnesylated moiety necessary for the maturation of functional Lamin A. It has been shown that Lamin A is a key protein for the mechanical integrity of the nucleus of cells, particularly in cells exposed to high mechanical stress, eg, arteries and the skin.⁶⁴ Targeting the Lamin A maturation pathway may, therefore, lead to effective antiaging pharmacotherapy. This could be done by inhibiting the farnesylation of prelamin, thus upregulating the production of functional Lamin A. Farnesyl transferase inhibitors have demonstrated a spectacular effect, by increasing the life span and reducing age-induced events in mice models of progeria.⁶⁵ Although the accumulation of toxic unfarnesylated lamin and prolamins in the nucleus may explain the incomplete response, the hope for affected patients motivated the early start of a clinical trial with lonafarnib (NCT00425607) in patients with progeria. This open-label trial with historical controls will hopefully demonstrate an improvement of outcome in this devastating disease. The translation of such results for less severe conditions is not yet envisaged.

Klotho is a cofactor of fibroblast growth factor 23, forming a heterodimer of which its function is to upregulate the expression of fibroblast growth factor receptors, notably at the site of renal tubules, increasing phosphate expression. Animal models invalidated for Klotho have been described as models of accelerated aging because of the occurrence of early osteoporosis together with extensive vascular calcifications, arteriosclerosis, and genital and skin atrophy.⁶⁶ Klotho pathway abnormalities are associated with numerous clinical conditions, and genetic variants of the Klotho gene have been associated with osteoporosis,⁶⁷ early coronary artery disease,⁶⁸ stroke and vascular dementia,⁶⁹ and renal failure.⁷⁰ Saito et al⁷¹ have shown that a rat model with increased risk factors (Otsuka Long Evans Tokushima Fatty) was protected against atherosclerosis and endothelial dysfunction when Klotho was overexpressed. At the present time, we are not aware of any pharmacological compound able to modulate Klotho expression.

Summary

CVD prevention remains an important issue in public health and preventive cardiology. Favorable age-adjusted trends in

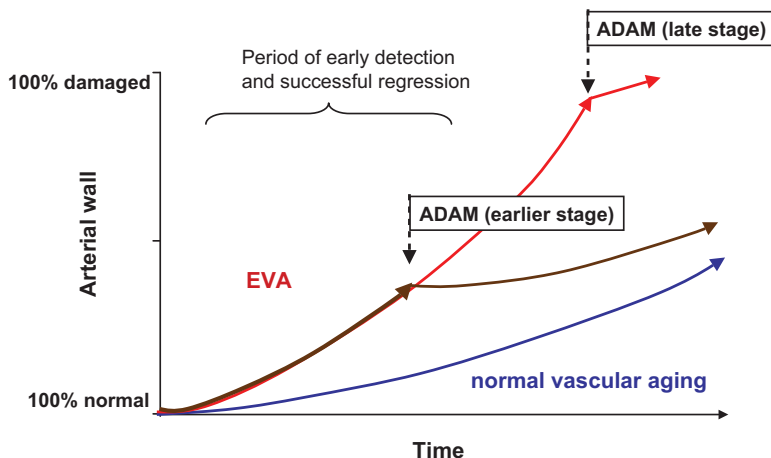


Figure 3. Time course for the development of EVA and start of intervention with ADAM in patients at increased cardiovascular risk.

decreasing CVD incidence and better control of CVD¹ and hypertension⁷² have been documented, a possible reflection of improving conditions for newborns and children in the Western world. There is, however, the dilemma to either go for more extensive blood sampling in a never-ending pursuit of new clinical risk markers⁴ with less and less addition to the estimation of the overall risk or to develop better methods for evaluating EVA and TOD. The ultimate goal is to find more effective ways for CVD prevention via ADAM (Figure 3). Current guidelines propose intensified risk factor control in patients at particularly high risk, eg, patients with diabetes mellitus and established CVD. Because the risk often remains high in spite of therapeutic efforts at this late stage, our conclusion is that new intervention trials are needed for early CVD prevention, based on screening for EVA in high-risk patients, eg, those with a positive family history for CVD or impaired glucose metabolism. In families with a high risk for premature myocardial infarction and stroke, there is also a fair chance of finding family members with early signs of CV aging. From both an ethical and a clinical perspective, it is fully acceptable to reach out and invite these individuals for a careful examination of CV risk factors, EVA, and other manifestations of TOD. Personal advice to improve lifestyle should be given and, in many cases, also targeted drug interventions according to guidelines.

In conclusion, the concept of EVA and ADAM, which represents a development of ideas that have been around for a few years,^{73,74} should benefit from the development of new methodologies, eg, PWV measurements, and the use of leukocyte telomere DNA as a marker of vascular telomere DNA⁷⁵ and risk of hypertension,⁷⁶ guiding novel therapeutic approaches.

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None.

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