Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis

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Summary

Background **Differences in systolic blood pressure (SBP) of 10 mm Hg or more or 15 mm Hg or more between arms have been associated with peripheral vascular disease and attributed to subclavian stenosis. We investigated whether an association exists between this difference and central or peripheral vascular disease, and mortality.**

Methods **We searched Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, Cochrane, and Medline In Process databases for studies published before July, 2011, showing differences in SBP between arms, with data for subclavian stenosis, peripheral vascular disease, cerebrovascular disease, cardiovascular disease, or survival. We used random effects meta-analysis to combine estimates of the association between differences in SBP between arms and each outcome.**

Findings **We identified 28 eligible studies for review, 20 of which were included in our meta-analyses. In five invasive studies using angiography, mean difference in SBP between arms was 36·9 mm Hg (95% CI 35·4–38·4) for proven subclavian stenosis (>50% occlusion), and a difference of 10 mm Hg or more was strongly associated with subclavian stenosis (risk ratio [RR] 8·8, 95% CI 3·6–21·2). In non-invasive studies, pooled findings showed that a difference of 15 mm Hg or more was associated with peripheral vascular disease (nine cohorts; RR 2·5, 95% CI 1·6–3·8; sensitivity 15%, 9–23; specificity 96%, 94–98); pre-existing cerebrovascular disease (five cohorts; RR 1·6, 1·1–2·4; sensitivity 8%, 2–26; specificity 93%, 86–97); and increased cardiovascular mortality (four cohorts; hazard ratio [HR] 1·7, 95% CI 1·1–2·5) and all-cause mortality (HR 1·6, 1·1–2·3). A difference of 10 mm Hg or higher was associated with peripheral vascular disease (five studies; RR 2·4, 1·5–3·9; sensitivity 32%, 23–41; specificity 91%, 86–94).**

Interpretation **A difference in SBP of 10 mm Hg or more, or of 15 mm Hg or more, between arms might help to identify patients who need further vascular assessment. A difference of 15 mm Hg or more could be a useful indicator of risk of vascular disease and death.**

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Introduction

Peripheral vascular disease is a risk factor for future cardiovascular events and mortality,[1] and it is associated with reduced arterial pressures in legs.[2,3] Early detection of the disease is important because interventions to promote smoking cessation, lower blood pressure, or offer statin therapy can reduce mortality.[4–6] Most cases, however, are clinically silent,[7] and gold-standard non-invasive identification of this disease requires detection of a reduced ankle-brachial pressure index at rest or after a stress test.[8] This measurement requires time, experience, and training;[9] it is not routinely undertaken in primary-care assessment of hypertensive patients and is not proposed within the UK vascular check programme.[10,11]

Data suggest that a difference in systolic blood pressure (SBP) of 10 mm Hg or more or of 15 mm Hg or more between arms might, like a reduced ankle-brachial pressure, suggest poor prognosis.[12–15] Researchers have linked a difference of more than 15 mm Hg with subclavian stenosis[14,16,17] and atherosclerotic plaque,[18,19] although no radiological investigation of atherosclerotic lesions in unselected populations has been undertaken. The latest guidance from the European Society of Hypertension and European Society of Cardiology advises that a difference between arms is due to peripheral vascular disease.[20] Although these guidelines are the first to identify the disorder as the pathological basis for differences, no evidence is cited to justify this statement and thus it seems to be based on consensus (Dominiczak, A, University of Glasgow, and Parati, G, Università degli Studi Milano-Bicocca, personal communications).

The new National Institute for Health and Clinical Excellence (NICE) clinical guideline for hypertension[21] states that a difference of less than 10 mm Hg can be regarded as normal; however, a difference of more than 20 mm Hg between arms is unusual, occurring in less than 4% of people and usually associated with underlying vascular disease. Our previous meta-analysis of studies of opportunistic populations at low risk of bias[22] showed a pooled prevalence for a difference of 20 mm Hg or more of 4·2%, but we also reported a prevalence of 19·6% for a difference of 10 mm Hg or more. The NICE guideline[21]

does not address differences of 10–20 mm Hg, perhaps because their clinical significance is unknown.

Bilateral brachial blood-pressure measurements can be easily done and are recommended in assessment of new hypertensive patients.[23] Detection of a difference in SBP between arms could be a pragmatic way to select patients at high risk of asymptomatic peripheral vascular disease in primary care. Although the need to check blood pressure in both arms is recognised in present guidelines,[21,23] the advice is not followed by most UK general practitioners,[24] which could be because of inertia in adoption of the workload[25] or because a clearly presented synthesis of the evidence for this intervention is lacking.[26]

How differences are measured is important; a simultaneous method obtaining repeated pairs of measurements with one or two automated sphygmomanometers avoids overestimation of prevalence.[27] However, this method needs additional resources, and many studies have used a pragmatic sequential measurement protocol[22] that can still detect the probable presence of differences between arms.[28]

We aimed to establish whether a difference in SBP between arms is associated with ipsilateral angiographically proven subclavian stenosis on the side of the arm with the lowest pressure, with peripheral or cardiovascular disease, and with an increased risk of cardiovascular-related or all-cause mortality.

Methods

Search strategy and selection criteria

We undertook a systematic review in accordance with recognised methods.[29] We searched the Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, and Medline In Process databases for reports published between each database's start date, and July 31, 2011. We used various search terms (webappendix). We searched one author's (CEC) reference archive and reference lists of included primary studies for additional studies. Included study authors were contacted for further information and unpublished data if necessary.

See Online for webappendix

Reports were reviewed by one author (CEC) and decisions were checked by a second (ACS or RST). We included cohort or cross-sectional studies of differences in blood pressure between arms in any adult population (aged ≥18 years) with data for central vascular disease, peripheral vascular disease, or death (table). Case reports were excluded, and no language exclusion criteria were applied. Information about study design, population, method of blood-pressure measurement, and outcomes were extracted to a standardised data form.

	Invasive assessment	Non-invasive assessment
Central vascular diseases		
Coronary	Angiography*	Documented history of cardiac disease (myocardial infarction or angina)
Cerebrovascular (carotid or cerebral)	Angiography*	Documented history of cerebrovascular event or transient ischaemic attack
Aortic arch	Angiography*	NA
Peripheral vascular diseases		
Subclavian stenosis	Angiography*	NA
Leg	NA	Measurement of reduced ankle brachial index (<0·9) or documented history of peripheral vascular disease in the leg
Mortality		
All cause	NA	Prospective recording of events
Cardiovascular related	NA	Prospective recording of events

NA=no data available. *Percentage stenosis varied between individual reports.

Table: **Vascular diseases and mortality outcomes assessed**

Statistical analysis

Data were processed in accordance with the Cochrane handbook.[30] We compared (as dichotomous outcomes) subclavian stenosis, peripheral vascular disease, cerebrovascular disease, and cardiovascular disease status (table) between groups defined by difference in SBP between arms with prespecified thresholds of either 10 mm Hg or more or 15 mm Hg or more, and calculated risk ratios (RRs) and 95% CIs. Mortality outcomes were compared with hazard ratios (HRs). The weighted mean difference in SBP between groups was reported for individuals with angiographically proven subclavian stenosis. When estimates could be combined, RRs, HRs, and means were pooled with a conservative random effects model; otherwise individual study estimates are reported.

We undertook two a priori specified subgroup analyses to assess whether associations varied by method of measurement of SBP difference (ie, sequential *vs* simultaneous) or by baseline cardiovascular risk of the cohort (ie, community *vs* hospital population). We estimated pooled sensitivity and specificity values with the hierarchical summary receiver operating characteristic model when four or more studies were available.[31,32] When fewer than four studies were available, we reported sensitivity and specificity values from individual studies. We did analyses with RevMan (version 5.1) and Stata (version 11.1).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors agreed to final submission. The corresponding author had full access to the data.

Results

We identified 691 unique reports by database searches and 159 from personal collections and citations. 28 studies met the inclusion criteria and 20 reported quantitative data for inclusion (figure 1; webappendix).

Studies typically included groups of individuals with raised cardiovascular risk compared with the general population—eg, patients undergoing cardiac surgery or angiography (nine studies),[16,33–40] those with known peripheral vascular disease (four studies),[41–44] hospital

inpatients (two studies),[45,46] or cardiology and vascular outpatients (four studies).[13,14,47,48] Investigators of nine studies collected data in primary-care settings or from community-based populations.[12,15,17,18,49–53] Two studies were of the same cohort; therefore, data for objective assessment of peripheral vascular disease were used in cross-sectional analyses[51] and prospective data in survival analyses.[12] Researchers of 12 studies (13 cohorts) used a method of repeated simultaneous bilateral blood-pressure measurements,[14,16,37,39,45–47,49–53] and seven repeated sequential measurements.[12–15,17,18,41] The rest used pairs of brachial blood-pressure measurements[33,34,44,48] or methods that were unclear.[35,36,38,40,42,43]

From five case series of patients with angiographically proven asymptomatic subclavian stenosis (defined as >50% occlusion for two studies,[35,43] but not defined for the other three; 135 cases),[39,40,44] we estimated mean blood pressure to be 36·9 mm Hg (95% CI 35·4–38·4) lower in the arm with stenosis than in the other. The difference was similar in two other studies that could not be pooled (41 mm Hg[33] and 21 mm Hg[36]); one further study[37] showed a mean intra-arterial pressure gradient of 28 mm Hg (95% CI 14·4–41·6) across stenoses of more than 75% in ten patients. A subgroup analysis showed no variation in the mean difference between studies with repeated simultaneous blood-pressure measurements and those with sequential single measurements (mean 33·5 mm Hg *vs* 37·1 mm Hg; mean difference 3·6 mm Hg, 95% CI −3·9 to 11·1, p>0·20).[39]

Investigators of three studies,[34,38,42] all using a sequential method of measurement, recorded prevalence of subclavian stenosis at angiography and between-arm differences. We could pool two of these datasets (n=532), to give an RR of 8·8 (95% CI 3·6–21·2, p<0·0001) for subclavian stenosis of more than 50% occlusion at angiography and a difference of 10 mm Hg or more.[34,42] English and colleagues[34] analysed differences of 20 mm Hg or higher in 458 patients to give an RR of 7·4 (2·9–18·7, p<0·0001). Sensitivity was 65% (95% CI 35–86) and specificity 85% (82–88) for identification of subclavian stenosis with a difference of 10 mm Hg or more; sensitivity was 35% (14–62) and specificity 94% (92–96) with a difference of 20 mm Hg or higher. In Calligaro and co-workers' investigation,[42] sensitivity was 75% (19–99) and specificity 75% (58–88) for identification of subclavian stenosis with a cutoff of 10 mm Hg or higher. Osborn and colleagues[38] reported that all four patients with a difference of 15 mm Hg or higher had a subclavian stenosis of more than 50% occlusion compared with none of 55 with a difference less than 15 mm Hg.

Only one study reported coronary angiogram findings and differences in SBP between arms.[16] Disease of at least one coronary artery was identified in 12 (63%) of 19 patients with differences of 15 mm Hg or more, compared with 153 (58%) of 264 patients with differences of less than 15 mm Hg (RR 1·1, 95% CI 0·8–1·6, p=0·64).

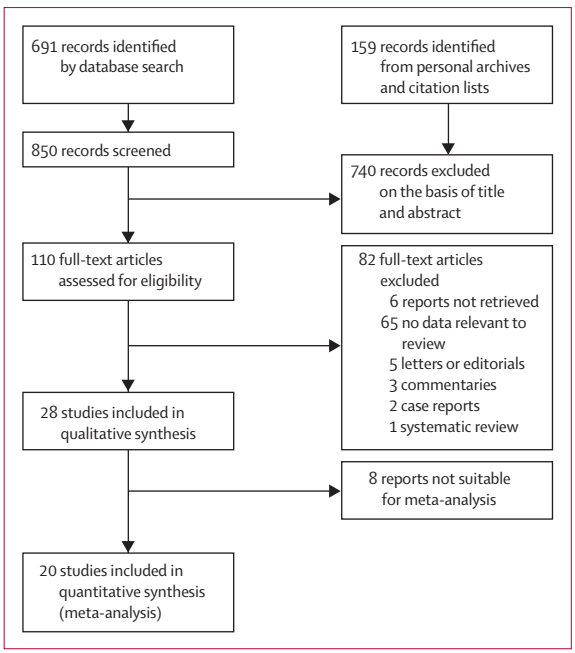

Figure 1: **Study selection**

Seven non-invasive cohorts reported an association between a difference between arms and history of coronary artery disease. When we compared groups with and without a difference of 15 mm Hg or higher, the pooled RR across six studies[16,18,41,47,50,51] showed no significant association (figure 2). Subgroup analysis showed that method of measurement of blood-pressure difference (simultaneous *vs* non-simultaneous) had no effect on this association (figure 2). When we restricted analysis to the four community-recruited cohorts,[18,47,50,51] the findings did not change (data not shown). Investigators of four non-invasive studies estimated the association between a difference of 10 mm Hg or more and coronary artery disease;[41,47,50,51] when pooled, we noted little evidence for an association (figure 2). Other studies that could not be included in a meta-analysis did not show an association between a difference and ischaemic heart disease (data not shown).[15,45,46] One angiographic study[33] (n=228) showed an association between a difference in SBP between arms of 15 mm Hg or more and aortic arch disease (RR 3·7, 95% CI 2·6–11·2, p<0·0001) and carotid stenosis (occlusion of more than 80%; RR 3·0, 95% CI 1·9–4·9, p<0·0001).

Five cohorts (four non-invasive studies)[18,33,50,51] reported prevalence of previous cerebrovascular accident or transient ischaemic attack (from clinical records). Pooled analysis showed a significant association between cerebrovascular disease and differences of 15 mm Hg or more (figure 3). Pooled sensitivity was 8% (95% CI 2–26) and specificity 93% (86–97). However, we noted no association when analysis was restricted to non-invasive studies using a simultaneous measurement method (figure 3).[50,51] Data for a difference of 10 mm Hg or more were available from two studies (both using simultaneous

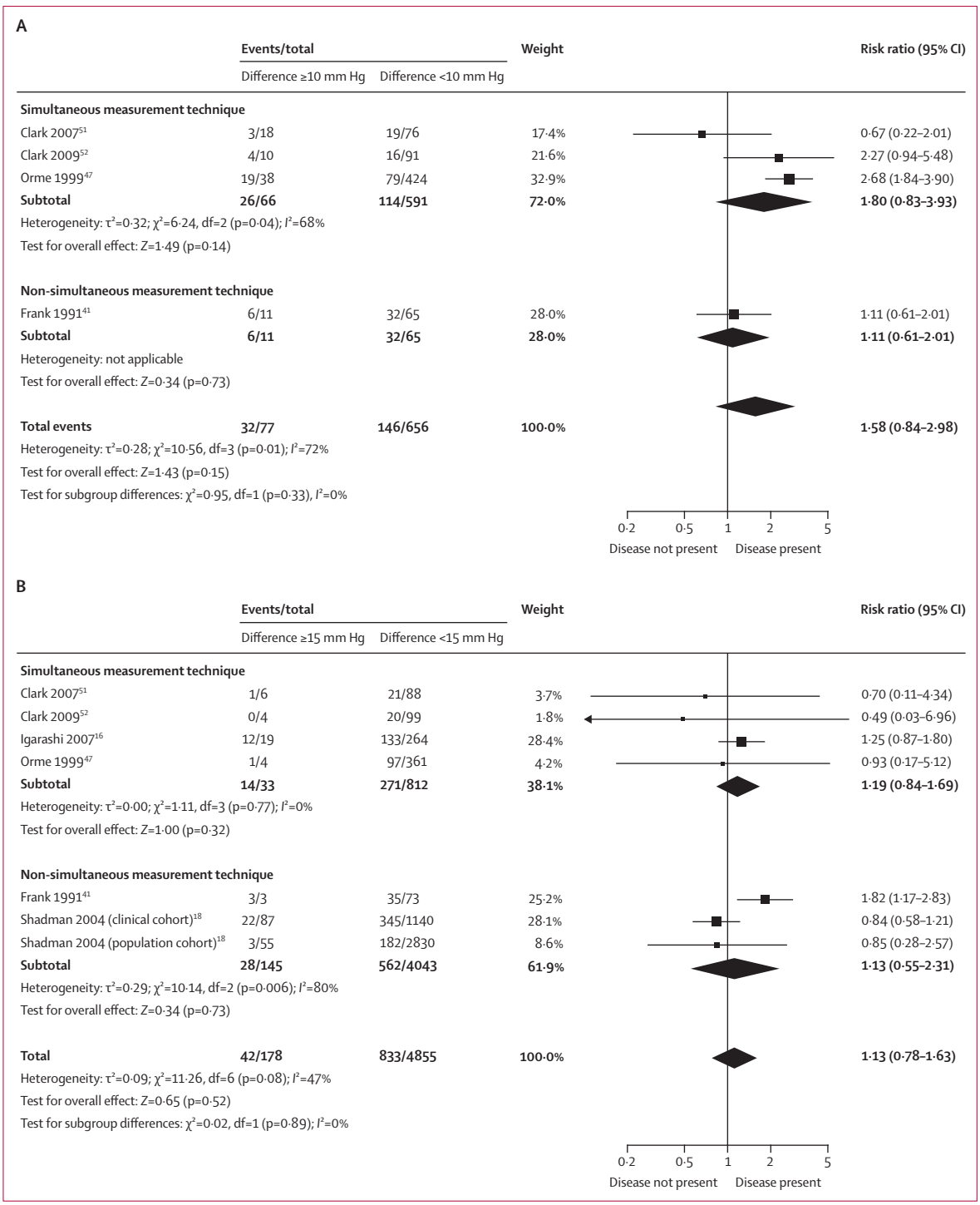

Figure 2: **Risk ratios for pre-existing coronary artery disease with and without differences in systolic blood pressure between arms of 10 mm Hg or more (A) and 15 mm Hg or more (B)**

measurement methods);[50,51] we identified no association between a difference of 10 mm Hg or more and cerebrovascular disease (figure 3).

We identified no studies showing a difference in SBP between arms associated with angiographically proven peripheral vascular disease in the leg. However, nine non-invasive studies showed that a difference of 15 mm Hg or more was linked with peripheral vascular disease in the leg, defined by direct measurement of ankle-brachial pressure index of less than 0·9 (five

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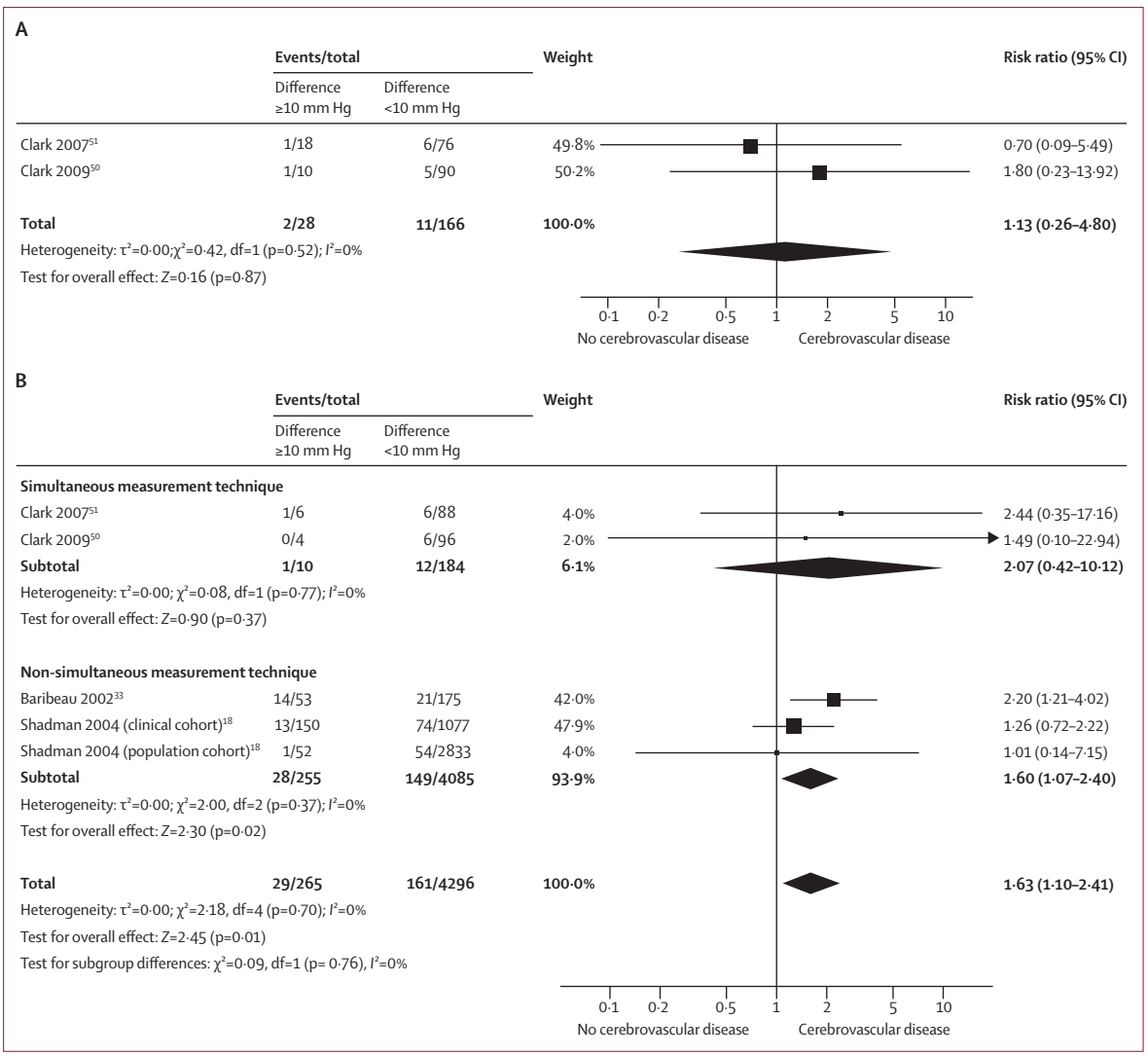

Figure 3: **Relative risk ratios for cerebrovascular disease with and without differences in systolic blood pressure of 10 mm Hg or more (A) and 15 mm Hg or more (B) between arms**

studies)[16–18,48,51] or by history of peripheral vascular disease (four studies; figure 4).[33,41,50,53] We noted little evidence that pooled RRs differed between studies that measured ankle-brachial pressure index (RR 2·7, 95% CI 1·3–5·5),[16–18,51] and those using history of peripheral vascular disease (RR 2·1, 95% CI 1·6–2·9; p=0·55).[33,41,50,53] Similarly, we detected little evidence that pooled values differed between studies using simultaneous[16,50,51,53] and sequential measurement methods[17,18,33,41] (figure 4). Pooled RRs did not differ significantly for community-recruited (3·4, 95% CI 2·0–6·0) and hospital-recruited (2·0, 1·0–2·9) cohorts (p=0·11). Pooled sensitivity for a difference of 15 mm Hg or more for peripheral vascular disease was 15% (95% CI 9–23) and specificity 96% (94–98).

Pooled data from five non-invasive studies with differences in SBP of 10 mm Hg or more[41,48,50,51,53] showed a significant association with peripheral vascular disease (figure 4). RRs did not differ between community-based cohorts, which all used simultaneous measurements,[50,51,53] and hospital-based cohorts, which used non-simultaneous methods (figure 4).[41,48] The RR was, however, higher for studies assessing peripheral vascular disease by ankle-brachial pressure index (RR 3·3, 95% CI 2·1–5·2)[48,51] than for those in which the disorder was defined by history alone (1·7, 1·3–2.7; p=0·02).[41,50,53] Pooled sensitivity of a difference of 10 mm Hg or higher for peripheral vascular disease was 32% (95% CI 23–41) and specificity 91% (86–94).

One other study[49] (which presented no numerical data that could be extracted) showed no significant difference in prevalence of peripheral vascular disease between those with and those without a difference of 10 mm Hg or more. Another general-population study[52] (n=1090; mean age

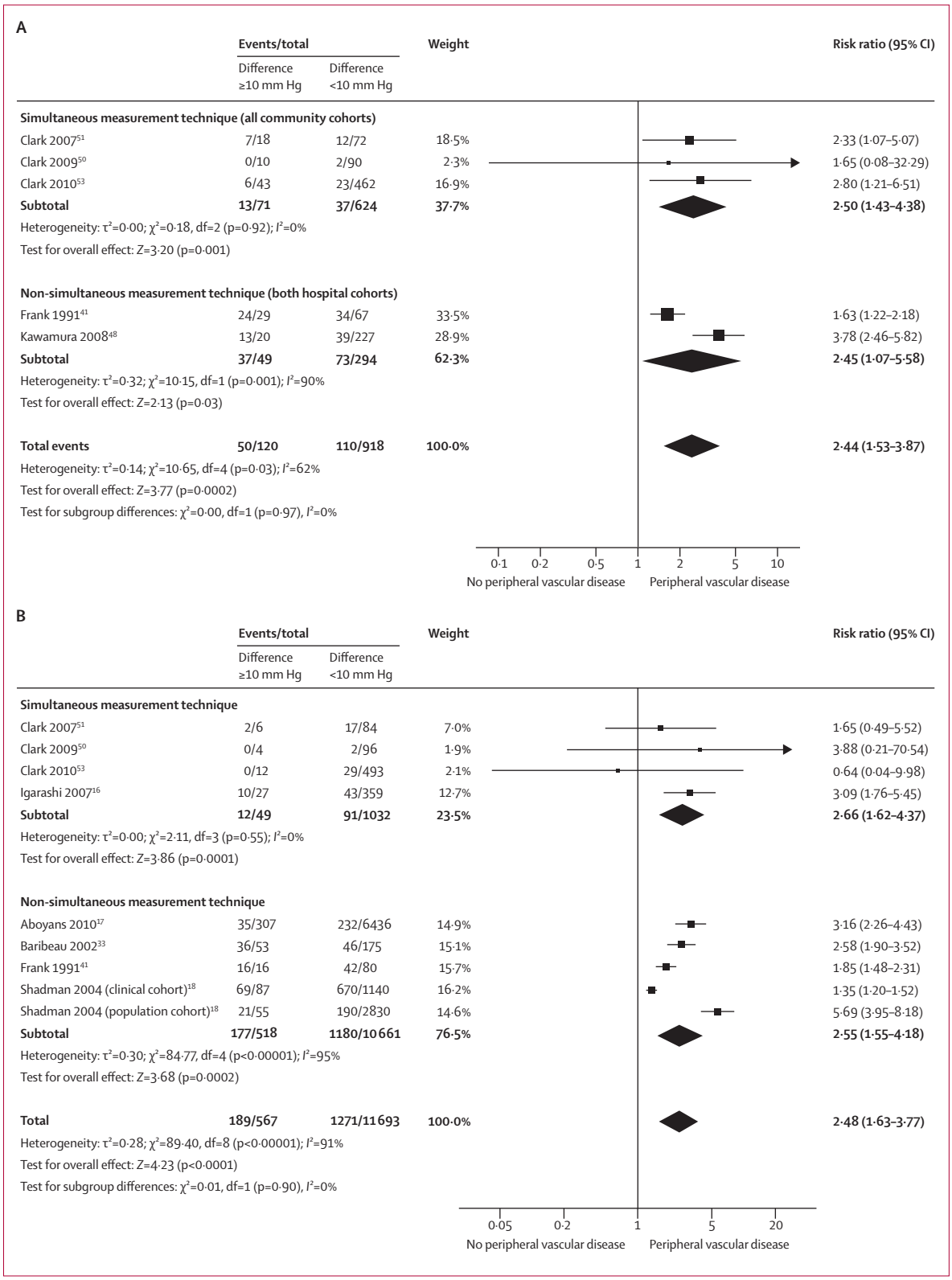

Figure 4: **Relative risk ratios for peripheral vascular disease with and without differences in systolic blood pressure of 10 mm Hg or more (A) and 15 mm Hg or more (B) between arms**

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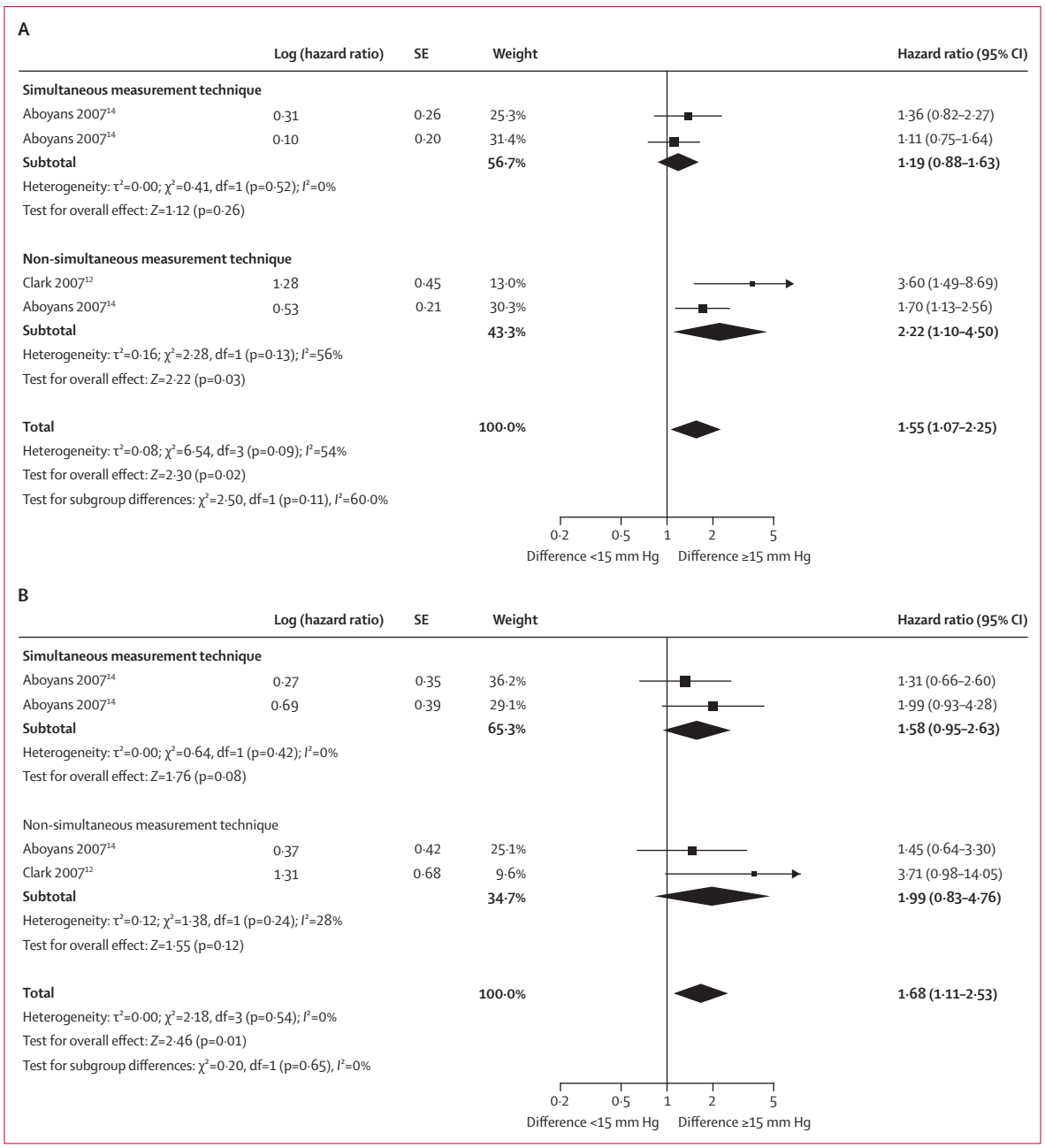

Figure 5: **Pooled hazard ratios for all-cause (A) and cardiovascular (B) mortality from prospective cohort studies with between-arm difference in systolic blood pressure of 15 mm Hg or more**

62·4 years) not included in the meta-analysis (authors were contacted but we received no reply) showed that prevalence of a difference of more than 10 mm Hg was 9·1% (95% CI 7·4–10·8), and that ankle-brachial pressure index and a difference in SBP were weakly negatively correlated (r=–0·23, p<0·001), which accords with other reports.[16,51]

Three studies showed associations between reduced survival and a difference between arms of 10 mm Hg or more,[13] 15 mm Hg or more,[14] or both.[12] In subgroup analysis, we noted weak evidence for a stronger association of all-cause mortality with a difference of 15 mm Hg or more in cohorts recruited with a non-simultaneous method of measurement than in studies in which simultaneous methods were used (figure 5). Two studies reported all-cause mortality for a difference of 10 mm Hg or higher with HRs of 1·3 (95% CI 1·0–1·6; 131 deaths in 421 patients; p=0·02)[13] and 3·3 (1·5–7·1; 26 deaths in 247 patients; p=0·003),[12] but the pooled HR was 1·9 (95% CI 0·8–4·7, p=0·17). Both studies used a non-simultaneous measurement method.

For cardiovascular-related mortality, the pooled HR from four cohorts (two studies)[12,14] showed a significant association with a difference of 15 mm Hg or more, with little evidence of a difference according to method of measurement (figure 5). Only one[12] reported an HR for cardiovascular mortality with a difference of 10 mm Hg or more, providing weak evidence of an association (HR 2·8, 95% CI 0·9–9·2, p=0·09; 11 deaths in 247 patients).

Discussion

A difference in SBP of 10 mm Hg or higher or 15 mm Hg or more between arms is associated with peripheral vascular disease with low sensitivity but high specificity. This finding is consistent for different methods of measurement or diagnosis for both community-recruited and hospital-recruited cohorts. A difference of 15 mm Hg or more is also associated with the presence of cerebrovascular disease. Data from prospective studies showed that a difference of 15 mm Hg or more is associated with increased all-cause and cardiovascular mortality.

Although our search was not restricted by language, no translation services were available. Data were extracted from non-English studies but some data could have been missed. We had insufficient studies for funnel-plot assessment of any outcome, and therefore we are unable to establish the effect of small study or publication bias on our findings.[54] Most researchers recruited patients with heightened cardiovascular risk compared with the general population—eg, those undergoing angiography for clinical reasons; only nine studies[12,15,17,18,49–53] used unselected community or primary-care cohorts. These cohorts consisted of people with either diabetes or hypertension, and results should be interpreted in this context. Subgroup analyses, however, indicated little difference in association with difference in SBP between these cohorts.

One meta-analysis showed that prevalence of a difference in SBP of 10 mm Hg or more between arms is roughly doubled when diagnosis is based on one pair of measurements, uses a sequential approach, or uses manual rather than automated measurements.[27] Only 12 of 28 studies in this review used the gold-standard method of repeated simultaneous measurements,[14,16,37,39,45–47,49–53] so accuracy of patient classification in the other studies cannot be assumed. Subgroup analyses, however, indicated little difference between the two methods of assessment. Diastolic pressures can also differ,[22] but only three studies meeting the inclusion criteria reported data for diastolic blood pressure and so no analyses were done.[41,47,51]

Reduced ankle-brachial pressure indices are strongly correlated with angiographic evidence of large-vessel disease in the leg.[2,55] Prevalence of large-vessel arterial disease in white Americans (mean age 66 years) is 11·7%,[7] and is grossly underestimated by assessment of claudication symptoms.[56,57] Several studies included in our report have shown either independent and significant associations of a difference with reduced ankle-brachial pressure, or negative correlations of magnitude of between-arm difference with ankle-brachial pressure. Our findings strengthen the hypothesis that a difference is due to peripheral vascular disease, and thus might represent a sign of clinical importance;[58] the association of a difference of 15 mm Hg or more with angiographic evidence of carotid or aortic arch disease further supports this notion.[33]

Consistency of RRs for different methods of measurement of differences in SBP between arms is surprising in view of the effect of measurement on prevalence.[22,27] One sequential measurement can exclude patients without a true between-arm difference,[28] but the trend towards an increased RR in survival studies not using a simultaneous measurement method suggests that bias is possible if a gold-standard assessment technique is not used. Future epidemiological studies of between-arm difference should use a repeated simultaneous measurement method.[27]

Although asymptomatic peripheral vascular disease is common in patients with coronary artery disease,[59] we did not identify an association of coronary artery disease with a difference in SBP. However, we did record an association between increased cardiovascular and all-cause mortality, suggesting that a difference does indicate a raised cardiovascular risk in a similar way to reduced ankle-brachial pressure index.[1]

Early identification of peripheral vascular disease allows interventions to be given and might improve outcomes. Screening in primary care is feasible but not widespread.[60] Overall prevalence of the disorder in our analyses was 12–15%. These figures are similar to published estimates of community prevalence, implying that these findings could be generalised.[7,61,62] The high specificities reported here suggest that detection of a difference might be useful in assessments designed to identify the disorder in patients at highest risk. Prevalences for a difference in community-based cohorts in our review suggest that less than 5% of patients would need such assessment if a cutoff of 15 mm Hg was adopted. The increased mortality with this cutoff would support such an intervention.

Three prospective studies reported increased mortality with a difference in SBP. The cohorts in these studies were recruited from vascular and renal clinics[13,14] or were primary-care patients with hypertension.[12] Only one cohort could be regarded as representative of a wider population.[14] Therefore this review suggests that a difference is an independent predictor of cardiovascular events and death in populations at high baseline cardiovascular risk, but this cannot be generalised to patients without cardiovascular risk factors.

Subclavian steal syndrome due to subclavian stenosis is usually associated with a difference in SBP of 10 mm Hg or higher between arms.[63] Detection is important when patients are assessed for coronary artery bypass graft to avoid angina due to coronary-subclavian steal phenomenon when the internal mammary artery is used. Minor

subclavian stenoses are common,[64,65] but our data suggest that mean difference exceeds 35 mm Hg for angiographically proven subclavian stenosis of more than 50%. Smaller differences of more than 10 mm Hg or 20 mm Hg have high specificity for angiographically proven subclavian stenosis, and differences of 10–16 mm Hg have been proposed as cutoff values to select patients for subclavian angiography to exclude stenosis preoperatively.[34,38,66,67] The sensitivities reported do not mean that a difference in SBP of less than 10 mm Hg, or of less than 15 mm Hg (ie, a negative result), can reliably rule out subclavian stenosis. These data are derived from patients referred for coronary angiography; no investigators have yet examined the pathological basis of a difference in unselected populations, and so the definition of subclavian stenosis should not be used in studies according to measurement of the difference alone.[14,17,18]

What constitutes a clinically important difference in SBP between arms is unclear. However, we have associated a difference with an increased likelihood of peripheral vascular disease and with prospective differences in survival. Further research is needed to establish the upper limit of normal between-arm differences, particularly for diastolic measurements. Further survival studies in populations recruited from community settings are needed to establish whether these findings can be generalised. Guidelines continue to describe a difference of 10 mm Hg or more as rare,[68] yet our own studies have suggested that prevalence ranges from 10% in diabetic patients to 20% in general and hypertensive populations.[12,22,50]

In conclusion, our findings suggest that a difference in SBP of 10 mm Hg or more or 15 mm Hg or more between arms could identify patients at high risk of asymptomatic peripheral vascular disease and mortality who might benefit from further assessment. Findings from our study should be incorporated into future guidelines for hypertension and blood-pressure measurement to justify bilateral brachial measurement in the assessment of individuals, and to promote targeted screening for peripheral vascular disease and aggressive risk factor management in subjects with a demonstrable systolic between-arm difference.

Contributors

CEC conceived the study and all authors were involved in study design. CEC developed the search strategy and acts as guarantor for the study. CEC, ACS, and RST selected studies. CEC, OCU, and RST extracted data and did analyses. CEC wrote the first draft and all co-authors contributed to various drafts. All authors agreed on the final manuscript, and CEC takes final responsibility.

Conflicts of interest

We declare that we have no conflicts of interest.

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