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Review

Incremental value of the measures of arterial stiffness in cardiovascular risk assessment

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Abstract

Predicting the occurrence of organ damage and future cardiovascular events is critical to improving patient prognosis through early personalized treatment. Although many tools have been developed and used for individuals' cardiovascular risk, they have limitations and unmet needs for improved risk stratification. For this purpose, arterial stiffness information can be practical. Arterial walls stiffen with age or prolonged exposure to various noxious stimuli such as high blood pressure, hyperglycemia, inflammation and oxidative stress. Differently from several methods of measuring arterial stiffness, pulse wave velocity (PWV) is most widely used for its non-invasive and easy measurement. It is well authorized that information on arterial stiffness is associated with the development of future cardiovascular events, independent from traditional cardiovascular risk factors, in various patient groups with specific diseases along with the general population. Moreover, when this information of arterial stiffness is associated with other risk stratification tools, it is possible to predict individuals' cardiovascular risk easier. Herein, we will review the incremental value of the measurement of arterial stiffness in cardiovascular risk assessment when combined with other risk factors such as traditional risk factors, biomarkers, other vascular testing and non-invasive cardiac imaging.

Keywords: Arterial stiffness; Cardiovascular risk; Incremental value; Pulse wave velocity; Risk assessment

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death and morbidity worldwide [1,2]. To improve the cardiovascular prognosis, it is essential to earlier detect high-risk individuals and provide the individualized treatment [3]. To do this, an appropriate method must be in place to assess individuals' risk. The most common way to predict cardiovascular risk is to identify traditional risk factors [4–8]. However, it has been reported that a substantial portion of individuals without conventional risk factors have experienced cardiovascular events [9]. Although several cardiovascular risk scores have been obtained based on the combination of these traditional risk factors and utilized for risk prediction [3,10], these risk scores are difficult to apply to Asians because they are computed based on the results of a study mainly targeting people in Western countries [11]. Cardiac biomarkers, such as C-reactive protein, natriuretic peptide, and troponin, are also helpful in risk classification; however, it requires considerable effort in methodology and some of which need more validation [12]. Non-invasive cardiac imaging tools, such as echocardiography, myocardial perfusion imaging (MPI) and coronary computed tomography angiography (CCTA), have high power for predicting future cardiovascular events, but these tests need cost and time and have side effects such as radiation exposure and nephrotoxicity [13,14].

Recently, interest in arterial stiffness in the cardiovascular field has been increasing. Artery stiffened with age or prolonged exposure to various noxious stimuli such as high blood pressure, hyperglycemia, inflammation, and oxidative stress [15–17]. There are various methods to measure arterial stiffness [17] and these measurements are useful for predicting cardiovascular risk [18,19]. Many studies have shown that the information of arterial stiffness was significantly associated with the occurrence of future cardiovascular events not only in the general population but also in patients with various diseases, even when confounding effects of multiple cardiovascular risk factors were adjusted [20–26]. Of note, it has been suggested that arterial stiffness information has additional value when used simultaneously with other risk stratification tools. Through this method, the prognostic value of arterial stiffness can be applied more effectively. Herein, the incremental value of the measures of arterial stiffness in cardiovascular risk assessment will be reviewed.

2. Measures of arterial stiffness

There are various measures of arterial stiffness such as pulse pressure (PP), pulse wave velocity (PWV) and augmentation index (AIx) [15–17,27]. These values can be obtained both non-invasively and invasively. Although invasive measurement of intra-arterial hemodynamic profiles by catheterization is the most accurate method, its use is hindered by invasiveness, cost, and time. Therefore, inva-

sive methods are used for validation purpose [28,29]. However, in patients undergoing invasive coronary angiography (CAG), invasive aortic pressure measurement is feasible without additional risk and cost; some studies have reported the usefulness of this measurement [28–32]. In other situations, most measures of arterial stiffness can be obtained by non-invasive methods. Given that the transmission speed of pulse wave passing through the arterial wall (pulse wave velocity, PWV) is proportional to the degree of arterial stiffness, the PWV is a direct and reliable measure of arterial stiffness [16,17,33,34]. The PWV can be simply obtained by dividing distance by the difference in the arrival time of the waveforms between the two different arterial points [17]. There are several types of PWV, depending on the location of the artery being measured. Among them, carotid-femoral PWV (cfPWV) and brachial-ankle PWV (baPWV) are the most widely used [34]. PP and AIx are also important indicators of arterial stiffness. As the velocity and amplitude of reflected waves in stiffened arteries increases, it merges earlier with forwarding waves, leading to increase AIx (the amount of pressure augmentation relative to PP) and PP [27]. Because of simplicity and generous clinical data, PWV has been the most widely used among various measures of arterial stiffness [17,33]. PWV can be measured non-invasively with commercially available equipment. Echocardiography, computed tomography, and magnetic resonance imaging are also applied to measure arterial stiffness. There are several different methods for measuring arterial stiffness using these imaging techniques, but the method of calculating aortic distensibility based on the change in the size of the aorta during systolic and diastole is mainly used [15]. However, they are only used for research purposes due to cost and technical issues.

3. Prognostic value of the measures of arterial stiffness

The most important clinical value of information on arterial stiffness is that it is associated with future cardiovascular events and we can use it in risk assessment. In a study that followed 2232 participants in the Framingham Heart Study cohort for 7.8 years, higher aortic PWV was associated with a 48% increase in cardiovascular disease risk in multivariable analysis [24]. In a 9.4-year follow-up study of 1678 general Danish peoples, for each 1 SD increase in cfPWV (3.4 m/s), there was a 16%–20% increase in the development of coronary artery disease (CAD), which was significant even after adjusting for several clinical factors [21]. Kim *et al*. [35] investigated 2561 hypertensive subjects and showed that higher baPWV ($\geq$1630 cm/s) was independently associated with a higher risk of the occurrence of cardiovascular events during a median follow-up period of 4.14 years. Other studies have also shown similar results of the prognostic value of PWV in hypertensive and diabetic patients [25,26,36,37]. In CAD patients, increased arterial stiffness was associated with future development of mortality and cardiovascular events [22,38,39]. In a recent study, both invasive and non-invasive measurements of PWV values in patients undergoing invasive CAG were all significant factors associated with the occurrence of coronary events [22]. Ki *et al*. [38] investigated 372 patients who underwent percutaneous coronary intervention (PCI), and demonstrated that a higher baseline baPWV value ($\geq$1672 cm/s) is a predictive marker for cardiac death after PCI. A higher baseline baPWV value was an independent factor predicting mortality and functional outcome in patients with acute stroke [23,40,41]. In a cohort of 241 patients with end-stage renal disease (ESRD) undergoing hemodialysis, each aortic PWV increase of 1 m/s was associated with a 1.4-fold increase in mortality during 72 months of clinical follow-up [42]. Other studies have also reported that the increase in arterial stiffness in chronic kidney disease (CKD) patients is an essential factor determining patients' cardiovascular prognosis [43,44]. The measures of arterial stiffness are also practical in predicting clinical outcomes in patients with heart failure [45,46]. In meta-analyses, both aortic PWV and baPWV are predictors of future cardiovascular events in various patient populations: every 1 SD increase in the aortic PWV and baPWV were associated with 47% and 19% increase respectively, in the risk of CVD [18,19]. Collectively, in the general population as well as in patients with various diseases, increased arterial stiffness was associated with increased cardiovascular risk. Based on the clinical usefulness of this arterial stiffness measurement information, European and Japanese guidelines recommend cfPWV and baPWV measurements, respectively, for risk assessment in hypertensive patients [47,48].

4. Pathophysiology

The mechanism by which increased arterial stiffness induces cardiovascular disease can be explained as follows. In stiffened artery, the transmission speed of the pulse wave moving along the arterial wall increases so that the reflected wave is combined with the forward wave at early stages, leading to systolic augmentation [27]. This further raises systolic blood pressure and lowers diastolic blood pressure. Increased systolic and pulse pressures cause left ventricular hypertrophy, which promotes left ventricular diastolic dysfunction and subendocardial ischemia [49]. Reduction in diastolic blood pressure in the stiffened aorta lowers coronary blood flow, further promoting myocardial ischemia [50,51]. Increased pulsatile nature of arterial pressure by arterial stiffening promotes the influx of lipids into the subendothelial layer, plaque progression, and weakening of fibrous cap, which leads to plaque rupture [52,53]. The increase in PP accelerates carotid artery atherosclerosis and cerebral small vessel damage [54,55]. Shared risk factors (high blood pressure, hyperglycemia, dyslipidemia, smoking, inflammation, endothelial cell dysfunction oxidative stress, etc.) between increased arterial stiffness and cardiovascular disease may be another important pathophysiology

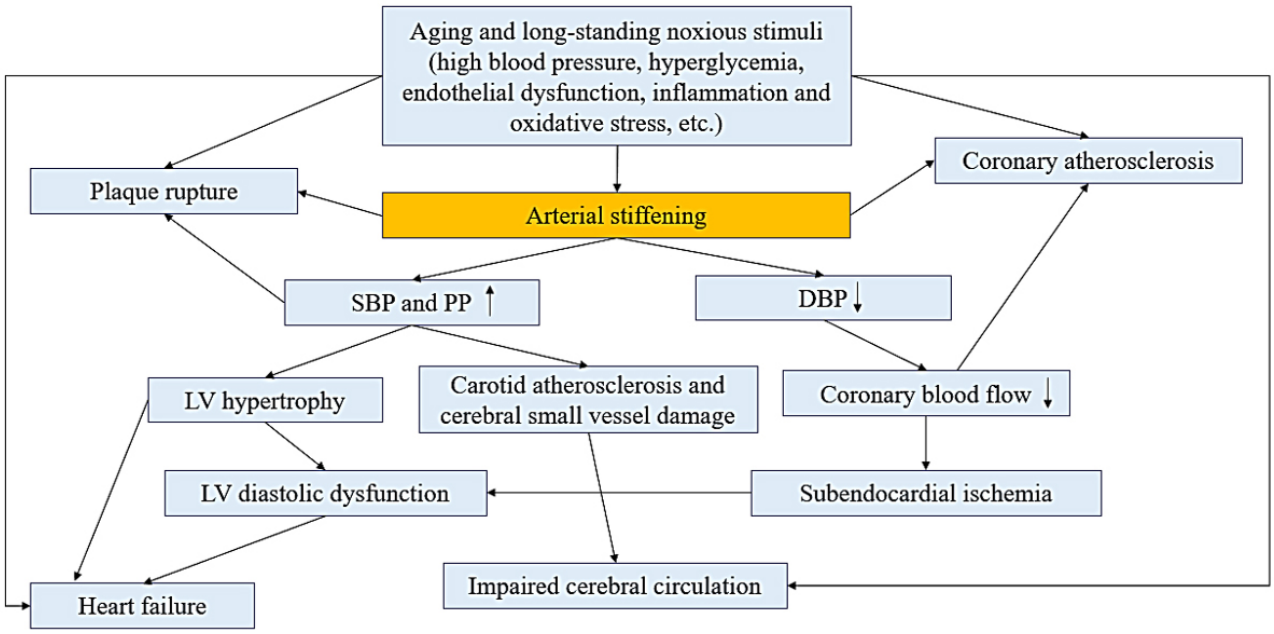

Fig. 1. Pathophysiology in the association of arterial stiffness with organ damage and the development of cardiovascular events. SBP, systolic blood pressure; PP, pulse pressure; DBP, diastolic blood pressure; LV, left ventricle; BBB, blood-brain barrier.

[33,34]. Possible underlying pathophysiology in the association of arterial stiffness with organ damage and the development of cardiovascular events is demonstrated in Fig. 1.

5. Incremental value of the measures of arterial stiffness in detecting of CAD

Using the information on arterial stiffness can help detect CAD. Wang *et al*. [56] demonstrated that carotid wall elastic modulus measured by shear wave elastography had incremental value in identifying obstructive CAD to clinical risk factors and other parameters. In that study, when carotid elasticity information was added to Framingham risk factor, ankle-brachial index, and global cardiac calcium score, the probability of detecting obstructive CAD was significantly increased (overall Chi-square, 9.95 to 15.86). It has been reported that the combination of increased cf-PWV had incremental predictive value to other risk factors for the detection of impaired coronary flow reserve (CFR) [57,58]. Tzortzis *et al*. [57] investigated 110 untreated hypertensive patients and reported that patients with carotid intima-media thickness (IMT) >1 mm, cfPWV >10.2 m/s or their combination had an odds ratio of 3.5, 5.0 and 11.2, respectively for a CFR <2.5. The same study group also demonstrated that cfPWV had incremental value in the determination of CFR when added to traditional risk factors and echocardiographic parameters [58]. In a study of 233 patients with myocardial ischemia, adding information on baPWV to myocardial perfusion imaging (MPI) results and clinical parameters significantly increased diagnostic accuracy in the detection of obstructive CAD in patients with mild ischemia, but not in those with moderate or severe ischemia on MPI [59]. This implies that baPWV may be more valuable with MPI for the detection of obstructive CAD, especially in patients with mild ischemia on MPI.

6. Incremental prognostic value of the measures of arterial stiffness

Kaolawanich *et al*. [60] investigated 520 patients who underwent adenosine stress cardiac magnetic resonance (CMR) and demonstrated that aortic PWV measured by CMR had incremental prognostic value to CMR results in the prediction of cardiovascular (CV) events during the median follow-up period of 46.5 months. In that study, patients with a higher PWV and positive ischemia on CMR had a significantly higher event rate compared to those with a lower PWV and negative ischemia (HR [hazard ratio], 8.94; $p < 0.001$). In a study that analyzed 350 patients with suspected CAD who underwent MPI, when baPWV information was added to traditional risk factors and the MPI results, the occurrence of cardiovascular events was predicted better (overall Chi-square, from 24.08 to 27.42; $p < 0.001$) [61]. Hwang *et al*. [62] looked at 523 patients with suspected CAD and reported that the addition of baPWV to clinical factors and CCTA findings significantly improved the prediction of cardiovascular events (overall Chi-square, 132 to 154; $p = 0.005$). In a study that followed 382 patients with acute coronary syndrome (ACS) (median follow-up period of 62 months), the addition of cardio-ankle vascular index (CAVI) to the GRACE risk score enhanced net reclassification improvement (NRI) and integrated discrimination improvement (IDI) (NRI, 0.337, $p = 0.034$; IDI, 0.028, $p = 0.004$) [63]. In 2232 participants in the Fram-

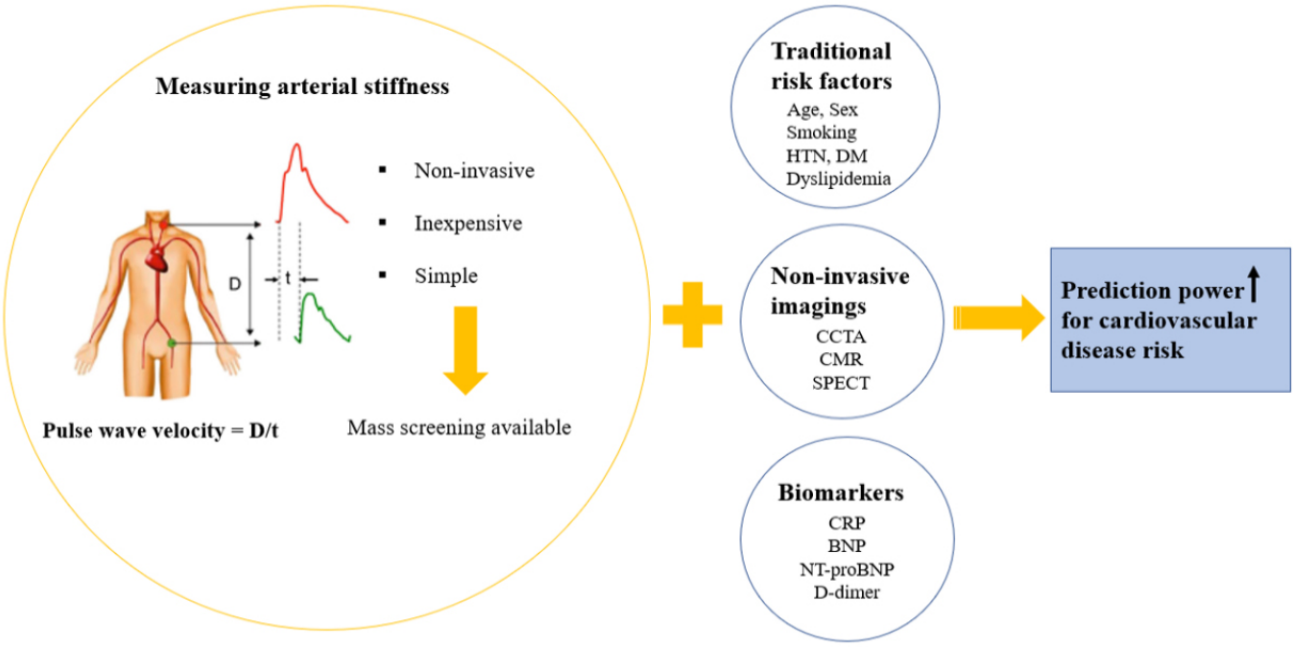

Fig. 2. Clinical use of the measures of arterial stiffness to increase prediction of cardiovascular prognosis. D, distance; t, time; HTN, hypertension; DM, diabetes mellitus; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; SPECT, single position emission computed tomography; CRP, C-reactive protein; BNP, Brain natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

ingham Heart Study, cfPWV significantly improved risk prediction for the occurrence of CV events when added to standard risk factors [24]. Both flow-mediated dilation (FMD) and baPWV increased prognostic value in CAD patients [64–66]. For an example, in a multi-center study performed in Japan, although both baPWV (for baPWV >1731 cm/s: HR, 1.86; 95% CI [confidence interval], 1.01–3.44) and FMD (for FMD >7.1%: HR, 0.27; 95% CI, 0.06–0.74) were associated with the future occurrence of coronary events of patients with stable CAD (n = 462, median follow-up period of 49.2 months), when the information from these two tests combined together, the predictive power of the patient was further improved (HR, 6.84; 95% CI, 1.84–44.31) [64]. Narayan *et al.* [67] analyzed the central arterial pressure waveforms of 838 elderly hypertensive patients and showed that when pressure time constants, an index of arterial stiffness, was added to the traditional cardiovascular risk factors, the predictive power of future CV events increased significantly. Similarly, in another study, the predictive power of future CVD was increased when information on multiple atherosclerotic indicators obtained from the analysis of central arterial pressure waveforms obtained from existing CV risk factors [68]. When cfPWV and CKD information were used simultaneously, the predictive power of long-term cardiovascular events increased in hypertensive patients [69]. A recent study reported that baPWV provided additional prognostic value in combination with clinical variables and high-sensitivity C-reactive protein (hs-CRP) in predicting CVD in patients with CV risk factors (overall Chi-square score, 126 to 167, $p < 0.001$) [70]. Another study showed that the use of combined information of baPWV and ankle-brachial index (ABI) provides increased value in the prognosis of CV events in patients with acute myocardial infarction [71]. Studies showing incremental prognostic value of the measures of arterial stiffness are summarized in Table 1 (Ref. [24,60–67,69–71]).

7. Clinical implications

Cardiovascular risk stratification is very important to provide individualized treatment appropriately, leading to improved prognosis [3]. Risk scores calculated using traditional risk factors, non-invasive imaging tests, and functional tests have been used to predict subjects' risk. However, even with these various methods, risk prediction was not satisfactory, and unmet needs remained. To be more specific, currently used cardiovascular risk scoring systems are Western-oriented, so it is not suitable for Asians [11], various imaging tests require expensive equipment, and there are concerns about radiation and radiocontrast toxicities [13,14]. In consideration of these points, there has been much interest in vascular function tests to predict the CV risk. In particular, PWV is the most widely used method for measuring arterial stiffness because it is non-invasive and simple to measure [15–17,33,34]. Arterial stiffness information itself has a high prognostic value in predicting the occurrence of future CVD in patients regardless of traditional risk factors. Many studies have proven this point

Table 1. Summary of the studies showing incremental prognostic value of the measures of arterial stiffness.

Source (year)	Population	Number of subjects (follow-up duration)	Clinical outcome evaluated	Measure of arterial stiffness	Summary of main finding
Kim *et al.* (2021) [70]	Subjects with CV risk factors	6572 (mean 3.75 years)	CV death, AMI, coronary revasc. and stroke	baPWV	The combination of hs-CRP and baPWV provided a better prediction of future CVD than either one by itself (HR, 7.08; $p < 0.001$).
Park *et al.* (2020) [71]	Patients with AMI	889 (mean 348 days)	Cardiac death, AMI, PCI, HF and stroke	baPWV	Adding baPWV to ABI increases the prognostic power for CV events (HR, 5.4; $p = 0.001$).
Maruhashi *et al.* (2018) [64]	Patients with CAD	462 (median 49.2 months)	Coronary events	baPWV	The combination of FMD and baPWV provides further risk stratification for recurrent coronary events than does FMD alone or baPWV alone (HR, 7.07; $p = 0.002$).
Hwang *et al.* (2018) [62]	Patients with suspected CAD	523 (median 43.9 months)	CV death, AMI, coronary revasc., stroke and hospitalization for CV causes	baPWV	The addition of baPWV to clinical risk factors and CCTA findings significantly improved the prediction of cardiovascular events (global Chi-square score, from 132 to 154; $p = 0.005$).
Lee *et al.* (2015) [61]	Patients with suspected CAD	350 (median 441 days)	CV death, ACS and ischemic stroke	baPWV	High baPWV had incremental prognostic value to traditional risk factors and abnormal MPI in predicting CV events (overall Chi-square score, from 24.08 to 27.42; $p < 0.001$).
Sugamata *et al.* (2014) [66]	Patients with stable CAD	923 (mean 64 months)	Cardiac death, AMI and UA requiring coronary revasc	baPWV	The combined addition of FMD and baPWV to the risk assessment algorithms significantly improved prognostic value in the prediction for CV events (IDI, 0.004; $p < 0.0001$ and NRI, 0.47; $p < 0.0001$).
Nagai *et al.* (2013) [65]	Elderly subjects	274 (mean 41 months)	Vascular events	baPWV	Both IMT and baPWV were taken into consideration, the efficacy increased as compared with each test alone (HR, 4.9; $p = 0.003$).
Ohishi *et al.* (2011) [69]	Patients with hypertension	531 (mean 7.0 years)	Death, AMI, angina, HF and stroke	cfPWV	Combination of high cfPWV and CKD were independent predictors for clinical events (HR, 2.15; $p = 0.033$).
Mitchell *et al.* (2010) [24]	General population	2232 (median 7.8 years)	AMI, UA, HF and stroke	cfPWV	After cfPWV was added to a standard risk factor model, there was a significant improvement in the prediction of CV events (IDI, 0.007; $p < 0.05$).
Kaolawanich, *et al.* (2020) [60]	Patients with suspected CAD	520 (median 46.5 months)	Mortality, ACS, HF, coronary revasc. and stroke	aPWV measured by CMR	Adding aortic stiffness to stress perfusion CMR could improve risk assessment and prediction for future CV events (HR, 2.41; $p < 0.001$).
Kirigaya, *et al.* (2020) [63]	Patients with ACS	387 (median 62 months)	CV death, ACS, HF and stroke	CAVI	For the incremental predictive value, the addition of CAVI to GRACE score enhanced NRI (0.337; $p = 0.034$) and IDI (0.028; $p = 0.004$).
Narayan, *et al.* (2015) [67]	General population	838 (mean 4.4 years)	AMI or stroke	Systolic time constant (carotid artery)	Addition of systolic time constant to the Framingham Risk Score was associated with an improvement in predictive accuracy for CV events (IDI, 0.0072; $p = 0.003$ and NRI, 0.27; $p = 0.02$).

CV, cardiovascular; AMI, acute myocardial infarction; revasc., revascularization; baPWV, brachial-ankle pulse wave velocity; hs-CRP, high sensitivity C-reactive protein; CVD, cardiovascular disease; HR, hazard ratio; PCI, percutaneous coronary intervention; HF, heart failure; ABI, ankle-brachial index; CAD, coronary artery disease; FMD, flow mediated dilation; CCTA, coronary computed tomography angiography; ACS, acute coronary syndrome; MPI, myocardial perfusion imaging; UA, unstable angina; IDI, integrated discrimination improvement index; NRI, net reclassification index; IMT, intima-media thickness; cfPWV, carotid-femoral pulse wave velocity; CKD, chronic kidney disease; aPWV, aortic pulse wave velocity; CMR, cardiac magnetic resonance; CAVI, cardio-ankle vascular index; GRACE, Global Registry of Acute Coronary Events.

over the past several centuries [18,19]. As described in this review, several studies have recently reported that the measures of arterial stiffness have incremental value in the estimation of cardiovascular risk when it adds to traditional risk factors, non-invasive imaging tests or biomarkers [24,60–67,69–71]. There is a limit to predicting individuals' cardiovascular risk with a single test, so combining the two test results can maximize its utility further. Considering this, clinicians and researchers will be able
to use arterial stiffness information more effectively. Additionally, arterial stiffness measurement is non-invasive, inexpensive and simple, which makes it more valuable for mass screening. However, it is important to remember that arterial stiffness information is not superior to the well-known cardiovascular risk factors, but is more useful when used together [72]. Clinical use of the measures of arterial stiffness to increase prediction of cardiovascular prognosis with other risk factors is demonstrated in Fig. 2.

8. Conclusions

Information on arterial stiffness provides incremental value in addition to traditional cardiovascular risk factors, imaging tests and biomarkers which predict cardiovascular risk. In particular, PWV, the most widely used measure of arterial stiffness, is simple and non-invasive, so it will be useful for predicting cardiovascular risk in combination with other tests as a mass screening tool.

Author contributions

HLK created the overall flow and outline of this review article. GPL and HLK wrote the initial manuscript. HLK revised manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. Hack-Lyoung Kim is serving as one of the Guest editors of this journal. We declare that Hack-Lyoung Kim had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Takatoshi Kasai.

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