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Review

Ambulatory arterial stiffness index: A systematic review and meta-analysis

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ABSTRACT

Objective: The dynamic relationship between 24 h diastolic and systolic ambulatory blood pressure (BP) expressed by the ambulatory arterial stiffness index (AASI) has been introduced as a novel measure of arterial function, which independently predicts cardiovascular mortality. This article reviews the published evidence on the features and the clinical relevance of AASI.
Methods: A systematic review and meta-analysis of the evidence on AASI from 51 cross-sectional and longitudinal studies in adults was conducted.
Results: Studies of the reproducibility of AASI have shown a mean difference between assessments at 0.014 (95% CI −0.001, 0.028; 3 studies, $n = 451$) and repeatability coefficients ranging from 0.24 to 0.40. AASI appears to be independently associated with age, systolic BP and pulse pressure, and inversely with the nocturnal systolic and diastolic BP decline. A moderate pooled association of AASI with 24 h pulse pressure (pooled correlation coefficient r 0.47, 95% CI 0.40, 0.54; 20 studies, $n = 29{,}186$) and pulse wave velocity (pooled r 0.30, 95% CI 0.19, 0.42; 9 studies, $n = 4123$) was demonstrated, as well as with other measures of arterial function and target-organ damage. The adjusted pooled hazard ratio for stroke corresponding to a study-specific one standard deviation increase in AASI was 1.26 (95% CI 1.08, 1.45; 3 studies, $n = 14{,}320$).
Conclusions: The available evidence suggests that AASI, obtained by ambulatory BP monitoring, predicts future cardiovascular events, particularly stroke, and is associated with indices of arterial function. The precise pathophysiological mechanisms remain obscure. Research is required to determine the usefulness of AASI as a therapeutic target in clinical practice.

Contents

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1. Introduction

Arterial stiffness has been the focus of growing research interest in recent years [1,2]. It is recognized as an important measure of target organ damage in hypertension and a potent predictor of cardiovascular morbidity and mortality and is increasingly used in the clinical assessment of hypertensive patients [3]. As a result, pulse wave velocity has been included in the 2007 European Society of Hypertension guidelines for the management of arterial hypertension among the indices of subclinical organ damage that may influence prognosis of hypertensive patients [4].

In 2006 the ambulatory arterial stiffness index (AASI) derived from ambulatory blood pressure (BP) monitoring (ABPM) was introduced as an index that predicts cardiovascular risk and particularly stroke in different populations [5–7]. AASI is defined as 1 minus the regression slope of diastolic on systolic BP values derived from a 24 h ABPM recording [8]. Thus, AASI reflects the dynamic relationship between systolic and diastolic BP, which is defined by hemodynamic arterio-ventricular properties, including arterial stiffness. In fact, for a given increase in diastolic BP, the increase in systolic BP is smaller in a compliant compared to a stiff artery [8,9]. While there has been a lot of discussion regarding the possible pathophysiological mechanisms whereby AASI predicts cardiovascular pathology, there is growing interest in its use in clinical practice simply because it consistently predicts future cardiovascular risk [5–7]. However, several issues regarding AASI remain to be clarified, such as the degree of its association with vascular and target organ damage, its independent cardiovascular prognostic value and its behavior in response to antihypertensive treatment.

This paper presents a systematic review and meta-analysis of the published evidence on AASI, which has the purpose of reviewing its prognostic value in terms of cardiovascular outcome independently and beyond other risk factors establishing while also evaluating its determinants, its reproducibility, its relationship with other indices of arterial function and target organ damage, and its potential as a target for treatment.

2. Methods

2.1. Search strategy

A systematic literature search was performed by two investigators independently (AK and ED) at PubMed, Embase and Cochrane Library databases during the period from 2006 (since AASI was first introduced) to November 2011, using the keyword 'ambulatory arterial stiffness index'. Additional studies were found from reference lists of identified articles.

2.2. Selection criteria, data extraction and statistical analysis

By taking the PRISMA guidelines into consideration (www.prisma-statement.org) a systematic review was performed. Eligible studies were full-text articles written in English and presenting data from cross-sectional, longitudinal, retrospective and prospective studies on AASI and addressing at least one of the following issues: (i) anthropometric and BP determinants of AASI, (ii) reproducibility of AASI, (iii) relationship of AASI with indices of subclinical arterial damage (pulse pressure, pulse wave velocity, augmentation index, ankle brachial index, carotid intima media thickness), as well as with other target organ damage (renal function indices, left ventricular mass), (iv) prognostic value of AASI in terms of cardiovascular outcome and/or all-cause mortality, (v) effects of antihypertensive treatment on AASI, and (vi) usefulness of AASI derivatives. Concerning the participants' characteristics, only studies in adults were included with no other exclusion criteria. One of the authors (AK) extracted descriptive, comparative and outcome data regarding AASI.

Meta-analysis was performed based on aggregate data from selected studies (not individual patients' data). Average values pooled by random or fixed (according to the observed heterogeneity) effects meta-analysis were estimated for: (i) correlations of AASI with arterial damage measures i.e. 24 h pulse pressure, pulse wave velocity, augmentation index and carotid intima media thickness, (ii) AASI differences in repeated assessments, (iii) hazard ratio for stroke (fatal and/or nonfatal) and for cardiovascular events and/or cardiovascular mortality corresponding to a study-specific AASI increase by one standard deviation. Publication bias was evaluated by means of Begg's funnel plots and Begg's and Egger's statistical tests [10,11]. Meta-analysis regression was performed using the Stata/SE 11, Texas, USA software. Heterogeneity was tested using I^2 statistics. Two-sided p values <0.05 were considered significant. Data are given as mean $\pm$ standard deviation, unless stated otherwise.

3. Results

The original search retrieved 222 articles/abstracts (140 from PubMed, 168 from Embase and none from Cochrane) of which 51 full text articles satisfied the inclusion criteria as follows: 36 studies, mainly of cross-sectional design, provided data on AASI determinants and/or on its relationship with the predefined indices of target organ damage [6–9,12–43]; 6 studies provided reproducibility data [7,17,44–47]; 10 studies reported prospective data on cardiovascular (and/or all-cause) morbidity and mortality (with two articles reporting results on the same population) [5–7,17,21,23,29,32,48,49] and 4 of these studies reported hazard ratios for cardiovascular mortality or events per 1 study-specific standard deviation increase in AASI [5,6,29,32], while 3 of these studies reported hazard ratios for strokes and were included in the meta-analysis [5,6,32]; 3 studies investigated the effects of antihypertensive drug treatment (2 prospective, 1 cross-sectional) [42,50,51]; 10 studies analyzed the usefulness of AASI derivatives [23,31,33,36,52–57]. Some articles provided data regarding more than one of the abovementioned issues. The flow diagram for the selection of the studies is presented in Fig. 1.

3.1. Determinants of AASI

A consistent finding in most of the studies is that, in bivariate and most importantly in multivariate analyses, AASI was independently associated with age, systolic BP and 24 h pulse pressure and inversely with the nocturnal systolic and diastolic BP decline (Table 1). Other variables, such as anthropometric characteristics (body mass index, female gender), heart rate, glucose and lipid parameters have also been shown to be associated with AASI values in some studies (Table 1). It should be noted that the ratio of night/day BP readings in ambulatory recording also appeared to affect AASI, with higher values of this ratio leading to lower AASI values, which was not taken into account in most of the studies [18].

3.2. Reproducibility of AASI

Six studies investigated the reproducibility of AASI (Table 2) [7,17,44–47], with a mean difference between the two assessments (3 studies, $n = 451$, time interval 2–68 days) at 0.014 (95% CI −0.001, 0.028). The reproducibility of AASI appears to be modest with repeatability coefficients ranging from 0.24 to 0.40 (Table 2).

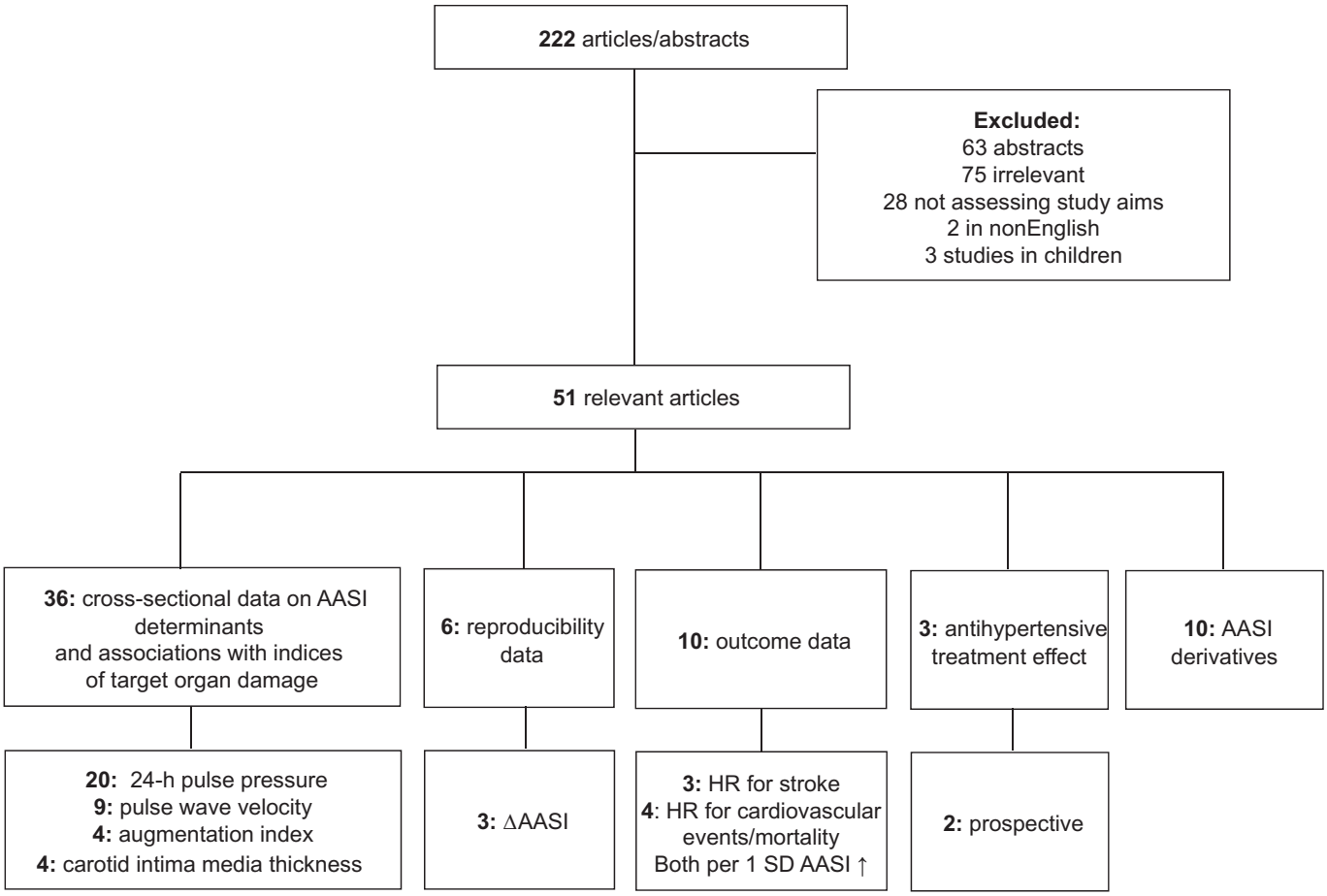

Fig. 1. Flow diagram for selection of studies.

3.3. Association of AASI with indices of subclinical arterial and other target-organ damage indices

Twenty studies ($n = 29{,}186$) examined the relationship of AASI with 24 h pulse pressure as an indirect index of arterial stiffness, with a pooled correlation coefficient at 0.47 (95% CI 0.40, 0.54) (Fig. 2). Furthermore, 9 studies ($n = 4123$) examined the relationship of AASI with carotid-femoral pulse wave velocity and the pooled correlation coefficient was 0.30 (95% CI 0.19, 0.42) (Fig. 3). In 1 of these studies the association of AASI with pulse wave velocity was insignificant [21], whereas in 3 of these studies this association was diminished after adjustment for other covariates (Table 3) [14,24,25]. Less evidence is available regarding the association of AASI with augmentation index (4 studies, $n = 2053$, pooled coefficient 0.27, 95% CI 0.14, 0.39) [9,14,25,38], and with carotid intima media thickness (4 studies, $n = 1276$, pooled coefficient 0.36, 95% CI 0.28, 0.44) [13,35,37,38].

Some studies investigated the association of AASI with renal damage indices (creatinine clearance, glomerular filtration rate, albumin-creatinine ratio), left ventricular mass index and one with ankle brachial index, with positive results in most cases (Table 3). Regarding the evaluation of publication bias, funnel plots for the pooled correlation of AASI with 24 h pulse pressure and pulse wave velocity are presented in Fig. 4. Formal testing with Begg's and Egger's tests did not identify publication bias ($p > 0.05$ in all tests).

3.4. AASI as a predictor of cardiovascular morbidity and mortality

Prospective studies that investigated the prognostic ability of AASI in terms of morbidity and mortality (all-cause and/or cardiovascular) are presented in Table 4. The fact that the endpoints (cardiovascular events, cardiovascular and/or all-cause mortality, stroke) and the units of AASI increase (SD, tertiles, quartiles, median values) were not common in these studies did not permit meta-analyses to be performed with respect to specific endpoints and accepted AASI cut-off values. However, 4 studies mentioned outcomes per one study-specific standard deviation increase in AASI (3 for stroke and 4 for cardiovascular events/mortality) [5,6,29,32]. The estimated hazard ratio for stroke (fatal and/or nonfatal) corresponding to a study-specific one standard deviation increase in AASI reported in 3 of the studies ($n = 14{,}320$) was 1.66 (95% CI 1.48, 1.86) (Fig. 5). When adjustment for age, sex, body mass index, cardiovascular risk factors and 24 h pulse pressure was applied, the estimated pooled hazard ratio for stroke was 1.26 (95% CI 1.08, 1.45). Likewise, the adjusted hazard ratio for cardiovascular events and/or cardiovascular mortality corresponding to a study-specific one standard deviation increase in AASI reported in 4 of the studies ($n = 14{,}867$) was 1.09 (95% CI 1.01, 1.18). Both Begg's and Egger's tests did not identify publication bias ($p > 0.05$).

3.5. Effects of antihypertensive treatment on AASI

Three studies have investigated AASI in relation to antihypertensive drug treatment. Berni et al. reported that low adherence to antihypertensive treatment was an independent predictor of increased AASI, independent of 24 h pulse pressure, age and nocturnal diastolic BP reduction [51]. Jin et al. followed 201 hypertensive subjects randomly assigned to treatment with atenolol or perindopril/indapamide for one year and demonstrated a significant

Table 1
Determination of AASI by anthropometric, biochemical and blood pressure parameters.

Study	Study population	*n*	Age (years)	Men (%)	ABP intervals (day/night, min)	AASI	Correlations and determinants of AASI
Li 2006 [9]	Random sample, 33% HTN	348	46.1 ± 15.5	46	20/45	0.36	Multivariate analysis: age, female gender, 24 h MAP, height (inverse)
Hansen 2006 [6]	Random sample, 43.5% HTN	1829	55.5 ± 10.7	53	15/30	0.56 ± 0.14	Bivariate correlations: age, height (inverse)
Ratto 2006 [12]	Untreated HTN	168	48 ± 9	66	15/30	0.51 ± 0.16	Bivariate correlations: age, 24 h SBP, 24 h PP, triglycerides
Leoncini 2006 [13]	Untreated HTN	188	47.3 ± 9.7	65	15/30	0.50 ± 0.17	Bivariate correlations: age, 24 h SBP, 24 h PP, triglycerides
Schillaci 2007 [14]	Untreated HTN	515	48 ± 11	56	15/15	0.31 ± 0.17	Bivariate correlations: age, 24 h SBP, 24 h MAP, nocturnal SBP and DBP reduction (inverse)
Kikuya 2007 [7]	Population study, 49% HTN	1542	61.7 ± 10.7	37	30/30	0.46 ± 0.1	Bivariate correlations: age, height (inverse), 24 h PP
Li 2007 [16]	Population sample-volunteers	677	47.6	46	20/45		Multivariate analysis: 24 h daytime and nighttime SBP/DBP
Gosse 2007 [17]	HTN	469	54 ± 14	60	15/15	0.54 ± 0.14	Bivariate correlations: age, height (inverse), 24 h SBP, 24 h PP, 24 h heart rate (inverse), fasting glucose
Dechering 2007 [18]	HTN	1325	47.7	47	15/30	0.48	Inverse correlation with the ratio of night/day BP readings
Baumann 2008 [19]	Evaluated for kidney donation, 29% HTN	106	48.5 ± 12.1	48	20/30	0.41 ± 0.18	Bivariate correlations: age, BMI, HDL-C (inverse), nocturnal SBP and DBP reduction (inverse)
Adiyaman 2008 [22]	IDACO database	7604	56.9 ± 13.9	54	30/30 or 15–30/30–60	0.46 ± 0.18	Multivariate analysis: age, 24 h MAP, height (inverse), 24 h heart rate (inverse)
Ben-Dov 2008 [23]	ABPM database	2918	56 ± 16	45	20/30	0.48	Bivariate correlations: age, 24 h SBP, SBP dipping (inverse), SD of awake SBP, diabetes, napping (inverse)
Mule 2008 [20]	Untreated HTN	143	44.1 ± 11.6	57	15/20	0.22 (median)	Bivariate correlations: age, 24 h SBP, 24 h PP, 24 h heart rate (inverse), nocturnal SBP and DBP reduction (inverse)
Muxfeldt 2008 [24]	Resistant HTN	391	64 ± 10.1	29	15/30	0.55 ± 0.14	Multivariate analysis: age, diabetes, nocturnal DBP reduction (inverse)
Jerrard-Dunne 2008 [25]	HTN	824	51 ± 14	49	30/60	0.35 ± 0.17	Bivariate correlations: age, female gender, 24 h SBP, 24 h MAP, 24 h PP, nocturnal SBP and DBP reduction (inverse), height (inverse), weight (inverse) Multivariate analysis: age, 24 h MAP, height (inverse)
Liu 2009 [27]	Healthy volunteers	67	28.3 ± 6.4	36	15/20	0.27 ± 0.16	Bivariate analysis: 24 h SBP, 24 h PP, 24 h MAP variability (inverse), nocturnal SBP and DBP reduction (inverse)
Laugesen 2009 [28]	Diabetics type 1 (67%) and nondiabetic controls	102	30 ± 10	71	20/60	0.35	Multivariate analysis: age, 24 h heart rate (inverse), MAU, nocturnal SBP reduction (inverse)
Muxfeldt 2010 [29]	Resistant HTN	547	65.9 ± 11.3	29	15/30	0.55 ± 0.14	Multivariate analysis: age, fasting glycemia, 24 h PP, nocturnal DBP reduction, height (inverse)
Wang 2010 [30]	Untreated participants	120	47 ± 11.3	54	30/60	0.25 ± 0.14	Multivariate analysis: 24 h PP, nocturnal SBP reduction (inverse), resting baroreflex sensitivity (inverse)
Stergiou 2010 [31]	HTN, 63% untreated	483	52.2 ± 12.3	60	15–20/15–20	0.33 ± 0.15	Multivariate analysis: age, 24 h PP, non-dipping
Bastos 2010 [32]	HTN, 47% untreated	1200	50.7 ± 12.7	54	20/30	0.30 ± 0.18	Bivariate analysis: age, BMI, office heart rate (inverse), 24 h SBP, nocturnal SBP reduction (inverse), 24 h PP
Garcia-Garcia 2011 [37]	HTN, 43% untreated	554	57.7 ± 12.8	61	20/30	0.38 ± 0.07	Bivariate analysis: age, time evolution of the HTN, heart rate (inverse), 24 h PP, waist circumference, BMI, total and LDL-C (inverse), HbA1c
Gomez-Marcos 2011 [38]	Primary care patients, Diabetics 29%	366	55.1 ± 11.9	61	20/30	0.38 ± 0.06	Diabetics: age, 24 h PP, night/day ratio of SBP/DBP Non-diabetics: age, office heart rate (inverse), 24 h PP, night/day ratio of SBP/DBP
Lee 2011 [39]	Untreated HTN	418	60.3 ± 15.5	52	15/30	0.58 ± 0.13	Multivariate analysis: age, diabetes, non-dipping, SD of heart rate, CV of PP and DBP
García-Ortiz 2011 [40]	HTN	356	55 ± 12	62	20/30	0.38 ± 0.06	Heart rate (inverse); 24 h SD of heart rate

ABP, ambulatory blood pressure; AASI, ambulatory arterial stiffness index; HTN, hypertensives; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; MAP, mean arterial pressure; PP, pulse pressure; BMI, body mass index; MAU, microalbuminuria; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; SD, standard deviation; CV, coefficient of variation.

Table 2
Studies assessing the reproducibility of AASI.

Study	Study population	*n*	Age (years)	Men (%)	Time interval between the 2 assessments	ABP intervals (day/night, min)	Reproducibility results
Gosse 2007 [17]	Healthy volunteers	38	NR	NR	2 weeks	15/15	RC 0.30; CV 25; pMV 58
Kikuya 2007 [7]	Untreated subjects	19	65.6 ± 3	21	3.1–4.6 years	30/30	pMV 53
Dechering 2008 [44]	Nijmegen cohort, HTN	152	46.2 ± 13.6	41	4–60 days (median 8)	15–30/30–60	ΔAASI 0.02 ± 0.16; RC 0.32; pMV 55
	Syst-Eur trial, elderly HTN	145	71 ± 6.5	39	2–57 days (median 31)		ΔAASI 0.02 ± 0.20; RC 0.40; pMV 61
Gosse 2009 [45]	PROOF cohort: NT	211	65	NR	2 years	15/30	RC 0.28; CV 22; pMV 58
	HTN	568					RC 0.26; CV 21; pMV 55
Laugesen 2010 [46]	Diabetics type 1	28	35 ± 11	54	2–68 days (median 3)	20/60	ΔAASI 0.01 ± 0.17; RC 0.34; pMV 68
Stergiou 2010 [47]	Untreated HTN	126	48.2 ± 10.7	56	2–4 weeks	20/20	ΔAASI 0.007 ± 0.12; RC 0.24; pMV 49.6; CV 40.3; CCC 0.60

ABP, ambulatory blood pressure; NT, normotensives; HTN, hypertensives; ΔAASI, mean difference between the two AASI assessments; RC, repeatability coefficient (2 * SD of differences); pMV, percentage of near-maximal variation (percentage of RC/4 * SD of the mean of the paired recordings); CV, coefficient of variation; CCC, concordance correlation coefficient; NR, not reported.

decrease in pulse wave velocity (−0.87 and −0.72 m/s respectively, $p < 0.001$ for both), while there was no significant change in AASI values (+0.006 and −0.019 respectively, $p > 0.05$ for both), and no drug class specific effects were found [42]. On the other hand, in a study of 188 hypertensive subjects followed for 3 months, Andreadis et al. showed that angiotensin receptor blockers are superior to calcium antagonists in reducing AASI [50].

3.6. AASI derivatives

Five studies investigated AASI based on home rather than ambulatory BP measurements (home arterial stiffness index [HASI]) [31,36,52,56,57]. Qureshi et al. reported a correlation between HASI and pulse wave velocity in a small group of patients [52]. Two subsequent studies however including much larger samples, found an inferiority of HASI compared to AASI in terms of correlation with pulse pressure and pulse wave velocity [31,36]. A recent study in 356 untreated hypertensives indicated that HASI did not add anything to the existing measures of arterial stiffness, but could aid in the detection of carotid atherosclerosis and renal damage, similar to pulse wave velocity [57]. Interestingly, HASI predicted cerebral infarction, independently of pulse pressure, in men and normotensive subjects who were followed-up for a median of 13.8 years [56].

Daytime and/or nighttime AASI derivatives (based on daytime and nighttime ambulatory BP values) have been found to be inferior compared to 24 h AASI in terms of correlations with 24 h pulse pressure [31]. Symmetrical AASI, which is corrected for its dependence on the systolic-diastolic BP correlation [53], was found to be related to parameters of renal disease, yet whether this relationship is an independent one it is debatable [33,55]. One study showed the symmetrical AASI to have prognostic value in terms of all-cause mortality [23].

4. Discussion

It is increasingly recognized that arterial stiffness is one of the most significant hemodynamic factors contributing to the development of the cardiovascular complications of hypertension

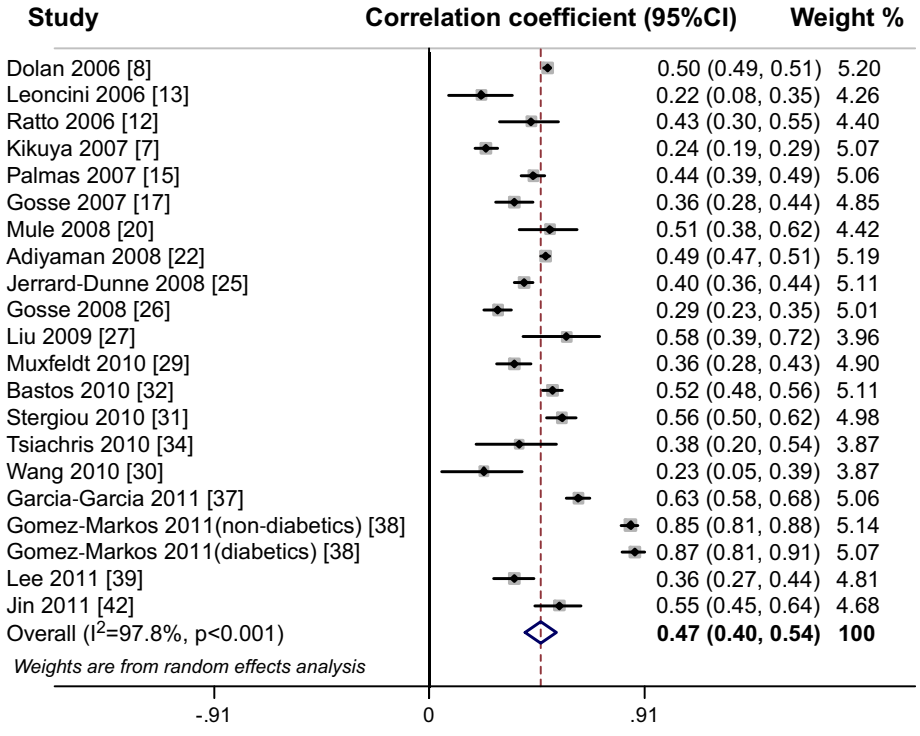

Fig. 2. Forest plot of pooled correlation coefficient of ambulatory arterial stiffness index with 24 h pulse pressure.

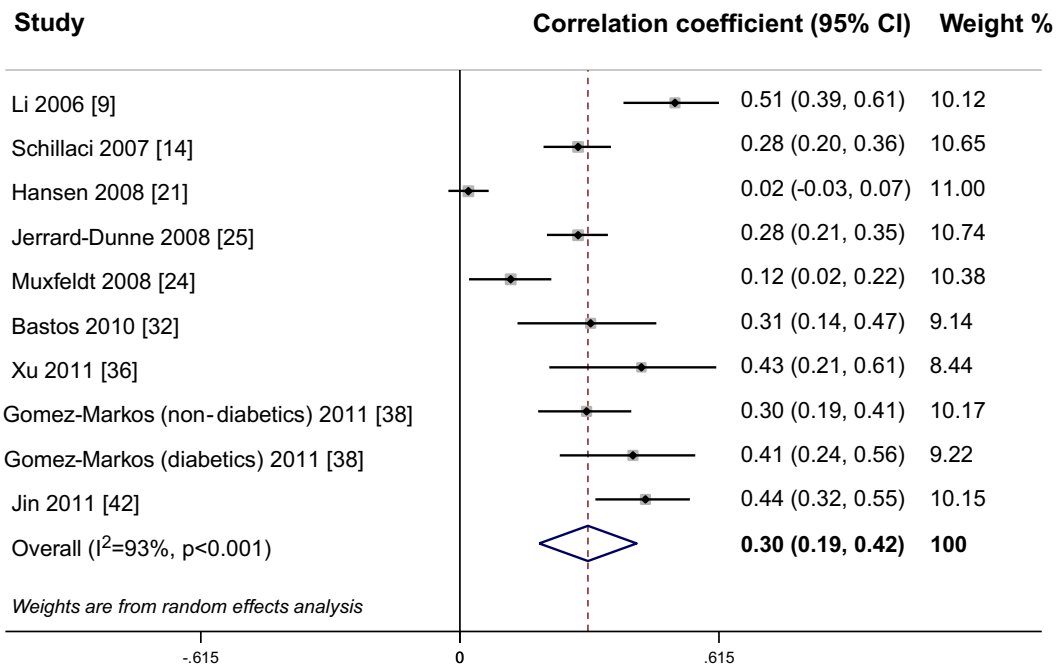

Fig. 3. Forest plot of pooled correlation coefficient of ambulatory arterial stiffness index with pulse wave velocity.

[2,3,58]. Arterial stiffness occurs predominantly in middle-aged and elderly individuals, who make up about three fourths of the hypertensive population and, who in turn, experience the majority of all hypertension-related events. Attention has turned, therefore, to the development of techniques that permit non-invasive assessment of arterial function, aiming to relate these measures with cardiovascular outcome. The most widely available techniques for assessing arterial stiffness are those measuring pulse wave velocity and augmentation index. Studies in patients with renal failure, diabetes mellitus, and hypertension along with those in normal population samples, have shown that both pulse wave velocity and augmentation index predict cardiovascular events [4,59,60]. However, it should be mentioned that while there is large agreement on the role of pulse wave velocity as a measure of arterial stiffness, augmentation index seems to be determined not only by arterial stiffness but also by anthropometric and hemodynamic parameters and is highly sensitive to drug effects [3]. This amount of supportive evidence has justified the inclusion of carotid-femoral pulse wave velocity as a recommended test for the evaluation of arterial target organ damage in the 2007 European Society of Hypertension guidelines for the management of hypertension [4].

This review and meta-analysis evaluated the available evidence for AASI as an alternative and readily available marker of arterial function and cardiovascular outcome. The main findings are that AASI: (i) predicts cardiovascular morbidity and mortality, particularly stroke, independently of other known risk factors, (ii) is determined by established predictors of arterial stiffness, such as age, systolic BP and pulse pressure, but also by ventriculo-arterial coupling factors, such as heart rate and BP variability, as well as by ABPM parameters, i.e. day:night ratio of BP measurements, (iii) has moderate reproducibility, and (iv) is associated with indices of arterial and other target organ damage.

A positive relationship of AASI with age, systolic BP and pulse pressure was demonstrated in most of the reviewed studies. However, it should be noted that, by definition, AASI is derived from BP parameters and thus the multiple reports on the correlation between AASI and pulse pressure or systolic BP do not necessarily reflect a true biological relationship. AASI values were also inversely related to the office or ambulatory heart rate [5]. In a recent study using a computer model of the arterial circulation, arterial stiffness along with vascular resistance and heart rate were identified as the main determinants of AASI [61]. Moreover, several studies have shown night BP reduction to have considerable impact on AASI values [14,62]. Thus, AASI cannot be considered as a marker of arterial stiffness but rather as a composite index reflecting cardiovascular properties, BP variability and diurnal cycle. Taking the above into account, it is not surprising that AASI presents several associations – moderate though – with pulse wave velocity, augmentation index and carotid intima-media thickness, whereas in other studies increases in AASI parallel changes in other measures of target organ damage, such as renal indices and left ventricular mass.

The introduction of AASI derivatives such as “symmetrical” AASI and AASI derived from home BP measurements (HASI) or from the daytime and nighttime periods separately, has not been shown to be superior compared to 24 h AASI [31,36]. Limited evidence in children and adolescents suggested a weak association of AASI with target organ damage [63].

Six studies examined the reproducibility of AASI with the reproducibility coefficients ranging from 0.24 to 0.40 and pMV values in the range of 50–68% (Table 2). A pMV value less than 25% has been suggested as a sensible cut-off value for a parameter to be clinically useful and pulse pressure has been reported with such values [64,65]. When compared to other aspects of ABPM, reproducibility of AASI also appeared to be inferior to that of nocturnal BP dip [66] but comparable or superior to that of other aspects of the BP profile, e.g. the morning surge [67].

The findings of the present meta-analysis indicate that AASI independently predicts cardiovascular events, especially stroke. As first described in the Dublin Outcome Study, AASI appears to be a more potent predictor of stroke than pulse pressure, particularly in normotensive individuals [5]. This relationship with stroke risk has been replicated in other studies that examined AASI as

Table 3
Association of AASI with other indices of arterial stiffness and target organ damage.

Study	Study population	*n*	Age (years)	Men (%)	ABP intervals (day/night, min)	AASI	Unadjusted *r* values (bivariate analysis)/beta coefficients (multivariate analysis) for associations
Dolan 2006 [8]	Dublin Outcome Study Untreated 76% HTN	11291	54.6 ± 14.6	47	30/30	0.41 ± 0.16	24 h PP 0.5 (significance not reported)
Li 2006 [9]	Volunteers, 33% HTN	166 (for PWV) 348 (for AIx)	48.2 ± 19.3 46.1 ± 15.5	42 46	20/45	0.36	PWV 0.51*; Central AIx 0.48*/0.39*; Peripheral AIx 0.50*/0.41*; Central PP 0.50*
Ratto 2006 [12]	Untreated HTN	168	48 ± 9	66	15/30	0.51 ± 0.16	24 h PP 0.43*; ACR 0.21*; CrCl 0.25*; adjusted RR for MAU per 1SD increase 2.29*
Leoncini 2006 [13]	Untreated HTN	188	47.3 ± 9.7	65	15/30	0.50 ± 0.17	24 h PP 0.22*; ACR 0.22*/0.50*; IMT 0.20*/0.20*; LVMI 0.13
Schillaci 2007 [14]	Untreated HTN	515	48 ± 11	56	15/15	0.31 ± 0.17	PWV 0.28*/0.06; AIx 0.25*; LVMI 0.17*/−0.04
Kikuya 2007 [7]	Population study, 49% HTN	1542	61.7 ± 10.7	37	30/30	0.46 ± 0.1	24 h PP 0.24*
Palmas 2007 [15]	Diabetics	1043	71	41	20/20	0.52 (median)	24 h PP 0.44*; follow-up ACR 0.17*
Gosse 2007 [17]	HTN	469	54 ± 14	60	15/15	0.54 ± 0.14	24 h PP 0.36*
Hansen 2008 [21]	Random sample	1678	54.8	52	15/30	NR	PWV 0.02
Baumann 2008 [19]	Kidney donors, 29% HTN	106	48.5 ± 12.1	48	20/30	0.41 ± 0.18	Dippers: 24 h PP 0.32* (normotensives) and 0.29* (hypertensives); Non-dippers 0.06
Mule 2008 [20]	Untreated HTN	143	44.1 ± 11.6	57	15/20	0.22 (median)	24 h PP 0.51*; GFR −0.30*/−0.19*
Adiyaman 2008 [22]	IDACO database	7604	56.9 ± 13.9	54	30/30 or 15-30/30-60	0.46 ± 0.18	24 h PP 0.49*
Jerrard-Dunne 2008 [25]	HTN	824	51 ± 14	49	30/60	0.35 ± 0.17	24 h PP 0.40* ($n = 1714$); PWV 0.28*/0.06 ($n = 622$); AIx 0.24*/−0.006 ($n = 824$)
Muxfeldt 2008 [24]	Resistant HTN	391	64 ± 10.1	29	15/30	0.55 ± 0.14	PWV 0.12*/−0.04
Gosse 2008 [26]	PROOF cohort, volunteers 65 years old, 27% HTN	1011 (969)	65	40	15/30	0.62 ± 0.13	24 h PP 0.29*
Laugesen 2009 [28]	Type 1 diabetics (67%) and nondiabetic controls	102	30 ± 10	71	20/60	0.35	Multivariate analysis: MAU 0.10*
Liu 2009 [27]	Healthy volunteers	67	28.3 ± 6.4	36	15/20	0.27 ± 0.16	24 h PP 0.58*
Muxfeldt 2010 [29]	Resistant HTN	547	65.9 ± 11.3	29	15/30	0.55 ± 0.14	24 h PP 0.36*
Bastos 2010 [32]	HTN, 47% untreated	1200	50.7 ± 12.7	54	20/30	0.30 ± 0.18	24 h PP 0.52*; PWV 0.31* ($n = 117$)
Robles 2010 [33]	HTN and/or renal disease (24% untreated)	166	55.2 ± 15.5	44	15/20	NR	CrCl −0.22*; GFR −0.15; ACR 0.20
Stergiou 2010 [31]	HTN, 63% untreated	483	52.2 ± 12.3	60	15-20/15-20	0.33 ± 0.15	24 h PP 0.56*
Tsiachris 2010 [34]	Untreated HTN	99	50.7	62	15/30	0.37	24 h PP 0.38*; PWV non-significant
Wang 2010 [30]	Untreated participants	120	47 ± 11.3	54	30/60	0.25 ± 0.14	24 h PP 0.23*; PWV non-significant
Triantafyllidi 2010 [35]	Untreated HTN	168	53 ± 12	53	15/20	0.45 ± 0.2	MAU 0.19*; IMT 0.34*/0.34* (dippers)
Xu 2011 [36]	Untreated, HTN (61%)	67	53.6	49	20/30	0.42 ± 0.11	PWV 0.43*
Garcia–Garcia 2011 [37]	HTN (43% untreated)	554	57.7 ± 12.8	61	20/30	0.38 ± 0.07	24 h PP 0.63*; IMT 0.42*/0.41*; ABI −0.10*/−0.36; GFR -0.21*/52.6*
Gomez-Marcos 2011 [38]	Primary Care patients Diabetics 29%	366	55.1 ± 11.9	61	20/30	0.38 ± 0.06	Diabetics: 24 h PP 0.87*; PWV 0.41*; AIx 0.24*; IMT 0.35*/0.31* Non-Diabetics: 24 h PP 0.85*; PWV 0.30*; AIx 0.09; IMT 0.42*/0.20*
Lee 2011 [39]	Untreated HTN	418	60.3 ± 15.5	52	15/30	0.58 ± 0.13	24 h PP 0.36*/0.02; LVMI 0.19*/0.05
Wang 2012 [41]	HTN in patients	948	53.3 ± 13.9	67	20/30	0.43 ± 0.15	GFR −37.05*/−9.76; ACR 0.89*/0.18
Jin 2011 [42]	HTN	201	55	69	15/15	0.43 ± 0.16	24 h PP 0.55*; PWV 0.44*

ABP, ambulatory blood pressure; AASI, ambulatory arterial stiffness index; HTN, hypertensives; PWV, pulse wave velocity; AIx, augmentation index; PP, pulse pressure; MAU, microalbuminuria, CrCl, creatinine clearance; ACR, albumin: creatinine ratio; GFR, glomerular filtration rate; RR, relative risk; IMT, carotid intima media thickness; ABI, ankle brachial index; LVMI, left ventricular mass index; MAP, mean arterial pressure; NR, not reported; * $p < 0.05$.

a continuous or binary variable (Table 4). Kikuya et al. reported a U-shaped association between AASI and mortality (all-cause and stroke) [7], yet this unclear finding was not replicated in other studies. In the present meta-analysis the estimated adjusted hazard ratios for stroke (fatal and/or nonfatal) and composite cardiovascular outcome corresponding to a study-specific one standard deviation increase in AASI were 1.26 and 1.09 respectively, both of which significant. These results are in agreement with a recently published meta-analysis of the longitudinal studies on the prognostic ability of AASI, which reported the relative risk of cardiovascular events and stroke for one standard deviation increase in AASI [68]. The authors also calculated the relative risk of high versus low AASI according to cut-off values which differed among studies (median, upper tertile or quartile, or other specified value) [68]. The two meta-analyses concluded that AASI has independent prognostic value, which appears to be stronger for stroke (25–30% increase in risk per one standard deviation increase in AASI value) than for total cardiovascular events (10–15%). However, more research is needed to determine the prognostic ability of AASI in specific populations, especially in comparison to the established indices of arterial stiffness. Moreover, it should be mentioned that the statistical association does not necessarily qualifies AASI for

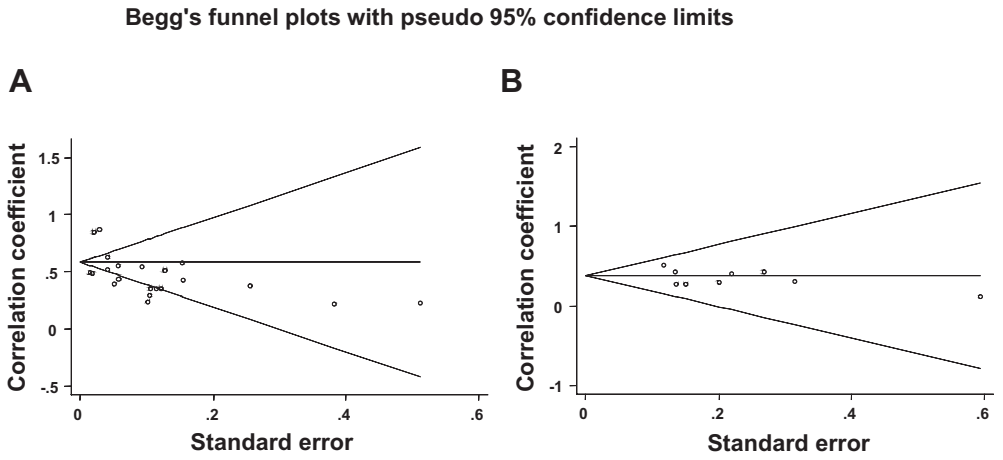

Fig. 4. Funnel plots of studies reporting correlation coefficients of ambulatory arterial stiffness index with (A) pulse pressure and (B) pulse wave velocity (random effects model).

clinical implementation. A reclassification analysis [69] demonstrating a significant reclassification improvement would be a central argument for the prognostic relevance of AASI in routine clinical practice.

The relationship between AASI and treatment is important if the index is to prove useful as a novel target of therapy in the future. However, the current evidence is very limited, with only two prospective studies reporting on this issue [42,50]. Andreadis et al. showed that the effect of antihypertensive treatment on AASI is not the same with different drug classes [50], whereas Jin et al. reported that antihypertensive drug treatment reduces pulse wave velocity but has no effect on AASI, and there are no differences between drug classes [42]. More research is needed to examine the AASI changes in response to antihypertensive treatment.

The findings of the present meta-analysis should be interpreted in the context of some methodological weaknesses. First, the analysis is mainly based on aggregate data rather than individual participants' data and derived from cross-sectional studies on the association of AASI with target organ damage, as well as prospective observational rather than interventional outcome studies. Thus, the implementation of rating scores which have been developed for the assessment of the quality of randomized trials was not feasible. Second, there is considerable variation in the results of the cross-sectional studies, mainly due to the fact that AASI is determined not only by the BP levels but also by other factors such as the ratio of night/day BP readings. Third, part of the differences between studies might be related to differences in devices used for ABPM. However, all the devices have been

Table 4
Prospective studies assessing the prognostic value of AASI.

Study	Population	*n*	Age (years)	Men (%)	Follow-up (years)	ABP intervals (day/night, min)	AASI	Unadjusted/Adjusted hazard ratio
Hansen 2006 [6]	Random sample 43.5% HTN	1829	55.5 ± 10.7	53	9.4	15/30	0.56 ± 0.14	Per 1 SD increase: CV events 1.07/1.06; stroke 1.58*/1.62*; CHD 0.96/0.96
Dolan 2006 [5]	Dublin Outcome Study Untreated 76% HTN	11291	54.6 ± 14.6	47	5.3	30/30	0.41 ± 0.16	Mortality per 1 SD increase: CV 1.59*/1.08; stroke 1.71*/1.21*; cardiac 1.57*/1.03
Kikuya 2007 [7]	Population study-49% HTN	1542	61.7 ± 10.7	37	13.3	30/30	0.46 ± 0.1	Mortality by quartiles: all-cause 0.81*/1.18−0.87/0.94−0.90/0.78* −1.57*/1.16; CV 0.92/1.41*−0.77/0.85 −0.79/0.65*−1.79*/1.29; stroke 1.02/1.56*−0.81/0.89−0.61/0.52* −1.99*/1.40
Gosse 2007 [17]	Referred HTN	469	54 ± 14	60	5.8	15/15	0.54 ± 0.14	RR of CV events according to tertiles (T): T3 vs. T1 4.7*/reported as NS
Ben-Dov 2008 [23]	ABPM Database	2918	56 ± 16	45	7	20/30	0.48 (0.24 symmetrical)	All-cause mortality per 1 SD increase: 1.31*/1.14 (symmetrical 1.23*/1.17*)
Palmas 2009 [48]	Diabetics	1178	71	41	6.6	20/20	0.52	All-cause mortality for the 3rd tertile: 1.36*(only adjusted values reported)
Muxfeldt 2010 [29]	Resistant HTN	547	65.9 ± 11.3	29	4.8	15/30	0.55 ± 0.14	Per 1 SD increase (only adjusted values reported): composite endpoint 1.46*; all-cause mortality 1.03; CV mortality 1.39
Bastos 2010 [32]	Referred HTN 47% untreated	1200	50.7 ± 12.7	54	8.2	20/30	0.30 ± 0.18	Per 1 SD increase: CV events 1.53*/1.67; stroke 1.58*/1.10; CHD 1.37*/0.98
Laugesen 2012 [49]	Diabetics	108	57	60	9.5	20/60 and 20/20	0.40	Unadjusted: AASI + 24 h PP ≥ median ↑ risk for CV events; Adjusted hazards analysis: 24 h PP but not AASI was independent predictor

ABP, ambulatory blood pressure; AASI, ambulatory arterial stiffness index; HTN, hypertensives; HR, hazard ratio; CV, cardiovascular; CHD, coronary heart disease; RR, relative risk.
* $p < 0.05$.

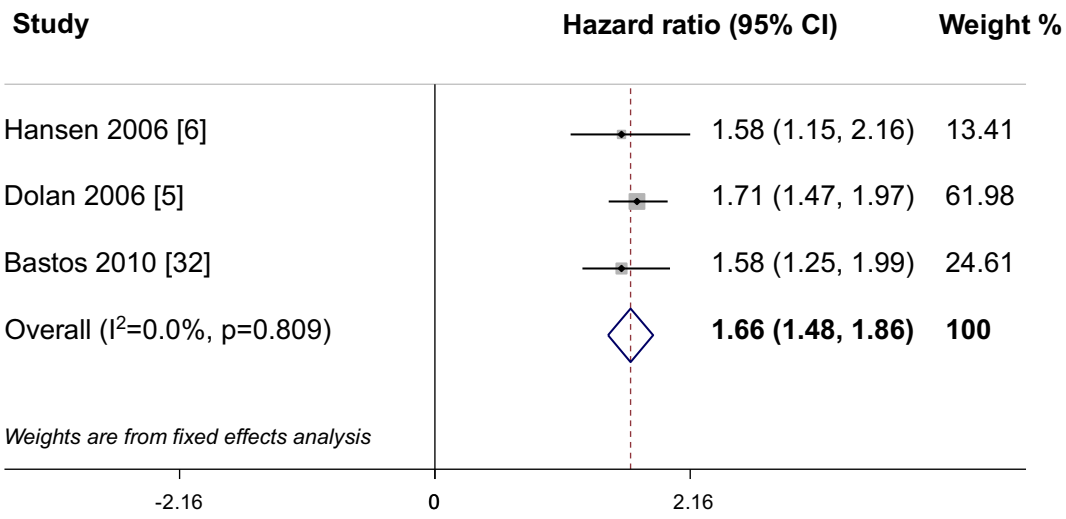

Fig. 5. Hazard ratio for stroke per 1 study-specific standard deviation increase of ambulatory arterial stiffness index.

clinically validated and therefore this factor is unlikely to have considerable influence on the results. Forth, it should be noted that for the evaluation of the prospective longitudinal studies there are no established cut-off values for AASI and no specific uniformly defined cardiovascular endpoints. Fifth, the reproducibility studies presented wide variation in the time interval between the two assessments and reported several different measures of reproducibility, making their comparison difficult.

Whether AASI is a true measure of arterial stiffness is still debatable and it has been suggested that the term name should be altered [14,70,71]. However, the debate on the underlying mechanisms of AASI regarding the pathophysiology of cardiovascular outcome should not detract attention from its independent prognostic significance. For example Hansen et al. reported an insignificant association between AASI and pulse wave velocity in 1678 subjects (data with highest weight in pooled coefficient), yet AASI was superior to pulse wave velocity in predicting stroke in this population [21]. Moreover, a number of studies, as well as the results of this meta-analysis, demonstrated an independent association of AASI with cardiovascular mortality and morbidity, especially stroke.

With the exception of pulse pressure, measures of arterial stiffness, such as pulse wave velocity, are not readily available in routine clinical practice, although the cost of the devices is reduced and its measurement is increasingly implemented. ABPM is more widely available and recommended by the recent UK NICE guidelines as an essential test for the diagnosis of hypertension [72]. Thus, the evaluation of AASI as an additional piece of information derived from routine ABPM seems to be feasible in the clinical setting. Indeed, the growing interest in AASI is probably due to its applicability to clinical practice from an ABPM recording, which also provides other important diagnostic information, such as the presence of white coat, masked, and nocturnal hypertension [73,74]. Given that ABPM is expected to be used more frequently in clinical practice it is timely to consider how best to derive as much information as possible from the technique. The clinical focus, therefore, should shift from merely processing mean day and nighttime BP to providing measures of variability and prognostic indices of outcome. Indeed, a composite index of cardiovascular risk derived from ABPM, including AASI, would be a worthwhile area of future research. Moreover, further research is required on treatment induced changes in AASI and its usefulness as a goal of treatment. Although debate will continue as to the mechanisms underlying AASI, there is now substantial evidence even allowing for the modest reproducibility of the index, that AASI provides a readily derived marker for future outcome.

In conclusion, within 6 years since the AASI concept has been first introduced, considerable evidence has accumulated. This index, which is readily available from ABPM, appears to be associated with several arterial function measures including arterial compliance and, more importantly, predicts stroke independently of other risk factors. Prospective studies evaluating the precise role of AASI as a therapeutic target in clinical practice are still awaited.

Conflict of interest

None declared for all authors.

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