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# 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



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# 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

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# 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 to brachial measurement where the latter is impractical, due to injury or disability. Limited data exist to guide interpretation of leg BP values for hypertension diagnosis and treatment; study-level systematic review findings suggest that, on average, systolic BP (SBP) is 17 mmHg higher in the leg than the arm. However, uncertainty about the applicability of this figure in routine clinical practice remains, due to substantial heterogeneity between previous studies.

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 meta-analyses using arm and leg SBP measurements for 38,795 individuals from 15 studies within the 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. Findings will be published in peer-reviewed journal articles and presentations at international conferences. A comprehensive dissemination strategy is in place, integrated with patient and public involvement, to translate findings into practice.

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## Plain English Abstract

Blood pressure is normally measured on the arm, but sometimes this is not possible due to stroke-related arm problems, missing arms (e.g. from birth, injury or surgical removal) or an arm disability. Blood pressure can be measured in the leg instead, however, leg readings are generally higher than in the arms. Guidance for blood pressure treatment is based on arm blood pressure readings only, so doctors and nurses cannot use this guidance to treat people who have leg blood pressure measurements.

This study aims to find a way to predict arm blood pressure using leg blood pressure, and to understand how leg blood pressure can be used to predict health outcomes.

We have collected arm and leg blood pressure readings from 38,795 people, from 15 completed studies around the world. We will use this data to investigate: (i) the relationship between blood pressures measured in the arm and leg in the same person; (ii) whether leg blood pressure and other patient characteristics (e.g. age) predict arm blood pressure; and (iii) how leg blood pressure predicts health events, such as heart attacks and strokes, and death.

Results from this study will provide people who cannot have arm blood pressure measurements with an accurate estimate of arm pressure from leg blood pressure so that doctors and nurses can interpret and apply current treatment guidelines appropriately. Working with our patient and public advisory group, we will make our findings widely available to other researchers, healthcare professionals and the public.

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## 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 inter-arm 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 co-authors.

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## 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 sub-optimal 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 (e.g. after bilateral mastectomy for breast cancer) or phocomelia (e.g. 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 to 40 mmHg have been suggested for the difference (i.e. 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 was published examining this relationship.[11] Based on 44 included studies, totalling 9,771 participants, ankle SBP was found to be 17.0 mmHg [95 % confidence intervals (CI) 15.4 to 21.3 mmHg] higher than arm BP in the general population; for diastolic BP there was no difference. These findings suggested that a threshold of 155/90 mmHg in the leg [equating to the National Institute for Health and Care Excellence (NICE) threshold of 140/90 mmHg 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

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history, cardiovascular disease risk, measurement method and device or methodological quality. Meta-regression 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 (for example, age or co-existing disease), methodological choices (for example, posture in BP measurement or sequential versus 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, whilst time consuming, offer advantages, such as checking of modelling assumptions, analysing variables on continuous scales and the possibility of assessing for non-linear relationships. 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.[13]

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?

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# 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 Inter-arm BP difference (INTERPRESS-IPD) Collaboration, established to undertake IPD meta-analyses examining the independent contribution of inter-arm BP difference to prediction of mortality and cardiovascular events.[14] The establishment of the Collaboration has been previously described.[14] 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.[15] 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 ABLE-BP dataset will include 38,795 individual records from 15 European, US and African studies that measured both arm and leg BP. Participants in the dataset have a mean age of 59 years (range: 18 to 99 years), 53 % are female and mean systolic/diastolic brachial BP is 136/80 mmHg. In total, 22,446 (58 %) have hypertension (defined as a formal clinical diagnosis and/or on

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antihypertensive treatment), 5,467 (14 %) have diabetes and 6,482 (17 %) have pre-existing ischaemic heart disease or stroke. Median follow-up period is 6.4 years, with 3,557 (9 %) participants experiencing cardiovascular events and 3,052 (8 %) dying within 10 years. We will present tables including descriptors (for example, 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 are 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 co-primary 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.[16] 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 and low ABI (< 0.90).

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## 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 standard deviation, median with interquartile ranges, or proportions.

### *Investigation of relationship between leg and arm blood pressure*

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. As part of planned subgroup analyses, we will also test classes of drugs, and, if significant, they may be entered into final models.

### *Prediction Modelling of arm blood pressure using leg blood pressure*

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 $tau^2$ 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.

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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).[17] 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 $tau^2$. 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.

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.[18-21] 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[22], 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 ankle-brachial indices. 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

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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 the mean arm – leg SBP difference for studies included in the analyses with studies in our previous study-level systematic review.[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.

## 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 toward drafting this protocol and the plain

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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 co-produce 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. 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 Individual Participant Data (PRISMA-IPD) statement. 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, NHS commissioners, the British and Irish Hypertension Society and local healthcare providers. We will co-produce 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 United Kingdom (UK; State of the Nation Stroke statistics - January 2017: The Stroke Association) and 75 % of these individuals report weakness of

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upper limb function that interferes with activities of daily living.[23] Self-monitoring and self-titration of BP lowering treatment achieves lower BPs in people at high risk of new or recurrent stroke.[24] 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 to 13 individuals per 100,000 population have upper limb prostheses in the UK and Norway.[25 26] In addition, over 1,700 amputations higher than wrist level occur annually in the UK.[27] 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.[28] Taking these data together, we conservatively estimate that between 6,000 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 mmHg in SBPs between arm and leg, or a conversion factor of x 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.

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## 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.

## Contributors

This protocol was first drafted by SM, CEC, FCW, JS, UM, KB and VA, then revised and edited by all authors. The final manuscript has been read and reviewed by all authors.

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

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## 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.

## Ethics approval and patient consent for publication

Not required.

## Provenance and peer review

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## Table 1 – characteristics of studies included in the ABLE-BP dataset

| Study name | Period of patient recruitment /Duration of trial | Sample size | 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| Aspirin in Asymptomatic Atherosclerosis (AAA)[29] | April 1998-October 2008 | 3334 | Scotland | Males and females, aged 50-75 years, living in central Scotland, free of clinical cardiovascular disease with an ABI < 0.95 | Initial fatal or non-fatal coronary event or stroke or revascularisation | Single sequence of BP readings using a Doppler probe (Huntleigh Healthcare, Cardiff) and aneroid desk sphygmomanometer (Accoson;A.C. Cossor Ltd, London, UK) with patient supine | 5 years with extended follow-up of 4.5 years. Mean 8.2 years | N/S | Self-reported diabetes | *Cardiovascular death*: Definite or probable fatal MI, death due to IHD, or fatal stroke due to infarction.<br><br>*Non-fatal events*: MI, stroke or TIA, coronary or peripheral revascularisation. angina, PAD |
| Chicago Walking and Leg Circulation Study (WALCS)[30] | 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.<br><br>*Non-fatal events*: MI, stroke, TIA, coronary or peripheral revascularisation, congestive heart failure, PAD, angina |
| Epidemiology of dementia in Central Africa (EPIDEMCA)[31] | 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 mmHg | 2-3 years | Self-reported BP lowering treatment; SBP ≥140 mmHg or DBP ≥90 mmHg | 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[32] | 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 (Hadeco, Kawasaki, Japan) and calibrated mercury sphygmomanometer with patient supine | Mean follow-up 49.8 months | SBP ≥140 mmHg, DBP ≥90 mmHg 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 |

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| Study name | Period of patient recruitment /Duration of trial | Sample size | 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | categorically attributed to a non-vascular cause<br>*Non-fatal events*:<br>MI, stroke or cardiovascular event |
| Heinz Nixdorf Recall Study[33] | 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, Kranzbuhler, Germany) with patients supine | Mean follow up: 109 months | SBP ≥140mmHg or DBP ≥90mmHg | Existing diagnosis or use of anti-diabetic medication | *Cardiovascular death or non-fatal event:*<br>First occurrence of MI based on symptoms, ECG signs, and enzymes, supported by necropsy if fatal |
| Invecchiare in Chianti (InCHIANTI)[34] | 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 mmHg.<br>Posterior tibial arteries measured twice with a handheld Doppler stethoscope (Parks model 41-A; Parks Medical Electronics, Inc, Aloha, Ore). | N/S | Self-reported, existing, recorded diagnosis, or use of BP lowering medication or SBP ≥140 mmHg or DBP ≥90 mmHg | Self-reported, existing recorded diagnosis, or use of anti-diabetic medication, or fasting glucose >7.0 mmol/L | *Cardiovascular death:*<br>Not defined.<br>*Non-fatal events:*<br>Diagnosis of heart disease, MI or angina, stroke or TIA |
| Lifestyle Interventions and Independence for Elders (LIFE) study[35] | 2010-2011/ 2.6 years | 1588 | USA | Ambulant community dwelling individuals, aged 70-89 years with a sedentary lifestyle (<20min per week physical activity) | Major mobility disability<br><br>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:*<br>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[36] | N/S | 2490 | Spain | Males and females living in 3 regions of Spain, aged 35-74 years. Free of | Incidence of vascular events | Three pairs of BP measurements in each arm, using an OMRON 705, with patients | 10 years | Patient reported, or use of BP lowering medication or SBP | Patient reported, or use of antidiabetic treatment or | *Cardiovascular death:*<br>not defined<br><br>*Non-fatal events*: |

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| Study name | Period of patient recruitment /Duration of trial | Sample size | 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | atherosclerotic disease, with an intermediate cardiovascular risk (10-year coronary risk of 5-15% or vascular death risk of 3-5%) selected at random | | seated. Legs measured with Vasera device VS-1500® (Fukuda Denshi) | | ≥140mmHg or DBP ≥90 mmHg | fasting glucose ≥ 126 mg/dL | Stroke or TIA, MI, angina, or revascularisation procedure |
| Action for Health in Diabetes (Look AHEAD)[37] | 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/m2, or ≥27 kg/m2 if taking insulin | A composite cardiovascular outcome: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalized angina<br><br>Secondary: Cognitive function | Two pairs of sequential BP measurements recorded in each arm, using continuous wave Doppler with a standard mercury sphygmomanometer, with patients supine | 4-5 year follow up | SBP ≥140mmHg, ≥DBP ≥90mmHg 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)[38] | 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 medication, or SBP ≥ 140mmHg or DBP ≥ 90mmHg | Fasting blood glucose ≥126 mg/dl or use of oral hypoglycemic 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[39] | 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 ≥ 140mmHg or DBP ≥ 90mmHg or use of BP lowering medication | 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 |
| Second Manifestations of ARTerial disease (SMART) study[40] | January 2002 – February 2014 | 7600 | The Netherlands | Males and females, aged 18-80 years, referred to University Medical | 3 point MACE (combination of non-fatal myocardial | Single pair of sequential BP measurements, using a Vasoguard Doppler | Mean follow-up:5.9 years | Blood pressure >140/90 mmHg at baseline or the use | Recorded diagnosis, self-reported diagnosis, use of | *Cardiovascular death:* Death from stroke, MI, congestive heart failure, rupture of abdominal aortic |

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| Study name | Period of patient recruitment /Duration of trial | Sample size | 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Center Utrecht, for treatment of clinically manifest vascular disease or cardiovascular risk factors | infarction, non-fatal stroke and death from vascular disease), total mortality and vascular mortality | probe, with patients supine | | of blood pressure lowering medication. | blood glucose lowering medicati on, or fasting glucose >7 mmol/L at recruitment combined with initiation of glucose lowering medication within first year of follow-up. Type 1 diabetes excluded. | aneurysm or vascular death from other causes<br><br>*Non-fatal events:*<br>Stroke (infarction or haemorrhagic), MI, retinal infarction, heart failure |
| Surrogate markers for Micro- and Macrovascular hard endpoints as Innovative diabetes tools (SUMMIT)[41] | 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:*<br>Fatal MI |
| Viborg Women Cohort (ViWoCo)[42] | October 2011-January 2013 | 1428 | Denmark | Females born in 1936, 1941, 1946 and 1951 living in the Municipal 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 2mmHg | Median follow-up 3.3 years | SBP ≥ 140 mmHg or DBP ≥ 90 mmHg | HbA1c ≥ 48 mmol/mol | *Cardiovascular death:*<br>Fatal event as below<br>*Non-fatal event:*<br>MI or ischaemic stroke leading to hospitalisation |
| Vietnam Experience Study[43] | 1986 | 4394 | USA | Male US army veterans who participated in the Vietnam war | Inter-arm differences, all-cause and cardiovascular mortality | Two pairs of sequential BP measurements, using standard mercury sphygmomanometer, with patients seated | 15 years | SBP ≥ 140 mmHg, DBP ≥ 90 mmHg or use of BP lowering medication | Fasting plasma glucose ≥ 7.0 mmol/l and/or use of medication for diabetes | *Cardiovascular death:*<br>Death due to major cardiovascular disease. |

BP = BP, DBP = diastolic BP, IHD = ischaemic heart disease, MI = myocardial infarction, N/S = not stated, PAD = peripheral arterial disease, SBP = systolic BP, TIA = transient ischaemic attack, ECG = electrocardiogram

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# 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



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# 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

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## 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 mmHg 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 meta-analyses using arm and leg SBP measurements for 33,710 individuals from 14 studies within the 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

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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 inter-arm 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 co-authors.

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## 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 sub-optimal 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 (e.g. after bilateral mastectomy for breast cancer) or phocomelia (e.g. 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 to 40 mmHg have been suggested for the difference (i.e. 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 was published examining this relationship.[11] Based on 44 included studies, totalling 9,771 participants, ankle SBP was found to be 17.0 mmHg [95 % confidence intervals (CI) 15.4 to 21.3 mmHg] higher than arm BP in the general population; for diastolic BP there was no difference. These findings suggested that a threshold of 155/90 mmHg in the leg [equating to the National Institute for Health and Care Excellence (NICE) threshold of 140/90 mmHg 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

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history, cardiovascular disease risk, measurement method and device or methodological quality. Meta-regression 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 (for example, age or co-existing disease), methodological choices (for example, posture in BP measurement or sequential versus 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, whilst 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?

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# 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 Inter-arm BP difference (INTERPRESS-IPD) Collaboration, established to undertake IPD meta-analyses examining the independent contribution of inter-arm 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 ABLE-BP dataset will include 33,710 individual records from 14 European, US and African studies that measured both arm and leg BP. Participants in the dataset have a mean age of 58 years (range: 18 to 99 years), 45 % are female and mean systolic/diastolic brachial BP is 135/80 mmHg. In total, 20,191 (60 %) have hypertension (defined as a formal clinical diagnosis and/or on

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antihypertensive treatment), 4,917 (15 %) have diabetes, 5,474 (17 %) have pre-existing ischaemic heart disease and 1,900 (6 %) have had a cerebrovascular event. Median follow-up period is 8.0 years, with 2,811 (9 %) participants experiencing cardiovascular events or death and 621 (2 %) dying within 10 years. We will present tables including descriptors (for example, 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 are 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 co-primary 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.

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## 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 standard deviation, median with interquartile ranges, or proportions.

### *Investigation of relationship between leg and arm blood pressure*

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. As part of planned subgroup analyses, we will also test classes of drugs, and, if significant, they may be entered into final models.

### *Prediction modelling of arm blood pressure using leg blood pressure*

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 $tau^2$ 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.

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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 $tau^2$. 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.

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 ankle-brachial indices. 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

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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 blood pressure 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

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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 toward 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 co-produce 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 Individual Participant Data (PRISMA-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, NHS commissioners, the British and Irish Hypertension Society and local healthcare providers. We will co-produce 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,

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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 United Kingdom (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 to 13 individuals per 100,000 population have upper limb prostheses in the UK and Norway.[27 28] In addition, over 1,700 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 6,000 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.

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To date, estimates suggest either a minimum difference of 15 mmHg in SBPs between arm and leg, or a conversion factor of x 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.

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## 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.

## Contributors

This protocol was first drafted by SM, CEC, FCW, JS, UM, LF, KB and VA, then revised and edited by all authors, including HS, PW, PL, RB and AJF. The final manuscript has been read and reviewed by all authors.

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*: Maëlenn Guerchet; *MESA*: Matthew Allison; *LIFE & WALCS*: Mary McDermott; *Look AHEAD*: Mark Espeland; *ViWoCo:* Marie Dahl; *SUMMIT*: Angela Shore; *MARK Study*: Rafel Ramos Blanes

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## 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.

## Ethics approval and patient consent for publication

Not required for secondary analyses of subset of INTERPRESS-IPD dataset.

A summary of the ethical approval granted for each individual study included in the ABLE-BP dataset are listed below (please see individual publications for more information):

WALCS: The protocol was approved by the North-western University Medical School and Catholic Health Partners Hospital institutional review boards.

EPIDEMCA: Ethical committees, supervised by Ministry of Public Health in Central African Republic and the CERSSA (Comité d'Ethique de la Recherche en Sciences de Santé) in the Repulic of Congo, approved the study protocol, as well as the CPP-SOOM-IV (Comité de la Protection des Personnes Sud-Ouest Outre-Mer) in France.

Fuencarral Health Center: The study was approved by the Comité de Ética e Investigación Clínica (CEIC) of the Hospital Carlos III in Madrid.

Heinz Nixdorf: The Medical Ethics Committee of Erasmus Medical Center approved the study.

InCHIANTI: Ethical approval for the InCHIANTI study was provided by the Italian National Research Council on Aging Ethical Committee.

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LIFE: The study protocol was approved by the institutional review boards at all participating sites.

MARK: The study received ethical approval from the Research Ethics Committee of the Institut d'Investigació en Atenció Primària Jordi Gol (Primary Care Research Institute Jordi Gol).

Look AHEAD: The Look AHEAD M&M protocol and consent forms were approved by local Institutional Review Boards prior to use.

MESA: The institutional review boards of the six field centers involved in the study approved the study protocol.

San Diego Population Study: The study received approval from the Committee on Investigations Involving Human Subjects at UCSD.

SMART: The study was approved by the Medical Ethics Committee of the University Medical Centre Utrecht.

SUMMIT: The study received ethical approval from the EU and all participating studies received insitutional ethics review and approval.

ViWoCo: The study was approved by the Regional Scientific Ethical Committee, a part of the Danish National Committee on Health Research Ethics (record number M-20100116) and the Danish Regional Data Protection Agency (record number 1–16–02-221-16).

Vietnam Experience Study: Ethical approval for the study protocol was given by the US Office for Technology Assessment, the Department of Health and Human Sciences Advisory Committee, the Agent Orange Working Group Science Panel, and a review panel from the US Centers for Disease Control.

## Provenance and peer review

Not commissioned; externally peer reviewed.

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## Table 1 – characteristics of studies included in the 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.<br><br>*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 mmHg | 2-3 years | Self-reported BP lowering treatment; SBP ≥140 mmHg or DBP ≥90 mmHg | 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 (Hadeco, Kawasaki, Japan) and calibrated mercury sphygmomanometer with patient supine | Mean follow-up 49.8 months | SBP ≥140 mmHg, DBP ≥90 mmHg 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<br>*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. | BP measured sequentially using Doppler probe (Logidop, Kranzbuhler, Germany) with patients supine | Mean follow up: 109 months | SBP >140 mmHg or DBP >90 mmHg | Existing diagnosis or use of anti-diabetic medication | *Cardiovascular death or non-fatal event:* First occurrence of MI based on symptoms, ECG signs, and enzymes, |

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| 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Secondary endpoints included ABI as a stroke predictor factors | | | | | supported by necropsy if fatal |
| Invecchiare in Chianti (InCHIANTI)[35] | 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 mmHg. Posterior tibial arteries measured twice with a handheld Doppler stethoscope (Parks model 41-A; Parks Medical Electronics, Inc, Aloha, Ore). | N/S | Self-reported, existing recorded diagnosis, or use of BP lowering medication or SBP ≥140 mmHg or DBP ≥90 mmHg | Self-reported, existing recorded diagnosis, or use of anti-diabetic 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 (<20min per week physical activity) | Major mobility disability<br><br>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 ≥140mmHg or DBP ≥90mmHg | Patient reported, or use of antidiabetic treatment or fasting glucose ≥ 126 mg/dL | *Cardiovascular death:* not defined<br><br>*Non-fatal events*: Stroke or TIA, MI, angina, or revascularisation procedure |

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| 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/m2, or ≥27 kg/m2 if taking insulin | A composite cardiovascular outcome: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalized angina<br><br>Secondary: Cognitive function | Two pairs of sequential BP measurements recorded in each arm, using continuous wave Doppler with a standard mercury sphygmomanometer, with patients supine | 4-5 year follow up | SBP ≥140 mmHg, ≥DBP > 90 mmHg 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 medication, or SBP ≥ 140mmHg or DBP ≥ 90mmHg | Fasting blood glucose ≥126 mg/dl or use of oral hypoglycemic 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 mmHg or DBP ≥ 90 mmHg or use of BP lowering medication | 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 |
| Second Manifestations of ARTerial 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 mmHg 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 | *Cardiovascular death:* Death from stroke, MI, congestive heart failure, rupture of abdominal aortic aneurysm or vascular death from other causes<br><br>*Non-fatal events:* Stroke (infarction or haemorrhagic), MI, retinal infarction, heart failure |

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| 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | glucose lowering medication within first year of follow-up. Type 1 diabetes excluded. | |
| 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 (ViWoCo)[43] | October 2011-January 2013 | 1428 | Denmark | Females born in 1936, 1941, 1946 and 1951 living in the Municipal 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 2mmHg | Median follow-up 3.3 years | SBP ≥ 140 mmHg or DBP ≥ 90 mmHg | HbA1c ≥ 48 mmol/mol | *Cardiovascular death:* Fatal event as below *Non-fatal event:* MI or ischaemic stroke leading to hospitalisation |
| Vietnam Experience Study[44] | 1986 | 4394 | USA | Male US army veterans who participated in the Vietnam war | Inter-arm differences, all-cause and cardiovascular mortality | Two pairs of sequential BP measurements, using standard mercury sphygmomanometer, with patients seated | 15 years | SBP ≥ 140 mmHg, DBP ≥ 90 mmHg 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. |

BP = BP, DBP = diastolic BP, IHD = ischaemic heart disease, MI = myocardial infarction, N/S = not stated, PAD = peripheral arterial disease, SBP = systolic BP, TIA = transient ischaemic attack, ECG = electrocardiogram

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# 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



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# 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

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## 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 mmHg 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 meta-analyses using arm and leg SBP measurements for 33,710 individuals from 14 studies within the 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.

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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 inter-arm 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 co-authors.

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## 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 sub-optimal 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 (e.g. after bilateral mastectomy for breast cancer) or phocomelia (e.g. 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 to 40 mmHg have been suggested for the difference (i.e. 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 was published examining this relationship.[11] Based on 44 included studies, totalling 9,771 participants, ankle SBP was found to be 17.0 mmHg [95 % confidence intervals (CI) 15.4 to 21.3 mmHg] higher than arm BP in the general population; for diastolic BP there was no difference. These findings suggested that a threshold of 155/90 mmHg in the leg [equating to the National Institute for Health and Care Excellence (NICE) threshold of 140/90 mmHg 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

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history, cardiovascular disease risk, measurement method and device or methodological quality. Meta-regression 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 (for example, age or co-existing disease), methodological choices (for example, posture in BP measurement or sequential versus 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, whilst 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?

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# 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 Inter-arm BP difference (INTERPRESS-IPD) Collaboration, established to undertake IPD meta-analyses examining the independent contribution of inter-arm 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 ABLE-BP dataset will include 33,710 individual records from 14 European, US and African studies that measured both arm and leg BP. Participants in the dataset have a mean age of 58 years (range: 18 to 99 years), 45 % are female and mean systolic/diastolic brachial BP is 135/80 mmHg. In total, 20,191 (60 %) have hypertension (defined as a formal clinical diagnosis and/or on

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antihypertensive treatment), 4,917 (15 %) have diabetes, 5,474 (17 %) have pre-existing ischaemic heart disease and 1,900 (6 %) have had a cerebrovascular event. Median follow-up period is 8.0 years, with 2,811 (9 %) participants experiencing cardiovascular events or death and 621 (2 %) dying within 10 years. We will present tables including descriptors (for example, 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 are 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 co-primary 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.

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## 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 standard deviation, median with interquartile ranges, or proportions.

### *Investigation of relationship between leg and arm blood pressure*

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 (e.g. 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 blood pressure using leg blood pressure*

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 $tau^2$ 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

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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 $tau^2$. 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.

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.

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### *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 ankle-brachial indices. 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 blood pressure 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.

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## 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 toward 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 co-produce 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 Individual Participant Data (PRISMA-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

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clinical guidelines, including the UK NICE guidance, NHS commissioners, the British and Irish Hypertension Society and local healthcare providers. We will co-produce 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 United Kingdom (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 to 13 individuals per 100,000 population have upper limb prostheses in the UK and Norway.[27 28] In addition, over 1,700 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 6,000 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.

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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 mmHg in SBPs between arm and leg, or a conversion factor of x 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.

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## 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.

## Contributors

This protocol was first drafted by SM, CEC, FCW, JS, UM, LF, KB and VA, then revised and edited by all authors, including HS, PW, PL, RB and AJF. The final manuscript has been read and reviewed by all authors.

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*: Maëlenn Guerchet; *MESA*: Matthew Allison; *LIFE & WALCS*: Mary McDermott; *Look AHEAD*: Mark Espeland; *ViWoCo:* Marie Dahl; *SUMMIT*: Angela Shore; *MARK Study*: Rafel Ramos Blanes

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## 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.

## Ethics approval and patient consent for publication

Not required for secondary analyses of subset of INTERPRESS-IPD dataset.

A summary of the ethical approval granted for each individual study included in the ABLE-BP dataset are listed below (please see individual publications for more information):

WALCS: The protocol was approved by the North-western University Medical School and Catholic Health Partners Hospital institutional review boards.

EPIDEMCA: Ethical committees, supervised by Ministry of Public Health in Central African Republic and the CERSSA (Comité d'Ethique de la Recherche en Sciences de Santé) in the Repulic of Congo, approved the study protocol, as well as the CPP-SOOM-IV (Comité de la Protection des Personnes Sud-Ouest Outre-Mer) in France.

Fuencarral Health Center: The study was approved by the Comité de Ética e Investigación Clínica (CEIC) of the Hospital Carlos III in Madrid.

Heinz Nixdorf: The Medical Ethics Committee of Erasmus Medical Center approved the study.

InCHIANTI: Ethical approval for the InCHIANTI study was provided by the Italian National Research Council on Aging Ethical Committee.

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LIFE: The study protocol was approved by the institutional review boards at all participating sites.

MARK: The study received ethical approval from the Research Ethics Committee of the Institut d'Investigació en Atenció Primària Jordi Gol (Primary Care Research Institute Jordi Gol).

Look AHEAD: The Look AHEAD M&M protocol and consent forms were approved by local Institutional Review Boards prior to use.

MESA: The institutional review boards of the six field centers involved in the study approved the study protocol.

San Diego Population Study: The study received approval from the Committee on Investigations Involving Human Subjects at UCSD.

SMART: The study was approved by the Medical Ethics Committee of the University Medical Centre Utrecht.

SUMMIT: The study received ethical approval from the EU and all participating studies received insitutional ethics review and approval.

ViWoCo: The study was approved by the Regional Scientific Ethical Committee, a part of the Danish National Committee on Health Research Ethics (record number M-20100116) and the Danish Regional Data Protection Agency (record number 1–16–02-221-16).

Vietnam Experience Study: Ethical approval for the study protocol was given by the US Office for Technology Assessment, the Department of Health and Human Sciences Advisory Committee, the Agent Orange Working Group Science Panel, and a review panel from the US Centers for Disease Control.

## Provenance and peer review

Not commissioned; externally peer reviewed.

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## Table 1 – characteristics of studies included in the 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.<br><br>*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 mmHg | 2-3 years | Self-reported BP lowering treatment; SBP ≥140 mmHg or DBP ≥90 mmHg | 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 (Hadeco, Kawasaki, Japan) and calibrated mercury sphygmomanometer with patient supine | Mean follow-up 49.8 months | SBP ≥140 mmHg, DBP ≥90 mmHg 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<br>*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. | BP measured sequentially using Doppler probe (Logidop, Kranzbuhler, Germany) with patients supine | Mean follow up: 109 months | SBP >140 mmHg or DBP >90 mmHg | Existing diagnosis or use of anti-diabetic medication | *Cardiovascular death or non-fatal event:* First occurrence of MI based on symptoms, ECG signs, and enzymes, |

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136/bmjopen-2020-040481 on 9 March 2021. Downloaded from

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Secondary endpoints included ABI as a stroke predictor factors | | | | | supported by necropsy if fatal |
| Invecchiare in Chianti (InCHIANTI)[35] | 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 mmHg. Posterior tibial arteries measured twice with a handheld Doppler stethoscope (Parks model 41-A; Parks Medical Electronics, Inc, Aloha, Ore). | N/S | Self-reported, existing recorded diagnosis, or use of BP lowering medication or SBP ≥140 mmHg or DBP ≥90 mmHg | Self-reported, existing recorded diagnosis, or use of anti-diabetic 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 (<20min per week physical activity) | Major mobility disability<br><br>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 ≥140mmHg or DBP ≥90mmHg | Patient reported, or use of antidiabetic treatment or fasting glucose ≥ 126 mg/dL | *Cardiovascular death:* not defined<br><br>*Non-fatal events*: Stroke or TIA, MI, angina, or revascularisation procedure |

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| 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/m2, or ≥27 kg/m2 if taking insulin | A composite cardiovascular outcome: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalized angina<br><br>Secondary: Cognitive function | Two pairs of sequential BP measurements recorded in each arm, using continuous wave Doppler with a standard mercury sphygmomanometer, with patients supine | 4-5 year follow up | SBP ≥140 mmHg, ≥DBP > 90 mmHg 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 medication, or SBP ≥ 140mmHg or DBP ≥ 90mmHg | Fasting blood glucose ≥126 mg/dl or use of oral hypoglycemic 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 mmHg or DBP ≥ 90 mmHg or use of BP lowering medication | 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 |
| Second Manifestations of ARTerial 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 mmHg 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 | *Cardiovascular death:* Death from stroke, MI, congestive heart failure, rupture of abdominal aortic aneurysm or vascular death from other causes<br><br>*Non-fatal events:* Stroke (infarction or haemorrhagic), MI, retinal infarction, heart failure |

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| 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | glucose lowering medication within first year of follow-up. Type 1 diabetes excluded. | |
| 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 (ViWoCo)[43] | October 2011-January 2013 | 1428 | Denmark | Females born in 1936, 1941, 1946 and 1951 living in the Municipal 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 2mmHg | Median follow-up 3.3 years | SBP ≥ 140 mmHg or DBP ≥ 90 mmHg | HbA1c ≥ 48 mmol/mol | *Cardiovascular death:* Fatal event as below *Non-fatal event:* MI or ischaemic stroke leading to hospitalisation |
| Vietnam Experience Study[44] | 1986 | 4394 | USA | Male US army veterans who participated in the Vietnam war | Inter-arm differences, all-cause and cardiovascular mortality | Two pairs of sequential BP measurements, using standard mercury sphygmomanometer, with patients seated | 15 years | SBP ≥ 140 mmHg, DBP ≥ 90 mmHg 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. |

BP = BP, DBP = diastolic BP, IHD = ischaemic heart disease, MI = myocardial infarction, N/S = not stated, PAD = peripheral arterial disease, SBP = systolic BP, TIA = transient ischaemic attack, ECG = electrocardiogram

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