ELSEVIER

Atherosclerosis 189 (2006) 61–69

ATHEROSCLEROSIS

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Review

Risk of mortality and cardiovascular disease associated with the ankle-brachial index: Systematic review

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Received 7 November 2005; received in revised form 7 March 2006; accepted 8 March 2006
Available online 18 April 2006

Abstract

Objective: To determine the strength and consistency with which a low ankle brachial pressure index (ABI), measured in the general population, is associated with an increased risk of subsequent death and/or cardiovascular events.
Design: Systematic review.
Data sources: Medline, Embase, reference lists and grey literature were searched; studies known to experts were also retrieved.
Main outcome measures: All cause mortality, fatal and non-fatal coronary heart disease and stroke.
Review methods: Longitudinal studies in which participants were representative of the general population (all ages, either sex) and which used any standard method for measurement and calculation of the ABI. Studies in which participants were selected according to presence of pre-existing disease or were post intervention (e.g. angioplasty or peripheral arterial grafting) were excluded.
Results: 11 studies comprising 44,590 subjects from six different countries were included. Despite clinical heterogeneity between studies, the findings were remarkably consistent in demonstrating an increased risk of clinical cardiovascular disease associated with a low ABI. A low ABI (<0.9) was associated with an increased risk of subsequent all cause mortality (pooled RR 1.60, 95% CI 1.32–1.95), cardiovascular mortality (pooled RR 1.96, 95% CI 1.46–2.64), coronary heart disease (pooled RR 1.45, 95% CI 1.08–1.93) and stroke (pooled RR 1.35, 95% CI 1.10–1.65) after adjustment for age, sex, conventional cardiovascular risk factors and prevalent cardiovascular disease.
Conclusions: The ABI may help to identify asymptomatic individuals in the general population who are at increased risk of subsequent cardiovascular events. Evaluation is now required of the potential of incorporating ABI measurement into cardiovascular prevention programmes.

Keywords: Ankle-brachial index; Cardiovascular disease

Contents

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0021-9150/$ – see front matter
doi:10.1016/j.atherosclerosis.2006.03.011

1. Introduction

Cardiovascular disease remains the single most common cause of death in the UK and other Western countries. Primary prevention programmes, based on the reduction of modifiable risk factors such as cigarette smoking, hypercholesterolaemia and hypertension in an entire general population, have proved expensive and only partially successful at reducing incidence of disease, suggesting that supplementary approaches are required to reduce the burden of disease further. Current secondary prevention strategies have proved effective in reducing the rate of further cardiovascular events in individuals with symptomatic cardiovascular disease, but the vast majority of cardiovascular events occur in the 'healthy' population, with only 20% occurring in subjects with pre-existing clinical disease [1]. The major public health challenge is therefore to prevent new cases of clinical disease from developing in the apparently healthy but 'at risk' population. One approach is the identification of people with markers of asymptomatic atherosclerosis, who may be at increased risk of developing symptomatic cardiovascular disease, followed by targeted preventive measures.

Several markers have been suggested as potential predictors of cardiovascular morbidity and mortality, including non-invasive measures of sub-clinical atherosclerosis, such as carotid artery intima-media thickness, carotid plaques, aortic calcification and the ankle-brachial index (ABI) [2]. Of these, the ABI (the ratio of systolic blood pressure in the ankle to that in the arm), sometimes called the ankle-arm index or ankle-brachial pressure index, has perhaps shown the most promise as a potential tool in clinical practice and has been most widely investigated. Cross-sectional studies indicate that the ABI is a marker of generalised atherosclerosis and the test is currently used clinically in the assessment of peripheral arterial disease of the lower limbs, with a lower ratio associated with more severe disease. Given the well-recognised association between peripheral arterial disease and other forms of atherosclerotic disease, several studies have investigated the ABI and risk of subsequent cardiovascular morbidity and mortality in the general population. These studies are reviewed systematically here.

2. Methods

2.1. Identification of studies

The aim was to identify all relevant longitudinal studies that examined the ABI as a marker of subsequent cardiovascular events, available for review by July 2005. We included longitudinal studies (with over 1000 person years of follow-up) in which participants were representative of the general population (all ages, either sex) and which used any standard method for measurement and calculation of the ABI. Studies in which participants were selected according to presence of disease (such as intermittent claudication or diabetes) or were post intervention (e.g. angioplasty or peripheral arterial grafting) were excluded. There were no language restrictions.

Studies were identified by computerised searches of Medline (1996–2005) and Embase (1980–2005), by reference to conference proceedings, by checking the reference lists of studies and review articles, and by contacting experts (members of the Ankle Brachial Index Collaboration), asking them about other studies that may have been published. We searched using common text-words for the term 'ABI', combined with text-words and Medical Subject Headings which were most likely to capture all studies with a prospective cohort design. Further details on the search strategy are available from the authors on request. Eligibility was determined by two reviewers, who also independently extracted the data. Disagreements were resolved by discussion.

2.2. Outcome measures and data extraction

Outcome measures included were all cause mortality and cardiovascular mortality and morbidity (including coronary heart disease, myocardial infarction and stroke). Outcomes other than events, such as progression of atherosclerosis (measured invasively or non-invasively at any site in the body), physical functioning or walking distance were excluded. For all studies, we extracted information on the type of participants, measurement of the ABI, duration of follow-up, outcomes and quality of the study. We rated quality according to pre-defined criteria that were most likely to affect the validity of the final results (Fig. 1). Studies scoring less than 4 out of a possible maximum 5 were excluded from further analysis.

2.3. Data analysis and statistical methods

We examined risk estimates for each study for four main outcomes: mortality (all cause), mortality (cardiovascular and cerebrovascular), fatal and non-fatal coronary heart disease and fatal and non-fatal stroke. The findings were reported using Forrest Plots. Modest heterogeneity was found in the study results (tests for heterogeneity: $\chi^2 = 18.59$, $p = 0.01$ (mortality – all cause), $\chi^2 = 11.66$, $p = 0.04$ (mortality – car-

diovascular and cerebrovascular), $\chi^2 = 13.03$, $p = 0.02$ (fatal and non-fatal CHD) and $\chi^2 = 5.07$, $p = 0.41$ (fatal and non-fatal stroke)). Relative risks were pooled using a random effects model (Review Manager, Version 4.2.7, The Cochrane Collaboration 2004©).

3. Results

We identified 680 citations, reviewed 50 full text articles, and identified 18 eligible papers according to our inclusion criteria (Fig. 1). Some major cardiovascular longitudinal studies in which ABI measurement was undertaken were excluded because subjects were categorised according to other peripheral arterial disease criteria (peripheral arterial bypass, amputation and/or abnormal flow velocities) in addition to ABI [3,4]. Two of the identified studies were subsequently excluded as they did not fulfil the quality criteria [5,6]. No articles written in languages other than English met the inclusion criteria. The sixteen included papers [7–22] reported findings from eleven separate population cohort studies, five of which were conducted in Europe and six in the US. Table 1 gives key details of these studies. For studies in which findings relevant to this review were published in more than one publication, only findings pertaining to the longest reported follow-up period of that study were included [7,16,20]. Five additional studies were also identified as being likely to fulfil the inclusion criteria, but no published results were available as they were still in progress (Health in Men Study, Australia; InChianti Study, Italy; Women's Health and Aging Study, USA; Health and Aging and Body Composition Study, USA and GetABI Study, Germany).

In the eleven included studies, the number of study participants ranged from 439 [7] to 14,839 [14], the ages of subjects at baseline ranged from 40–55 years [10] to 74–95 years [19] and all but four studies [7,9,10,12,13] included both men and women. Duration of follow-up ranged from 4 years [19] to 12 years [20]. The potentially confounding effects of age and sex were controlled for in all studies. Prevalent cardiovascular or coronary heart disease was controlled for in all but one of the studies [22], either by adjustment of the final results or omitting subjects with disease at baseline. All but one of the studies [19] also controlled for a variety of cardiovascular risk factors, including smoking, hypertension and hyperlipidaemia. Most, but not all [12,16,17], of the studies reported the relative risk of an outcome (all cause mortality, cardiovascular mortality, coronary heart disease and/or stroke) for an ABI cut-point of 0.9. In these studies, the prevalence of an ABI < 0.9 ranged from 3.8% [10] to 20.0% [19]. Six studies also omitted subjects with an ABI > 1.5 [9,11–13,17–20], on the basis that such readings could be measurement artefacts reflecting the presence of rigid or calcified walls. All studies used a recognised method of measurement for the ABI, involving either a Doppler [9–13,16–20,22], a DinaMap [14] or an alternative pulse sensor [7]. All but two studies [10,20] used the mean of two blood pressure readings at both the

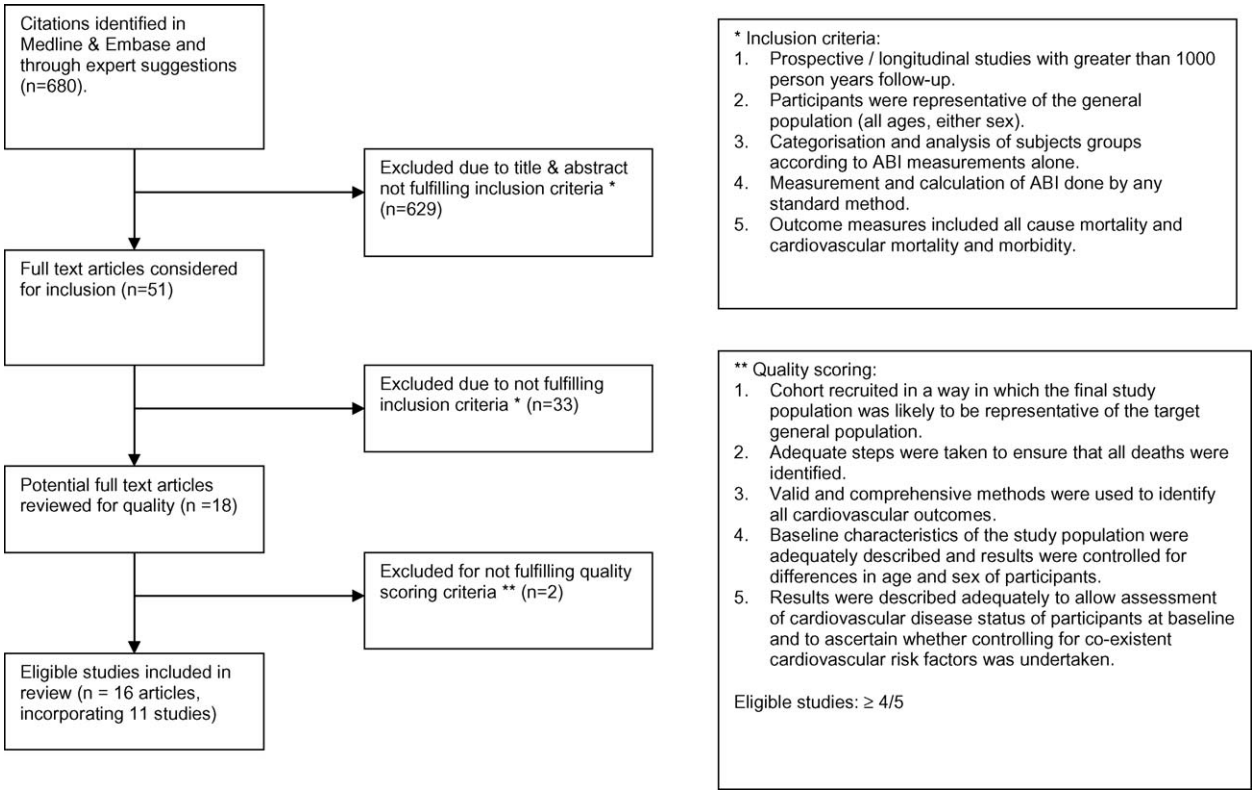

Fig. 1. Flow chart of eligibility of studies included in the review.

Table 1
Key characteristics of included studies and quality score

References	Study (country)	Study population/size	Age range (at base line)	Follow-up (years)	ABI Cut-points reported	Definitions of outcome measures included in review[a]	Factors adjusted for in multivariate analysis	Quality Score
Ogren [7,8]	Sweden Men Born in 1914 Study	439 men born in 1914, residing in Malmo	68 years	8 mean: 6.9	<0.9	Mortality (all cause) Mortality (fatal MI & IHD) IHD (fatal IHD & fatal/non-fatal MI)	Hypertension, smoking, alcohol, hypertriglyceridaemia, prevalent IHD [7] Hypertension, smoking, hyperlipidaemia, prevalent IHD & carotid stenosis [8]	5
Vogt [9]	U.S.	1492 white women participating in the Multicenter Study of Osteoporotic Fractures	65–93 years	4.3	≤0.9 ABI ≥ 1.5 excluded	Mortality (all cause) Mortality (total CV & CeV) Fatal CHD	Age, smoking, diabetes, WHR, BMI, cholesterol, BP, exercise, prevalent CVD	5
Kornitzer [10]	Belgium Belgian ABPI Study	2023 male factory workers	40–55 years	10	≤0.9	Mortality (all cause) Mortality (fatal MI/stroke & sudden death) Fatal CHD	Age, smoking, HDL & LDL cholesterol Prevalent CHD and IC excluded	4
Newman [11]	US Cardiovascular Health Study	5714 black and white men and women, sampled from a defined sample of Medicare eligible persons from 4 US communities	≥65 years	6 mean: 5.1	<0.9 ABI ≥ 1.5 excluded	Mortality (all cause) Mortality (fatal MI/stroke & sudden death) CHD (fatal & non-fatal MI) Stroke (fatal & non-fatal)	Age, gender, race, smoking, diabetes, cholesterol, triglycerides, glucose, insulin, fibrinogen, factor VII, BMI Prevalent CVD excluded	5
Abbott [12,13]	Hawaii, US Honolulu Heart Program	2863 men of Japanese ancestry residing on Oahu.	71–93 yrs	3–6	<0.8 Vs >1.0 [12] 0.8–1.0 Vs >1.0 [12] <0.9 [13] ABI >1.5 excluded	CHD (fatal CHD & non-fatal MI) [12] Stroke (fatal & non-fatal) [13] Ischaemic stroke (fatal & non-fatal) [13]	Age, gender, fibrinogen, cholesterol, BMI, BP, diabetes, distance walked, smoking, alcohol intake. Prevalent CHD & vascular surgery excluded [12] (& prevalent stroke [13])	4
Tsai [14]	US ARIC study	14,839 black and white men and women, sampled from 4 US communities.	45–64 yrs	7	≤0.9	Ischaemic stroke (fatal & non-fatal)	Age, gender, Race, centre, BP, hypertension, diabetes, smoking, cholesterol, prevalent CVD Prevalent stroke excluded.	5
Hooi [15,16]	Netherlands Limburg Study	3649 men and women selected from GP lists.	40–78 yrs	7.2	<0.7 Vs >0.95 [15] 0.70–0.95 Vs >0.95 [15] <0.95 [16]	Mortality (all cause) [15,16] Mortality (total CV & CeV) [15,16] Fatal CHD [16], fatal MI [16], fatal stroke [16] Non-fatal CHD [16], Non-fatal MI [16]	Age, gender, smoking, hypertension, diabetes, hypercholesterolemia, prevalent CVD.	5

Hollander [17] Van der Meer [18]	Netherlands Rotterdam Study	6913 [17]/6389 [18] men and women residing in a district in Rotterdam.	≥55 yrs	7–10 [18] Mean: 6.1 [17]	<1.01 Vs >1.17 [17] 1.01–1.17 Vs >1.17 [17] <0.8 [18] <0.9 [18] <0.97 Vs >1.21 [18] ABI >1.5 excluded	Stroke (fatal & non-fatal) [17] CHD (fatal & non-fatal MI) [18]	Age, gender, Diabetes, smoking, BP, cholesterol, prevalent CVD [17] Prevalent stroke excluded [17] Age, gender, Smoking, BMI, cholesterol, BP, diabetes, aspirin, other medication [18] Prevalent CVD excluded [18]	5
Murabito [19]	US Framingham Heart Study	674 male and female survivors of the Framingham study	74–95 yrs	4	<0.9 ABI >1.5 excluded	Mortality (all cause) CHD (fatal & non-fatal) Stroke (fatal & non-fatal)	Age, gender, prevalent CVD. (& systolic BP, atrial fibrillation—for stroke only)	4
Lee [20] Leng [21]	UK Edinburgh Artery Study	1592 men and women sampled from GP practices.	55–74 yrs	12 [20] 5 [21]	≤0.9 ABI ≥ 1.5 excluded	Mortality (all cause) Mortality (total CV & CeV) CHD (fatal & non-fatal MI) Fatal MI Non-fatal MI Stroke (fatal & non-fatal)	Age, gender, diabetes, BP, HDL & total cholesterol, smoking, prevalent CVD [20]. Prevalent symptomatic IC excluded [20]. Age, gender, diabetes, prevalent CHD [21].	5
Resnick [22]	US Strong Heart Study	4393 male and female American Indians living in tribal communities in three states.	45–74 yrs	8.3	<0.9 Vs 0.9–1.4 >1.4 Vs 0.9–1.4	Mortality (all cause) Mortality (total CV & CeV)	Age, gender, diabetes, lipids, hypertension, renal function, fibrinogen.	4

ABI, ankle brachial pressure index; BMI, body mass index; BP, blood pressure; CeV, cerebrovascular; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HDL, high density lipoprotein; IC, intermittent claudication; IHD, ischaemic heart disease; LDL, low density lipoprotein; WHR, waist hip ratio.

[a] Stroke: ischaemic and haemorrhagic stroke unless stated otherwise.

Table 2
summary of pooled age and sex adjusted RRs associated with low ankle brachial index by outcome group

Outcome group	Age and sex adjusted RRs[a]		
	Number of studies	Pooled RRs (95% CI)	Test for heterogeneity
All cause mortality	5	2.35 (1.66–3.32)	$P < 0.001$
Cardiovascular and cerebrovascular mortality	5	3.34 (2.12–5.28)	$P = 0.002$
Fatal and non-fatal coronary heart disease	4	2.13 (1.54–2.94)	$P = 0.003$
Fatal and non-fatal stroke	5	1.86 (1.43–2.42)	$P = 0.07$

[a] Age and sex adjusted RRs (if both genders included in study). N.B: Not reported by all studies.

ankle and the arm to calculate the ABI. Blood pressure was measured in both ankles (with the exception of ARIC [14] in which blood pressure was measured in one ankle chosen at random) with the lower (mean) ankle blood pressure used in the calculation of ABI used in the analysis. Most studies measured blood pressure in the right arm only, with the exception of three studies [7,15,16,19] in which blood pressure was measured in both arms—the higher (mean) blood pressure was then used to calculate ABI.

3.1. Age and sex adjusted relative risks

To set the context for the main, multivariate analysis, Table 2 gives a summary of pooled estimates for relative risks associated with a low ABI (cut-point 0.9) adjusted only for age and sex. Only five [9–11,20,22] of the eight studies [7,9–11,16,19,20,22] that examined the association between low ABI and at least one of the specified outcomes reported age and sex adjusted relative risks. The remaining three studies [7,16,19] reported only multi-adjusted relative risks (adjusted for traditional cardiovascular risk factors and prevalent cardiovascular disease) and results from these studies are included in the main multivariate analysis (Fig. 2). Following adjustment for age and sex, a low ABI was associated with a significantly increased risk of the specified outcome(s) in all of the individual studies except for stroke in one study [20]. Pooling of the results gave an estimated age and sex adjusted relative risk of 2.35 (95% CI 1.66–3.32) for all cause mortality, 3.34 (95% CI 2.12–5.28) for cardiovascular mortality and 2.13 (95% CI 1.54–2.94) for coronary heart disease (fatal and non-fatal events combined). The findings for stroke were slightly weaker, albeit still significant, with a pooled relative risk of 1.86 (95% CI 1.43–2.42) for fatal and non-fatal events combined.

3.2. Multivariate adjusted relative risks

Fig. 2 shows Forrest plots of the relative risks associated with a low ABI for each study by outcome measure, following adjustment for traditional cardiovascular risk factors and (where appropriate) prevalent cardiovascular disease. For all-cause mortality, a low ABI remained significantly associated with an increased risk in five out of the eight studies [7,9,11,16,22], with a pooled multivariate adjusted RR of 1.60 (95% CI 1.32–1.95) (Fig. 2a). Similar associations were observed for cardiovascular mortality, which although attenuated compared to the age and sex adjusted RRs, remained significant in five [9–11,16,22] out of six studies with a pooled multivariate adjusted RR of 1.96 (95% CI 1.46–2.64) (Fig. 2b).

After multivariate adjustment, the association between outcome and a low ABI also decreased in both magnitude and significance for coronary heart disease (Fig. 2c) and stroke (Fig. 2d). However, pooled multivariate adjusted RRs remained significant at 1.45 (95% CI 1.08–1.93) and 1.35 (95% CI 1.10–1.65) for coronary heart disease and stroke, respectively.

4. Discussion

In this systematic review of eleven, high quality, population-based cohort studies, we confirmed that a low ABI is associated with subsequent all cause mortality, cardiovascular mortality, coronary heart disease and stroke with a high degree of consistency. The main multivariate analysis showed significant associations in the presence of important co-variables, including a range of conventional cardiovascular risk factors and prevalent cardiovascular disease, indicating that the ABI may help to identify asymptomatic individuals at increased risk of cardiovascular disease, over and above their conventional risk factor profile. Prior to this review, the association between ABI and subsequent cardiovascular events had been explored only in individual studies, apart from one systematic review which excluded several large studies mostly due to publication after January 2004 [23]. The current paper represents an up-to-date and comprehensive systematic review of the ABI as a marker of all cause mortality and cardiovascular mortality and morbidity.

Although the ABI is known to vary with gender and age (a low ABI is generally, though not exclusively, found in men and women aged over 50 years [24]), we were unable to examine in detail the effect of these variables on the association between ABI and cardiovascular risk due to the lack of individual patient data. However, an association between ABI and subsequent disease was seen in studies including a range of different age groups and in both sexes. In addition, two studies reported an association between ABI and cardiovascular mortality in both men and women separately [11,16] and in subjects both younger and older than 75 years [11]. In these studies, the association was slightly stronger in men and in subjects $\leq$75 years.

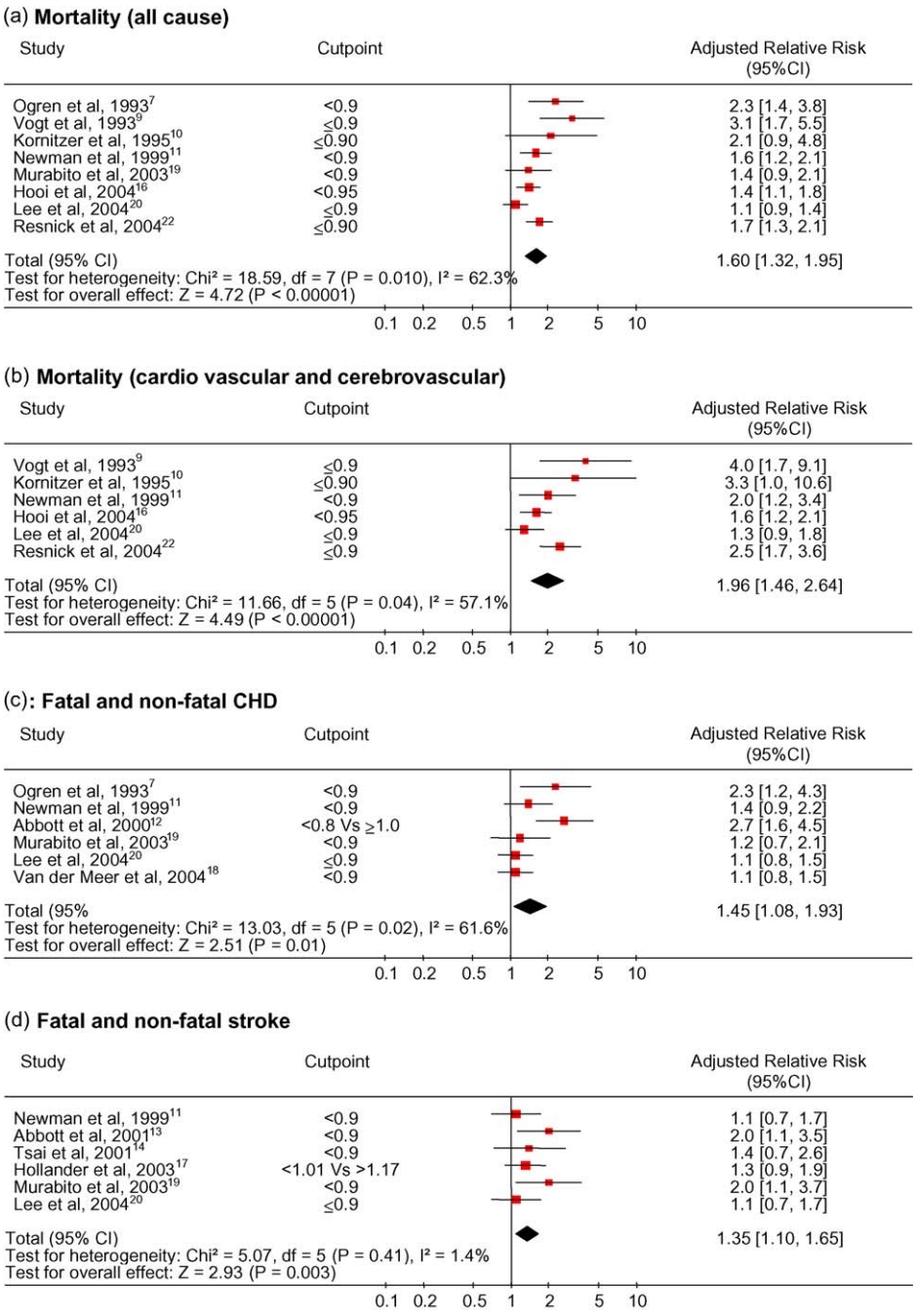

Fig. 2. Forrest plots—adjusted relative risks associated with low ankle brachial index for Mortality (all cause), Mortality (cardiovascular and cerebrovascular), CHD (fatal and non-fatal), stroke (fatal and non-fatal). (a): Mortality (all cause); (b): mortality (cardiovascular and cerebrovascular); (c): Fatal and non-fatal CHD; (d): Fatal and non-fatal stroke.

There are several limitations to this review. The current lack of a universally accepted ABI cut-point as the best predictor of cardiovascular events was reflected in a range of different cut-points used in individual studies, and this made it difficult to directly compare study outcomes. The measurement techniques used to calculate the ABI also differed between studies. Most investigators used the mean of two readings at two separate sites to calculate the ABI, whereas others used just one reading. Also, some investigators used the lower of both right and left ankle pressures and the higher of both arm pressures to calculate the ABI, while others used pressures in only one ankle and/or arm at random. There was considerable variation in the range of confounding variables used in multivariate adjustment, although most investigators included the conventional cardiovascular risk factors of smoking, hypertension and hypercholesterolaemia. In many respects, these inter-study differences led to a heterogeneous group of studies, which, in addition to variation

between study populations, made it remarkable that the overall findings associating ABI with cardiovascular risk were so constant.

It should be noted that we reviewed only published studies (an important means of ensuring quality through the peer-review process [25]) and it is possible that unpublished studies may have contained valid results that conflicted with our conclusions. During the writing of this review, five studies which were likely to fulfil the inclusion criteria but which had not published data were brought to our attention (Health in Men study, Australia; InChianti Study, Italy; the Women's Health and Aging Study, USA; the Health, Aging and Body composition Study, USA and the GetABI Study, Germany). However, lack of publication was due to the studies being still in progress, rather than any potentially negative results, and so publication bias is less likely.

The American Heart Association has described the ABI as a simple (patient acceptable) and inexpensive diagnostic test for lower-extremity peripheral arterial disease, which, among well-trained operators, has excellent test-retest reliability and, in symptomatic patients, high validity for stenosis $\geq$50% in leg arteries (sensitivity $\approx$90% and specificity $\approx$98%) [2,26]. Our review lends considerable support to the Association's assertion that the ABI is now emerging as a powerful and independent marker of future coronary events (and of fatal cardiovascular events and stroke). It also supports the recommendation that an ABI < 0.9 may be a useful addition to the assessment of disease risk in selected populations, including people whose risk assessment is neither clearly low risk nor high risk as assessed by presence or absence of traditional risk factors [26] and people aged 50 years and over. To date, several risk formulas and tables based on conventional cardiovascular risk factors, such as the Framingham Risk Score [27], have been used to predict an individual's risk of a subsequent cardiovascular event. Our findings suggest that the ABI has the potential to add to the sensitivity, specificity and predictive values of such cardiovascular risk tables. In addition, a low ABI may be sufficient in its own right to identify high-risk individuals who could benefit from aspirin or other secondary preventive measures. Before such preventive therapies are recommended however (necessitating some form of ABI 'screening' of the general population), it is essential that randomised controlled trials are performed to demonstrate their effectiveness in such a group of high risk individuals.

Although ABI measurement is simple and quick, and could theoretically be carried out fairly easily in general practice, studies on the feasibility of ABI testing for the assessment of overall cardiovascular risk are lacking. In the UK, ABI measurement has been used increasingly in general practice since district nurses started checking circulation in patients with venous ulceration before applying graduated compression. There is therefore a pool of growing expertise and increasing awareness of the test among general practitioners. In the USA, a survey of primary care clinicians was undertaken to identify clinician-defined factors that were perceived to foster acceptance of, or create barriers to, the use of the ABI to detect peripheral arterial disease [28]. The ABI was perceived to be a clinically useful diagnostic test. The majority of clinicians believed that the ABI was a useful tool in the diagnosis and management of both symptomatic (96%) and asymptomatic (89%) peripheral arterial disease, with 88% of clinicians believing that it was feasible to incorporate measurement of the ABI into daily practice.

This review demonstrates the remarkable consistency between individual studies on a wide range of different populations in concluding that a low ABI increases cardiovascular risk (as well as demonstrating an association with cardiovascular risk independent of conventionally-measured risk factors), thereby increasing the generalisability of our findings. The evidence is now compelling that the ABI may help to identify subjects in the general population who are at increased risk of subsequent cardiovascular events, including those who are currently asymptomatic. However, further research requires a meta-analysis of individual patient data from all relevant studies to (i) calculate accurate sensitivity, specificity and likelihood ratios, (ii) explore potential differences in the relationship between ABI and cardiovascular risk by age and sex, (iii) determine the extent to which risk scores improve on addition of the ABI and (iv) determine the best ABI cut-points to categorise risk. It is also necessary to explore more fully the feasibility and acceptability of ABI measurement for cardiovascular risk prediction in general practice and other clinical settings. In general, the findings of our review indicate that it is now time to evaluate the potential of incorporating the ABI into population-based cardiovascular prevention programmes.

Acknowledgements

JP and GF conceived the idea for the review. JP designed the study. CH and JP extracted and analysed the data and cowrote the manuscript. GF and GM contributed to data analysis and commented on drafts. Members of the ABI collaboration had the opportunity to comment on a final draft of the paper. JP is guarantor. Photocopying/inter-library loans for some of the articles was paid for by the ABI Collaboration (supported by an educational grant from Sanofi Aventis).

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