

BMJ Open Arm Based on LEg blood pressures (ABLE-BP): can systolic leg blood pressure measurements predict systolic brachial blood pressure? Protocol for an individual participant data meta-analysis from the INTERPRESS-IPD Collaboration

Sinead T J McDonagh ¹, James P Sheppard ², Fiona C Warren,¹ Kate Boddy ³, Leon Farmer,⁴ Helen Shore,⁴ Phil Williams,⁴ Philip S Lewis,⁵ Rachel Baumber,⁶ Jayne Fordham,⁷ Una Martin,⁸ Victor Aboyans,⁹ Christopher E Clark ¹, on behalf of the INTERPRESS-IPD Collaborators

To cite: McDonagh STJ, Sheppard JP, Warren FC, *et al.* Arm Based on LEg blood pressures (ABLE-BP): can systolic leg blood pressure measurements predict systolic brachial blood pressure? Protocol for an individual participant data meta-analysis from the INTERPRESS-IPD Collaboration. *BMJ Open* 2021;**11**:e040481. doi:10.1136/bmjopen-2020-040481

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-040481>).

Received 15 May 2020
Revised 13 December 2020
Accepted 09 January 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Dr Christopher E Clark;
c.e.clark@exeter.ac.uk

ABSTRACT

Introduction Blood pressure (BP) is normally measured on the upper arm, and guidelines for the diagnosis and treatment of high BP are based on such measurements. Leg BP measurement can be an alternative when brachial BP measurement is impractical, due to injury or disability. Limited data exist to guide interpretation of leg BP values for hypertension management; study-level systematic review findings suggest that systolic BP (SBP) is 17 mm Hg higher in the leg than the arm. However, uncertainty remains about the applicability of this figure in clinical practice due to substantial heterogeneity.

Aims To examine the relationship between arm and leg SBP, develop and validate a multivariable model predicting arm SBP from leg SBP and investigate the prognostic association between leg SBP and cardiovascular disease and mortality.

Methods and analysis Individual participant data (IPD) meta-analyses using arm and leg SBP measurements for 33 710 individuals from 14 studies within the Inter-arm blood pressure difference IPD (INTERPRESS-IPD) Collaboration. We will explore cross-sectional relationships between arm and leg SBP using hierarchical linear regression with participants nested by study, in multivariable models. Prognostic models will be derived for all-cause and cardiovascular mortality and cardiovascular events.

Ethics and dissemination Data originate from studies with prior ethical approval and consent, and data sharing agreements are in place—no further approvals are required to undertake the secondary analyses proposed in this protocol. Findings will be published in peer-reviewed journal articles and presented at conferences. A comprehensive dissemination strategy is in place, integrated with patient and public involvement.

PROSPERO registration number CRD42015031227.

Strengths and limitations of this study

- This individual participant data (IPD) meta-analysis uses the INTERPRESS-IPD Collaboration (IPD from 24 international cohorts, originally created to explore the association between interarm differences in blood pressure (BP) and mortality risk), the largest known dataset to allow an in-depth exploration of the relationship between arm and leg systolic BP (SBP) and the role of leg SBP in cardiovascular risk estimation.
- An IPD approach maximises statistical power and allows a consistent approach toward all available data that cannot be achieved with study-level meta-analyses.
- Inclusion of a number of international cohorts in this IPD meta-analyses will maximise the generalisability of the findings.
- Methods of data collection and reporting of results vary between included cohorts and this is acknowledged as a limitation of the data. We are aware of other studies with arm and leg BP data that are not included in the INTERPRESS-IPD Collaboration. However, the dataset is large enough to allow robust analysis and sufficient subgroup and sensitivity analyses to answer questions that cannot be addressed by study-level meta-analyses.
- Patient and public involvement (PPI) activities have been, and will be, undertaken throughout every stage of this project and we include three PPI advisors and a PPI facilitator as coauthors.

INTRODUCTION

Blood pressure (BP) is normally measured on the upper arm, and all guidelines for the

diagnosis and treatment of high BP are based on such measurements.^{1–3} When brachial BP measurement is not possible, other measurement sites are required. Uncertainty over interpretation of non-brachial BP measurement may result in inaccurate BP estimates, leading to suboptimal management of hypertension, risking avoidable cerebrovascular or ischaemic cardiac events.⁴ In the clinical setting, this may be a temporary problem due, for example, to fractures, wounds, vascular access devices or during surgical procedures. However, for some people, there are permanent barriers to brachial BP measurement, such as amputation, bilateral lymphoedema (eg, after bilateral mastectomy for breast cancer) or phocomelia (eg, secondary to thalidomide).⁵ Brachial BP measurement may also be inaccurate, and difficult to self-administer, where there is altered muscle tone or hemiplegia following stroke.^{6,7} It is also unreliable in the presence of bilateral subclavian, axillary or brachial artery stenoses due to atheroma or arteritides.⁸ In any of these circumstances, measurement of BP in the leg is a suitable alternative for monitoring BP, diagnosing and treating hypertension. However, at present, only limited data exist to guide interpretation of the leg systolic BP (SBP) values.

Historically, ranges of 10–40 mm Hg have been suggested for the difference (ie, leg minus arm) between SBP measured in the arm and leg in healthy individuals.^{9,10} Recently, a systematic review and study level meta-analysis of observational studies were published examining this relationship.¹¹ Based on 44 included studies, totalling 9771 participants, ankle SBP was found to be 17.0 mm Hg (95% CIs 15.4 to 21.3 mm Hg) higher than arm BP in the general population; for diastolic BP, there was no difference. These findings suggested that a threshold of 155/90 mm Hg in the leg (equating to the National Institute for Health and Care Excellence (NICE) threshold of 140/90 mm Hg in the arm)³ might be used for diagnosing hypertension when ankle BPs are the only measurements available. However, significant statistical heterogeneity was observed in all analyses, which could not be explained in subgroup or sensitivity analyses according to cardiovascular disease history, cardiovascular disease risk, measurement method and device or methodological quality. Metaregression by age and arm SBP level was also uninformative.¹¹

Study-level aggregate meta-analyses are limited in the conclusions that can be drawn, because they combine studies with different patient characteristics (eg, age or coexisting disease), methodological choices (eg, posture in BP measurement or sequential vs simultaneous measurement) and analytical approaches. These limitations can potentially be overcome by obtaining the original individual participant data (IPD) from cohorts.¹² Such IPD meta-analyses, while time consuming, offer advantages, such as checking of modelling assumptions, analysing variables on continuous scales and the possibility of assessing for non-linear relationships.¹³ They offer the ability to uniformly adjust findings for other variables, thus potentially accounting and adjusting for

heterogeneity between findings in a way that study-level meta-analyses cannot.¹⁴

We propose to undertake IPD meta-analyses to answer the following research questions:

1. What is the mean difference, in the absence of peripheral arterial disease, between SBP measured in the arm and SBP measured in the leg in the same individuals?
2. To what extent do these differences vary according to patient characteristics and methods of measurement, and what are the impacts of cerebrovascular and cardiac diseases on the difference between arm and leg pressures?
3. Can a model be developed and validated to predict arm SBP, based on leg SBP measurements and other patient characteristics, to inform interpretation of individual leg SBP readings?
4. How does leg BP, in comparison with models based on arm BP, predict cardiovascular events and/or mortality?

METHODS AND ANALYSIS

Aims and objectives

This IPD meta-analysis has the following aims

1. To examine the relationship between arm and leg SBP, taking into account patient characteristics such as age, baseline BP and medical history.
2. To derive and validate a prediction model to permit estimation of an equivalent brachial SBP based on leg SBP measurements.
3. To determine the independent prognostic value of leg SBP in predicting cardiovascular events and mortality risk.

Data sources and description of the dataset

This study will use an observational cohort design, undertaking IPD meta-analyses of data held by the interarm BP difference (INTERPRESS-IPD) Collaboration, established to undertake IPD meta-analyses examining the independent contribution of interarm BP difference to prediction of mortality and cardiovascular events.¹⁵ The establishment of the Collaboration has been previously described.¹⁵ In brief, literature searches and author contacts were used to identify studies likely to hold records of BP in both arms. A subset of these studies measured Ankle–Brachial Index (ABI) at recruitment, thus providing data for arm and leg BPs.¹⁶ Individual data sharing agreements are in place with the lead authors of each participating study; their consent has been obtained for the proposed analyses and corresponding authors for each participating study will contribute to publications arising from these analyses. Core data, held for the primary INTERPRESS-IPD research outputs, will undergo additional cleaning and merging of relevant additional variables prior to combination into a new, expanded, single dataset.

The new Arm Based on LEg-BP (ABLE-BP) dataset will include 33 710 individual records from 14 European,

USA and African studies that measured both arm and leg BP. Participants in the dataset have a mean age of 58 years (range: 18–99 years), 45% are women and mean systolic/diastolic brachial BP is 135/80 mm Hg. In total, 20 191 (60 %) have hypertension (defined as a formal clinical diagnosis and/or on antihypertensive treatment), 4917 (15 %) have diabetes, 5474 (17 %) have pre-existing ischaemic heart disease and 1900 (6 %) have had a cerebrovascular event. Median follow-up period is 8.0 years, with 2811 (9 %) participants experiencing cardiovascular events or death and 621 (2 %) dying within 10 years. We will present tables including descriptors (eg, country, method of BP measurement, description of cohort) of each study to assess comparability and describe the dataset. A summary of the included studies and their characteristics is given in [table 1](#).

Outcomes

The primary outcome (systolic arm-leg BP difference) for the analyses will be defined as the lower leg posterior tibial artery BP minus the higher arm BP measured on the brachial artery. The coprimary outcome will be arm SBP predicted from leg BP. Primary analyses will use observed data only (see missing data—below).

Secondary outcomes are the prognostic value of leg BPs for prediction of cardiovascular events and mortality.

Quality assessment

The methodological quality and risk of bias for studies contributing data has been assessed using the Quality assessment In Prognostic Studies (QUIPS) score, modified for IPD analysis.¹⁷ These assessments will be used to inform sensitivity analyses focusing on the highest quality studies. This quality assessment covers domains on selection bias, attrition, and accuracy of measurement, analysis and confounding.

Participant selection

Participants with ankle or arm BP missing at recruitment will be excluded from the analyses. We will also exclude participants with a diagnosis of peripheral arterial disease, low ABI (<0.90) and those studies where participant entry criteria was based on selected ABI.

Statistical analysis

Descriptive analyses

Descriptive statistics will be used to describe participant characteristics at the study level, including age, sex, ethnic group, body mass index (BMI), arm and leg BP, and history of cardiovascular diseases (and risk factors). Data will be presented as means with SD, median with IQR or proportions.

Investigation of relationship between leg and arm BP

We will report the mean arm-leg differences for each study. These will be examined in a two-stage meta-analysis. Estimates of heterogeneity from these analyses will be used to determine whether to conduct a further one-stage analysis with study entered as a random or as a fixed effect.

We will explore cross-sectional relationships between arm and leg BP in univariable and multivariable models with all available data, using hierarchical linear regression. Estimates will be adjusted for age, sex, baseline BP, smoking status, serum cholesterol and medical history at recruitment. Recording of medication use varies across cohorts; we will perform secondary analyses that include use of specific classes of antihypertensive medication (eg, calcium channel blockers, renin-angiotensin system blockers) using data from only those studies that recorded the relevant information. Should drug use be a significant predictor of outcome when included with other significant variables, it will be retained in the models derived from these secondary analyses. Depending on the results of our quality assessment of primary studies, we will perform sensitivity analyses to include only those studies evaluated to be at low risk of bias. No further secondary or sensitivity analyses are planned.

Prediction modelling of arm BP using leg BP

Using a subset of participants with complete case data for candidate variables both identified above, and set a priori, we will model brachial SBP on leg SBP using random effects meta-analysis models. We will use one-stage and two-stage methods, and assess heterogeneity using the I^2 and τ^2 statistics. One-stage models will comprise hierarchical linear regression models (participants nested by study). Further models will investigate the association between arm-leg difference and participant characteristics (using a series of models with one characteristic per model). Predictor variables to be included a priori in the modelling will include age, sex, BMI, smoking status, ethnicity, diagnosis of diabetes, hypertension or any cardiovascular disease, total cholesterol and baseline ankle BP.

The predictive model for arm SBP will be developed using one-stage meta-analysis with hierarchical linear regression models, as described above. We will derive the model using a subset of the complete case data (derivation dataset) and validate the model using the remaining data (validation dataset).¹⁸ The primary studies will be allocated to the derivation or validation datasets such that both datasets include participants of both genders and reflect the geographical origin of the studies.

Prognostic modelling

Prognostic models based on leg SBP will be derived for all-cause and cardiovascular mortality and fatal or non-fatal cardiovascular events. Heterogeneity will be assessed using I^2 and τ^2 . We will aim to perform one-stage random effects time-to-event models based on flexible parametric models; should such models fail to converge, we will use fixed effect Cox proportional hazards models, stratified by study. Using the covariates described above, and again dividing the dataset into a derivation and validation cohort, we will derive and validate a suitable model. For prognostic modelling, we will exclude participants with any pre-existing cardiovascular disease.

Table 1 Characteristics of studies included in the Arm Based on LEg-BP (ABLE-BP) dataset

Study name	Period of patient recruitment/duration of trial	Sample size (n enrolled in study)	Country of origin	Eligibility criteria	Primary outcome measure	Blood pressure measurement methods	Intended maximum duration of follow-up	Definition of hypertension	Definition of diabetes	Definition of cardiovascular death and non-fatal cardiovascular event
Chicago Walking and Leg Circulation Study (WALCS) ³¹	1998–2000	440	USA	Patients without lower extremity peripheral artery disease who were recruited for the non-PAD comparator group.	Subclavian stenosis as a marker for total and cardiovascular disease mortality	Two sequences of BP readings recorded using a 12 cm pneumatic cuff and a hand held Doppler probe (Nicolet Vascular Pocket Dop II, Golden, Colo) with patient supine	Mean follow-up was 4.8 years.	Patient history or use of BP lowering therapy	Patient history or use of oral antidiabetic drugs and/or insulin	Cardiovascular death: any fatal cardiovascular cause. Non-fatal events: MI, stroke, TIA, coronary or peripheral revascularisation, congestive heart failure, PAD, angina
Epidemiology of dementia in Central Africa (EPIDEMCA) ³²	November 2011–December 2012	880	Central African Republic/ Republic of Congo	Males and females, aged ≥65 years living in areas of Central African Republic and Republic of Congo	Diagnosis of dementia and Alzheimer's disease and associated risk factors	Two sequences of BP measurements recorded using standard mercury sphygmomanometer, as part of ABI protocol with patients supine. BP rounded to nearest 5 mm Hg	2–3 years	Self-reported BP lowering treatment; SBP ≥140 mm Hg or DBP ≥90 mm Hg	Self-reported or blood glucose >126 mg/dL fasting or >200 mg/dL in non-fasting	Cardiovascular death: stroke, MI or other cardiovascular or cerebrovascular diseases—based on interview of relatives during verbal autopsy at follow-up. Non-fatal events: stroke, MI, other heart disease
Fuencarral Health Center ³³	2003–2004	1102	Spain	Males and females, aged 60–79 years, with no known PAD	Low ABI and incidence of death due to cardiovascular causes	BP measured sequentially with Doppler 8-MHz probe (Hadedco, Kawasaki, Japan) and calibrated mercury sphygmomanometer with patient supine	Mean follow-up 49.8 months	SBP ≥140 mm Hg, DBP ≥90 mm Hg or use of BP lowering treatment	Baseline glucose ≥126 mg/dL (>7 mmol/L) on 2 occasions or use of antidiabetic agents	Cardiovascular death: Fatal stroke, MI, sudden death without other cause, death after vascular surgery or procedure, death attributed to heart failure, bowel or limb infarction, any other death not categorically attributed to a non-vascular cause Non-fatal events: MI, stroke or cardiovascular event
Heinz Nixdorf Recall Study ³⁴	2000–2003	4617	Germany	Males and females, aged 45–74 years, in an unselected urban population from the Ruhr area	Coronary artery calcium as predictor for fatal and non-fatal MI. Secondary endpoints included ABI as a stroke predictor factors	BP measured sequentially using Doppler probe (Logidop, Kranzbühler, Germany) with patients supine	Mean follow-up: 109 months	SBP >140 mm Hg or DBP >90 mm Hg	Existing diagnosis or use of antidiabetic medication	Cardiovascular death or non-fatal event: first occurrence of MI based on symptoms, ECG signs, and enzymes, supported by necropsy if fatal

Continued

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Table 1 Continued

Study name	Period of patient recruitment/duration of trial	Sample size (n enrolled in study)	Country of origin	Eligibility criteria	Primary outcome measure	Blood pressure measurement methods	Intended maximum duration of follow-up	Definition of hypertension	Definition of diabetes	Definition of cardiovascular death and non-fatal cardiovascular event
Invecchiare in Chianti ³⁵ (InCHIANTI)	August 1998–March 2000	1091	Italy	Males and females, aged ≥65 years, living in Greve and Bagno	Physiological factors influencing walking ability	Single pair of sequential brachial BP readings using standard mercury sphygmomanometer, with patients supine. BP rounded to nearest 5 mm Hg. Posterior tibial arteries measured twice with a handheld Doppler stethoscope (Parks model 41-A; Parks Medical Electronics, Aloha, Ore).	N/S	Self-reported, existing, recorded diagnosis or use of BP lowering medication or SBP ≥140 mm Hg or DBP ≥90 mm Hg	Self-reported, existing recorded diagnosis, or use of antidiabetic medication, or fasting glucose >7.0 mmol/L	Cardiovascular death: not defined. Non-fatal events: diagnosis of heart disease, MI or angina, stroke or TIA
Lifestyle Interventions and Independence for Elders (LIFE) study ³⁶	2010–2011/2.6 years	1588	USA	Ambulant community dwelling individuals, aged 70–89 years with a sedentary lifestyle (<20 min per week physical activity)	Major mobility disability Secondary: association between ABI and cognitive function	Two pairs of sequential measurements recorded in each arm using handheld Doppler, with patients supine	2 years	Self-reported or measurement	Self-reported	Cardiovascular fatal or non-fatal events: MI, angina, stroke or TIA, carotid artery disease, congestive heart failure or PAD requiring hospitalisation, outpatient revascularisation for PAD, ruptured abdominal aortic aneurysm
Improving Intermediate Risk management (MARK) study ³⁷	N/S	2490	Spain	Males and females living in 3 regions of Spain, aged 35–74 years. Free of atherosclerotic disease, with an intermediate cardiovascular risk (10-year coronary risk of 5%–15% or vascular death risk of 3%–5%) selected at random	Incidence of vascular events	Three pairs of BP measurements in each arm, using an OMRON 705, with patients seated. Legs measured with Vasera device VS-1500 (Fukuda Denshi)	10 years	Patient reported, or use of BP lowering medications or SBP ≥140 mm Hg or DBP ≥90 mm Hg	Patient reported, or use of antidiabetic treatment or fasting glucose ≥126 mg/dL	Cardiovascular death: not defined Non-fatal events: stroke or TIA, MI, angina, or revascularisation procedure

Continued

Table 1 Continued

Study name	Period of patient recruitment/duration of trial	Sample size (n enrolled in study)	Country of origin	Eligibility criteria	Primary outcome measure	Blood pressure measurement methods	Intended maximum duration of follow-up	Definition of hypertension	Definition of diabetes	Definition of cardiovascular death and non-fatal cardiovascular event
Action for Health in Diabetes (Look AHEAD) ³⁸	June 2001–March 2004	339	USA	Overweight and obese individuals with type 2 diabetes aged 45–76 years, and had a body mass index, 25 kg/m ² , or ≥27 kg/m ² if taking insulin	A composite cardiovascular outcome: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalised angina	Two pairs of sequential BP measurements recorded in each arm, using continuous wave Doppler with a standard mercury sphygmomanometer, with patients supine	4–5 years follow-up	SBP ≥140 mm Hg, ≥DBP > 90 mm Hg or taking BP lowering medication	Self-reported verified from medical records, current treatment, or fasting glucose of ≥126 mg/dL	Cardiovascular death: MI, congestive heart failure, death after cardiovascular intervention, surgery or due to arrhythmia, stroke, presumed cardiovascular death, rapid unexplained cardiovascular death. Non-fatal events: stroke, MI, angina, coronary artery bypass grafting or percutaneous coronary intervention, congestive heart failure, carotid endarterectomy, peripheral arterial bypass or angioplasty
Multi Ethnic Study of Atherosclerosis (MESA) ³⁹	2000–2002	6770	USA	Males and females, aged 45–84 years, free of clinical cardiovascular diagnoses at baseline	Association of subclavian stenosis with markers of cardiovascular disease	Single pair of sequential BP measurements, using hand-held Doppler instrument and 5-mHz probe, with patients supine	N/S	Self-reported history with use of BP lowering medications, or SBP ≥140 mm Hg or DBP ≥90 mm Hg	Fasting blood glucose ≥126 mg/dL or use of oral hypoglycaemic agents or insulin	Cardiovascular death: death due to atherosclerotic coronary heart disease, stroke, other cardiovascular disease. Non-fatal events: stroke, TIA, MI, angina, revascularisation procedure
San Diego Population Study ⁴⁰	1994–1998	2388	USA	Males and females, aged 29–91 years, attending a clinic for assessment of PAD and venous disease	Prevalence of PAD	Two pairs of BP measurements, using a continuous-wave Doppler ultrasound, with patients supine	N/S	SBP ≥140 mm Hg or DBP ≥90 mm Hg or use of BP lowering medications	Self-reported or use of antidiabetic medications	Cardiovascular death: not defined Non-fatal events: MI, stroke, angina, coronary angioplasty or bypass graft, or carotid endarterectomy

Continued

Table 1 Continued

Study name	Period of patient recruitment/duration of trial	Sample size (n enrolled in study)	Country of origin	Eligibility criteria	Primary outcome measure	Blood pressure measurement methods	Intended maximum duration of follow-up	Definition of hypertension	Definition of diabetes	Definition of cardiovascular death and non-fatal cardiovascular event
Second Manifestations of Atrial disease (SMART) study ⁴¹	January 2002–February 2014	7600	The Netherlands	Males and females, aged 18–80 years, referred to University Medical Center Utrecht, for treatment of clinically manifest vascular disease or cardiovascular risk factors	3 point MACE (combination of non-fatal myocardial infarction, non-fatal stroke and death from vascular disease), total mortality and vascular mortality	Single pair of sequential BP measurements, using a Vasoguard Doppler probe, with patients supine	Mean follow-up: 5.9 years	Blood pressure >140/90 mm Hg at baseline or the use of blood pressure lowering medication.	Recorded diagnosis, self-reported diagnosis, use of blood glucose lowering medication, or fasting glucose >7 mmol/L at recruitment combined with initiation of glucose lowering medication within first year of follow-up.	Cardiovascular death: Death from stroke, MI, congestive heart failure, rupture of abdominal aortic aneurysm or vascular death from other causes
Surrogate markers for Micro- and Macrovascular hard endpoints as Innovative diabetes tools (SUMMIT) ⁴²	November 2010–June 2013	334	England	Adults over 18 with and without diabetes and/or cardiovascular disease		6 pairs of simultaneous BP readings using two Omron 705 devices swapped after 3 readings, with patients supine	N/S	Self-reported history of hypertension	HbA1c≥48 mmol/mol	Cardiovascular death: fatal MI
Viborg Women Cohort (VWoCo) ⁴³	October 2011–January 2013	1428	Denmark	Females born in 1936, 1941, 1946 and 1951 living in the Municipality of Viborg, Denmark	Presence of cardiovascular disease and diabetes mellitus	One pair of simultaneous BP readings, using Omron M2 devices, with patients supine, rounded to nearest 2 mm Hg	Median follow-up 3.3 years	SBP ≥140 mm Hg or DBP ≥90 mm Hg	HbA1c≥48 mmol/mol	Cardiovascular death: fatal event as below
Vietnam Experience Study ⁴⁴	1986	4394	USA	Male US army veterans who participated in the Vietnam war	Interarm differences, all-cause and cardiovascular mortality	Two pairs of sequential BP measurements, using standard mercury sphygmomanometer, with patients seated	15 years	SBP ≥140 mm Hg, DBP ≥90 mm Hg or use of BP lowering medication	Fasting plasma glucose ≥7.0 mmol/L and/or use of medication for diabetes	Cardiovascular death: death due to major cardiovascular disease.

ABI, ankle-brachial index; BP, blood pressure; DBP, diastolic blood pressure; ECG, Electrocardiogram; IHD, ischaemic heart disease; N/S, not stated; PAD, peripheral arterial disease; SBP, systolic BP; TIA, transient ischaemic attack.

Using internationally recognised 10-year risk scores, such as the European Systematic COronary Risk Evaluation (SCORE) and Atherosclerotic Cardiovascular Disease (ASCVD) pooled cohort equations, we will compare the outcome of such cardiovascular risk scores using arm based on leg SBP data with the *actual* arm SBP data.^{19–22} Besides their wide use in clinical practice, these two scores have been selected to assess two different outcomes, as SCORE predicts cardiovascular mortality, while ASCVD predicts fatal and non-fatal cardiovascular events (cardiovascular death, non-fatal MI and stroke). Model goodness of fit will be compared using the likelihood ratio test, the Akaike Information Criterion,²³ and for time-to-event models, the Harrell's C statistic.

Missing data and sensitivity analyses

For all included studies, the primary analyses will use observed data only. Participants from other cohorts included within the INTERPRESS-IPD Collaboration lack leg BP data but do have brachial BP measurements and ABIs. We will explore whether accurate back-calculation of leg pressures is feasible using these data. To achieve this, we will establish a clear understanding of the study formulae used to derive ABI, including discussion with authors as necessary. We will then trial this approach using datasets that do contain leg pressures to confirm validity. If feasible, we will back-calculate missing leg SBPs and add these data to the observed data for sensitivity analyses to check the primary models. We will also perform sensitivity analyses incorporating height into the final models, where available. Further sensitivity analyses, using multiple imputation of arm and/or leg SBP and participant data for the one-stage meta-analyses where arm-leg or arm SBP is the outcome, and for the time-to-event analyses will also be undertaken. The results of these models will be compared with the primary outcome models using observed data only. Finally, we will repeat the primary analyses excluding studies deemed to be of low or moderate quality based on modified QUIPS scores.

Publication and inclusion bias

Inclusion bias will be assessed by comparing our pooled estimate of the mean arm—leg SBP difference for studies included in the ABLE-BP analyses with studies using sequential BP measurement methods in our previous study-level systematic review using a two-stage meta-analysis.¹¹ Publication bias will not be assessed; we believe that there is limited potential for publication bias, as the primary studies from which we derive data were not originally designed to compare arm and leg BPs. Although we are performing secondary analyses in a subset of an established dataset (INTERPRESS-IPD Collaboration), which is an efficient and cost-effective approach, we must acknowledge that the INTERPRESS-IPD dataset was not established for the purpose of defining the arm-leg SBP relationship and therefore there is a possibility that other data exist that fall outside the scope of the original search terms.

Patient and public involvement

The development of this protocol has had considerable patient and public involvement (PPI). Prior to funding, a draft was reviewed by three public advisors improving the overall clarity in general, and in specific areas, such as focussing the research questions on aspects of arm and leg BP that interest users. We convened two prefunding PPI workshops to raise awareness about involvement in systematic reviews and gain critical feedback for the project. This feedback resulted in a clearer definition of the population being studied, greater clarity about benefits for patients and reinforcement of our user dissemination plans. We have established a PPI advisory group for the project, led by KB (an academic PPI facilitator) and comprising one stroke survivor and two Thalidomide Trust beneficiaries; they will shape the research by fully participating in quarterly management meetings. The group have contributed towards drafting this protocol and the plain English abstract. We plan two key workshops to ensure that the review findings reach the end user in an accessible way. First, a summary writing workshop with the PPI advisory group to achieve a clear plain language summary and to coproduce a dissemination plan targeted at patients and the public. Second, we will convene a larger public event on the subject of understanding cardiovascular risk, within which the findings of this research can be presented in context.

Ethics and dissemination

This is a secondary analysis of anonymised IPD which has been obtained from studies where participants have already given consent and approval to participate (see 'ethics approval and patient consent for publication' declaration). We have sought written permission for use of IPD from each individual study lead investigator included in the INTERPRESS-IPD Collaboration. We will therefore not seek further ethical approval to undertake these analyses.

The study will be reported in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of IPD statement.²⁴ Findings will be published as open access articles in high-impact peer-reviewed journals and presented at international conferences. We will seek to inform national, European and global developers of clinical guidelines, including the UK NICE guidance, National Health Service commissioners, the British and Irish Hypertension Society and local healthcare providers. We will coproduce a targeted dissemination plan for the public and specific patient groups and our funding charities, in conjunction with the project PPI advisory group. We also plan to undertake a public dissemination event for patients, clinicians and providers or commissioners regarding the importance of, and relationship between, arm and leg BPs and understanding the importance of BP measurement in cardiovascular risk estimation—the findings from this study will be presented. The INTERPRESS-IPD Collaboration is a large, international dataset with both arm and leg BPs,

and is available for further research activity in this area in the future.

DISCUSSION

There are 1.2 million stroke survivors living in the UK (State of the Nation Stroke statistics—January 2017: The Stroke Association) and 75% of these individuals report weakness of upper limb function that interferes with activities of daily living.²⁵ Self-monitoring and self-titration of BP lowering treatment achieves lower BPs in people at high risk of new or recurrent stroke.²⁶ However, this is either impossible or difficult for many stroke survivors with significantly impaired upper limb function, and for individuals with other barriers to BP measurement in the arm. Data suggest a prevalence of 12–13 individuals per 100 000 population have upper limb prostheses in the UK and Norway.^{27 28} In addition, over 1700 amputations higher than wrist level occur annually in the UK.²⁹ Congenital upper limb deformities are also important; for example, the UK Thalidomide Trust has 460 beneficiaries who are now aged in their late 50s. Hypertension is a particular concern in this cohort, and over half of beneficiaries report upper limb damage.³⁰ Taking these data together, we conservatively estimate that between 6000 and 10 000 adults may be living with significant congenital or acquired upper limb loss in the UK. As a population, these individuals are in particular need of accurate estimates of BP to understand and mitigate their cardiovascular risk, stroke being an important avoidable consequence.

Thus, barriers to accurate upper arm BP measurement exist for a substantial minority of the UK population, and corresponding proportions across other countries. Whenever circumstances require leg BP measurement, it is important to be able to interpret the readings correctly. This is the focus of our proposal. Our data originate from cohorts across Europe, North America and Africa; therefore, we expect our findings to be applicable across the globe.

To date, estimates suggest either a minimum difference of 15 mm Hg in SBPs between arm and leg, or a conversion factor of $\times 0.88$, as a rule of thumb.^{5 11} This study aims to provide the first evidence-based method for estimating individual brachial SBP and cardiovascular risk from leg SBP measurements. Our findings will support clinicians and patients in detecting and managing hypertension more effectively where leg measurements are required.

Author affiliations

¹Primary Care Research Group, University of Exeter, Exeter, UK

²Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

³NIHR CLAHRC South West Peninsula (PenCLAHRC), University of Exeter, Exeter, UK

⁴Patient and Public Involvement Advisor, Exeter, UK

⁵Department of Cardiology, Stockport NHS Foundation Trust, Stockport, UK

⁶Royal National Orthopaedic Hospital Stanmore, Stanmore, UK

⁷Mid Devon Medical Practice, Exeter, UK

⁸Institute of Clinical Sciences, University of Birmingham, Birmingham, UK

⁹Department of Cardiology, Centre Hospitalier Universitaire de Limoges, Limoges, France

Twitter James P Sheppard @jamesheppard48 and Christopher E Clark @INTERPRESS_IPD

Collaborators The following collaborating authors contributed data to the original INTERPRESS-IPD Collaboration and the subsequent ABLE-BP project: Vietnam Experience Study: James White; INCHIANTI: Luigi Ferrucci; Heinz-Nixdorf Recall Study: Raimund Erbel; SMART: Jan Westerink; San Diego Population Study: Michael Criqui; Fuencarral Health Center: Carlos Lahoz; EPIDEMCA: Maëlen Guerchet; MESA: Matthew Allison; LIFE & WALCS: Mary McDermott; Look AHEAD: Mark Espeland; ViWoCo: Marie Dahl; SUMMIT: Angela Shore; MARK Study: Rafael Ramos Blanes

Contributors This protocol was first drafted by STJM, CEC, FCW, JPS, UM, LF, KB and VA, then revised and edited by all authors, including HS, PW, PSL, RB and JF. The final manuscript has been read, reviewed and approved by all authors.

Funding The INTERPRESS-IPD Collaboration was established with a grant from the NIHR Research for Patient Benefit programme (award/grant number: PB-PG-0215-36009). This current project is supported by the Stroke Association (award/grant number: SA PG 19/100043) and by the Thalidomide Trust (award/grant number: not applicable).

Disclaimer The views expressed are those of the authors and not necessarily those of the Stroke Association, the Thalidomide Trust, the NIHR, the NHS or the Department of Health.

Competing interests CEC has been loaned a bilateral blood pressure monitor for unrestricted evaluation by Microlife AG, and has received honoraria from Bayer AG. No company has had, or will have, any involvement in the design or conduct of this study.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Sinead T J McDonagh <http://orcid.org/0000-0002-0283-3095>

James P Sheppard <http://orcid.org/0000-0002-4461-8756>

Kate Boddy <http://orcid.org/0000-0001-9135-5488>

Christopher E Clark <http://orcid.org/0000-0002-7526-3038>

REFERENCES

- Whelton PK, Carey RM, Aronow WS. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines. *J Am Coll Cardiol* 2017.
- Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021–104.
- National Institute for Health and Clinical Excellence. *Hypertension: the clinical management of primary hypertension in adults*, CG127. London: National Institute for Health and Clinical Excellence, 2011.
- Hwang KO, Aigbe A, Ju H-H. Barriers to accurate blood pressure measurement in the medical office. *J Prim Care Community Health* 2018;9:215013271881692.
- Shiga T, Shimbo T, Yoshizawa A. Multicenter investigation of lifestyle-related diseases and visceral disorders in thalidomide embryopathy at around 50 years of age. *Birth Defects Res A Clin Mol Teratol* 2015;103:787–93.
- Dewar R, Sykes D, Mulkerrin E, et al. The effect of hemiplegia on blood pressure measurement in the elderly. *Postgrad Med J* 1992;68:888–91.

- 7 Maduagwu SM, Umeonwuka CI, Mohammad HH, *et al.* Reference arm for blood pressure measurement in stroke survivors. *Middle East J Rehabil Health Stud* 2018;5:e62368.
- 8 Aboyans V, Kamineni A, Allison MA, *et al.* The epidemiology of subclavian stenosis and its association with markers of subclinical atherosclerosis: the multi-ethnic study of atherosclerosis (MESA). *Atherosclerosis* 2010;211:266–70.
- 9 Pascarelli EF, Bertrand CA. Comparison of blood pressures in the arms and legs. *N Engl J Med* 1964;270:693–8.
- 10 Stewart HJ, Newman AA, Evans WF. Levels of blood pressure in both arms and legs in normal subjects and patients suffering from certain diseases. *Am J Med* 1946;1:451–63.
- 11 Sheppard JP, Albasri A, Franssen M, *et al.* Defining the relationship between arm and leg blood pressure readings: a systematic review and meta-analysis. *J Hypertens* 2019;37:660–70.
- 12 Debray TPA, Damen JAAG, Snell KIE, *et al.* A guide to systematic review and meta-analysis of prediction model performance. *BMJ* 2017;356:i6460.
- 13 Tudur Smith C, Marcucci M, Nolan SJ, *et al.* Individual participant data meta-analyses compared with meta-analyses based on aggregate data. *Cochrane Database Syst Rev* 2016;9:MR000007.
- 14 Abo-Zaid G, Sauerbrei W, Riley RD. Individual participant data meta-analysis of prognostic factor studies: state of the art? *BMC Med Res Methodol* 2012;12:56.
- 15 Clark CE, Boddy K, Warren FC, *et al.* Associations between interarm differences in blood pressure and cardiovascular disease outcomes: protocol for an individual patient data meta-analysis and development of a prognostic algorithm. *BMJ Open* 2017;7:e016844.
- 16 Aboyans V, Criqui MH, Abraham P, *et al.* Measurement and interpretation of the Ankle-brachial index. *Circulation* 2012;126:2890–909.
- 17 Hayden JA, van der Windt DA, Cartwright JL, *et al.* Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280.
- 18 Altman DG, Vergouwe Y, Royston P, *et al.* Prognosis and prognostic research: validating a prognostic model. *BMJ* 2009;338:b605.
- 19 Hippisley-Cox J, Coupland C, Vinogradova Y, *et al.* Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336:1475–82.
- 20 Goff DC, Lloyd-Jones DM, Bennett G, *et al.* 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American heart association task force on practice guidelines. *Circulation* 2014;129:S49–73.
- 21 D'Agostino RB, Vasan RS, Pencina MJ, *et al.* General cardiovascular risk profile for use in primary care: the Framingham heart study. *Circulation* 2008;117:743–53.
- 22 Conroy R *et al.* Estimation of ten-year risk of fatal cardiovascular disease in Europe: the score project. *Eur Heart J* 2003;24:987–1003.
- 23 Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr* 1974;19:716–23.
- 24 Stewart LA, Clarke M, Rovers M, *et al.* Preferred reporting items for a systematic review and meta-analysis of individual participant data. *JAMA* 2015;313:1657–65.
- 25 Lawrence ES, Coshall C, Dundas R, *et al.* Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. *Stroke* 2001;32:1279–84.
- 26 McManus RJ, Mant J, Haque MS. Effect of self-monitoring and medication Self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical TrialSelf-monitoring and Self-titration for HypertensionSelf-monitoring and Self-titration for hypertension. *JAMA* 2014;312:799–808.
- 27 Kyberd PJ, Beard DJ, Morrison JD. The population of users of upper limb prostheses attending the Oxford limb fitting service. *Prosthet Orthot Int* 1997;21:85–91.
- 28 Østlie K, Skjeldal OH, Garfelt B, *et al.* Adult acquired major upper limb amputation in Norway: prevalence, demographic features and amputation specific features. A population-based survey. *Disabil Rehabil* 2011;33:1636–49.
- 29 Cordella F, Ciancio AL, Sacchetti R, *et al.* Literature review on needs of upper limb prosthesis users. *Front Neurosci* 2016;10:209–09.
- 30 Newbronner E, Glendinning C, Atkin K, *et al.* The health and quality of life of thalidomide survivors as they age – evidence from a UK survey. *PLoS One* 2019;14:e0210222.
- 31 McDermott MM, Greenland P, Liu K, *et al.* Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA* 2001;286:1599–606.
- 32 Guerchet M, Mbelesso P, Ndamba-Bandzouzi B, *et al.* Epidemiology of dementia in central Africa (EPIDEMCA): protocol for a multicentre population-based study in rural and urban areas of the central African Republic and the Republic of Congo. *Springerplus* 2014;3:338.
- 33 Lahoz C, Barrionuevo M, Garcia-Fernandez T. Cardiovascular morbidity-mortality associated to ankle-brachial index in the general population. [Spanish]. *Revista Clinica Espanola* 2014;214:1–7.
- 34 Erbel R, Möhlenkamp S, Moebus S, *et al.* Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the heinz Nixdorf recall study. *J Am Coll Cardiol* 2010;56:1397–406.
- 35 Clark CE, Thomas D, Llewellyn D. Inter-arm blood pressure and risk of cognitive decline in the elderly. *Br J Gen Pract* 2020.
- 36 Espeland MA, Newman AB, Sink K, *et al.* Associations between Ankle-brachial index and cognitive function: results from the lifestyle interventions and independence for elders trial. *J Am Med Dir Assoc* 2015;16:682–9.
- 37 Martí R, Parramon D, García-Ortiz L, García-Regalado N, García-Gil M, *et al.* Improving intermediate risk management. mark study. *BMC Cardiovasc Disord* 2011;11:61.
- 38 Espeland MA, Beavers KM, Gibbs BB, *et al.* Ankle-brachial index and inter-artery blood pressure differences as predictors of cognitive function in overweight and obese older adults with diabetes: results from the action for health in diabetes movement and memory study. *Int J Geriatr Psychiatry* 2015;30:999–1007.
- 39 Bild DE *et al.* Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871–81.
- 40 Wassel CL, Loomba R, Ix JH, *et al.* Family history of peripheral artery disease is associated with prevalence and severity of peripheral artery disease: the San Diego population study. *J Am Coll Cardiol* 2011;58:1386–92.
- 41 Kranenburg G, Spiering W, de Jong PA, *et al.* Inter-arm systolic blood pressure differences, relations with future vascular events and mortality in patients with and without manifest vascular disease. *Int J Cardiol* 2017;244:271–6.
- 42 Clark CE, Casanova F, Gooding K. Inter-arm blood pressure difference and arterial stiffness. *J Hyperten* 2014;32:e30.
- 43 Dahl M, Frost L, Søgaard R, *et al.* A population-based screening study for cardiovascular diseases and diabetes in Danish postmenopausal women: acceptability and prevalence. *BMC Cardiovasc Disord* 2018;18:20.
- 44 White J, Mortensen LH, Kivimäki M, *et al.* Interarm differences in systolic blood pressure and mortality among US army veterans: aetiological associations and risk prediction in the Vietnam experience study. *Eur J Prev Cardiol* 2014;21:1394–400.