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Accurate blood pressure measurement

Dean Stewart Picone

BBiotechMedRes, BMedRes(Hons)

A thesis submitted in fulfilment of the degree of Doctor of Philosophy

November 2017

Menzies Institute for Medical Research

University of Tasmania

Hobart, Tasmania, Australia

Declarations by author

Originality

This thesis contains no material that has previously been accepted for a degree or diploma by the University of Tasmania, or any other institution, except by way of background information and of which is duly acknowledged in the thesis. To the best of my knowledge and belief, this thesis contains no material that has previously been published or written by another person, except where due acknowledgement is made in the text of the thesis, nor does this thesis contain any material that infringes copyright. I have acknowledged, where appropriate, the specific contributions made by my co-authors of published and submitted manuscripts.

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Ethical Conduct

All research associated with this thesis abides by the international and Australian codes on human and animal experimentation, and full ethical approval from the relevant institutions was obtained for all studies outlined in this thesis. All individual participants provided written informed consent for involvement in the respective research studies.

Dean Stewart Picone

Publications by the author and statement of co-author contribution to papers contained within this thesis

The following papers are incorporated into the Chapters of this thesis and were either published or submitted for publication in peer reviewed scientific journals during the course of candidature. The papers appear as they were published (or submitted) with minor modifications to fit in context with this thesis.

Chapter 2

Picone DS, Schultz MG, Otahal P, Aakhus S, Al-Jumaily AM, Black JA, Bos WJ, Chambers JB, Chen CH, Cheng HM, Cremer A, Davies JE, Dwyer N, Gould BA, Hughes AD, Lacy PS, Laugesen E, Liang F, Melamed R, Muecke S, Ohte N, Okada S, Omboni S, Ott C, Peng X, Pereira T, Pucci G, Rajani R, Roberts-Thomson P, Rossen NB, Sueta D, Sinha MD, Schmieder RE, Smulyan H, Srikanth VK, Stewart R, Stouffer GA, Takazawa K, Wang J, Westerhof BE, Weber F, Weber T, Williams B, Yamada H, Yamamoto E, Sharman JE. Accuracy of cuff measured blood pressure: compendium of three separate systematic reviews and individual participant data meta-analyses. *Journal of the American College of Cardiology*. 2017. 70(5):572-586.

Author contributions:

D.S. Picone - Study conception and design, literature search, data collection, extraction, analysis and interpretation, manuscript preparation

M.G. Schultz - Study conception and design, literature search, data collection, extraction and interpretation, manuscript preparation

P. Otahal - Data analysis, critical manuscript revision

S. Aakhus, A.M. Al-Jumaily, J.A. Black, W.J. Bos, J.B. Chambers, C.H. Chen, H.M. Cheng, A. Cremer, J.E. Davies, N. Dwyer, B.A. Gould, A.D. Hughes, P.S. Lacy, E. Laugesen, F. Liang, R. Melamed, S. Muecke, N. Ohte, S. Okada, S. Omboni, C. Ott, X. Peng, T. Pereira, G. Pucci, R. Rajani, P. Roberts-Thomson, N.B. Rossen, D. Sueta, M.D. Sinha, R.E. Schmieder, H. Smulyan, R. Stewart, G.A. Stouffer, K. Takazawa, J. Wang, B.E. Westerhof, F. Weber, T. Weber, B. Williams, H. Yamada, E. Yamamoto - Data collection, critical manuscript revision

V.K. Srikanth - Study conception and design, critical manuscript revision

J.E. Sharman - Study conception and design, data interpretation, critical manuscript revision

Chapter 3

Picone DS, Schultz MG, Peng X, Black JA, Dwyer N, Roberts-Thomson P, Chen C-H, Cheng H-M, Pucci G, Wang J, Sharman JE. Discovery of new blood pressure phenotypes and relation to accuracy of cuff devices used in daily clinical practice. *Hypertension.* 2018; 71(6):1239-1247

Author contributions:

D.S. Picone - Study conception and design, data collection, analysis and interpretation, manuscript preparation

M.G. Schultz - Study conception and design, data analysis and interpretation, manuscript preparation

X. Peng – Data collection and analysis, critical manuscript revision

J.A. Black, N. Dwyer, P. Roberts-Thomson, C-H. Chen, H-M. Cheng, G. Pucci, J. Wang – Data collection, critical manuscript revision

J.E. Sharman - Study conception and design, data interpretation, critical manuscript revision

Chapter 4

Picone DS, Schultz MG, Peng X, Black JA, Dwyer N, Roberts-Thomson P, Sharman JE. The best calibration methods to estimate aortic blood pressure. Accepted by *Journal of Hypertension,* July 2018

Author contributions:

D.S. Picone - Study conception and design, data collection, analysis and interpretation, manuscript preparation

M.G. Schultz - Study conception and design, data analysis and interpretation, manuscript preparation

X. Peng – Data collection and analysis, critical manuscript revision

J.A. Black, N. Dwyer, P. Roberts-Thomson – Data collection, critical manuscript revision

J.E. Sharman - Study conception and design, data interpretation, critical manuscript revision

We, the undersigned agree with the above stated contributions for each of the above published peer reviewed manuscripts contained within this thesis:

_____

Professor James E. Sharman

Primary candidate supervisor

Menzies Institute for Medical Research, University of Tasmania

_____

Professor Alison Venn

Director

Menzies Institute for Medical Research, University of Tasmania

Additional Publications that do not form part of the Thesis

The following nine publications or papers in submission for publication in peer reviewed scientific journals arose from research activities during the candidature and whilst related, do not form part of the primary thesis.

Picone DS, Schultz MG, Climie RED, Srikanth V, Sharman JE, Aortic-to-brachial stiffness gradient and kidney function in type 2 diabetes, *Journal of Hypertension*, 2016. 34(6): 1132-1139

Climie RED*, **Picone DS***, Keske MA, Sharman JE, Brachial-to-radial systolic blood pressure amplification in patients with type 2 diabetes mellitus, *Journal of Human Hypertension*, 2016. 30(6): 404-409. *Joint first authors

Peng X, Schultz MG, **Picone DS,** Black JA, Dwyer N, Roberts-Thomson P, Davies JE, Sharman JE, Arterial reservoir characteristics and central-to-peripheral blood pressure amplification in the human upper limb, *Journal of Hypertension*, 2017. 35(9): 1825-31.

Climie RED, **Picone DS**, Sharman JE, Longitudinal changes in excess pressure independently predict declining renal function among healthy individuals – a pilot study, *American Journal of Hypertension*, 2017. 30(8): 772-775.

Moore MN, Schultz MG, Nelson MR, Black JA, Dwyer N, Hoban E, Jose M, Kosmala W, Przewlocka-Kosmala M, Zachwyc J, Otahal P, **Picone DS**, Roberts-Thomson P, Veloudi P, Sharman JE Identification of the optimal protocol for automated office blood pressure measurement among patients with treated hypertension, *American Journal of Hypertension*, published online ahead of print, October 2017

Armstrong MK, Schultz MG, **Picone DS**, Sharman JE, Blood pressure-independence of aortic-to-brachial artery stiffness ratio is dependent on disease status, *Under review by American Journal of Hypertension*, November 2017

Terblanche NCS, **Picone DS**, Otahal P, Sharman JE, Effectiveness and safety of lowering oxytocin doses on maternal outcomes during elective caesarean section: Systematic review, *Manuscript in preparation*, November 2017

Schultz MG, **Picone DS**, Nikolic SB, Williams AD, Sharman JE, Exaggerated blood pressure response to early stages of exercise stress testing and presence of hypertension, *Journal of Science and Medicine in Sport*, 2016. 19(12):1039-1042

Schultz MG, Otahal P, **Picone DS**, Sharman JE Clinical Relevance of Exaggerated Exercise Blood Pressure, *Journal of the American College of Cardiology*, 2015. 66(16): 1843-1845.

Abstracts and presentations at scientific conferences that relate to this thesis

Picone DS, Schultz MG, Peng X, Black JA, Dwyer N, Roberts-Thomson P, Srikanth V, Sharman JE. Discovery of a new blood pressure phenotype from invasive central-to-peripheral recordings: implications for brachial cuff accuracy and cardiovascular risk assessment. **First prize for Best Young Investigator oral presentation**, ARTERY16, Copenhagen, Denmark, October 2016

Picone DS, Schultz MG, Otahal P, Black JA, Dwyer N, Hughes A, Liang F, Rajani R, Roberts-Thomson P, Srikanth V, Takazawa K, Sharman JE. Principal findings of the invasive blood pressure meta-analysis consortium (INSPECT) on the accuracy of brachial cuff blood pressure devices. Oral presentation, International Society of Hypertension, Seoul, South Korea, September 2016

Picone DS, Schultz MG, Peng X, Black JA, Dwyer N, Hughes A, Roberts-Thomson P, Srikanth V, Sharman JE. Novel blood pressure phenotypes identified from invasive aortic-to-peripheral amplification: impact on accuracy of brachial cuff measurement. Moderated Poster, Pulse of Asia 2016, Seoul, South Korea, September 2016

Picone DS, Otahal P, Schultz MG, Black JA, Chen CH, Davies JE, Dwyer N, Liang F Roberts-Thomson P, Srikanth VK, Wang JG, Yamada H, Sharman JE. More accurate methods of blood pressure measurement are needed: individual patient meta-analyses and experimental confirmation with invasive and non-invasive blood pressure. Poster presentation. High Blood Pressure Research Council of Australia Annual Scientific Meeting, Melbourne, December 2015

Dedication

To my parents, David and Annette and my partner Devi for their eternal love, support and patience throughout my candidature.

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Abstract

Cardiovascular disease is the leading global cause of mortality and morbidity and high blood pressure (BP) is the single greatest risk factor. Cuff measured BP is used in clinical practice to diagnose and guide management of high BP, with treatment of high BP resulting in a reduction of cardiovascular risk. For these reasons, BP measurement is among the most important medical tests performed, yet the conventional cuff method may be inaccurate. The overall aims of this research were to determine: the accuracy of cuff measured BP; if distinct BP phenotypes exist that relate to cuff BP accuracy and; haemodynamic factors that influence estimation of BP.

In study 1 (Chapter 2), the accuracy of cuff measured BP compared with intra-arterial brachial and aortic BP was examined via three individual participant data meta-analyses among data from the 1950's to 2016. Intra-arterial brachial systolic BP was higher than aortic values. Cuff BP had variable accuracy for measuring intra-arterial brachial and aortic BP, and this significantly influenced correct BP classification. Indeed, the concordance of cuff BP across hypertension categories (normal, pre-hypertension, hypertension stages 1 and 2) compared with intra-arterial brachial BP was 60%, 50%, 53% and 80%, and compared with intra-arterial aortic BP was 79%, 57%, 52% and 76%.

In study 2 (Chapter 3), cuff measured BP and intra-arterial BP waveforms from the aorta, brachial and radial arteries were examined in 126 patients undergoing coronary angiography. Four novel BP phenotypes were discovered based on variability in aortic-to-brachial and brachial-to-radial systolic BP amplification. Cuff BP was unable to discriminate between the phenotypes ($p>0.5$ all comparisons), and among two phenotypes completely missed patients at potentially higher risk due to raised aortic BP. The key findings were confirmed by additional data in 255 patients, supplied by four independent, international collaborators

In study 3 (Chapter 4), intra-arterial BP from 107 individuals undergoing coronary angiography was used to determine the best peripheral BP waveform calibration method for the estimation of aortic BP, as well as haemodynamic factors that may influence accuracy. BP waveforms calibrated with brachial mean arterial BP/diastolic BP estimated aortic systolic BP more accurately than brachial systolic BP/diastolic BP calibration. However, systolic BP amplification had a major influence on the accuracy of estimated aortic systolic BP.

In summary, this thesis revealed the extent of inaccuracy in cuff measured BP compared to intra-arterial BP. Moreover, distinct BP phenotypes were discovered which were related to cuff inaccuracy. Finally, systolic BP amplification was found to influence the accuracy of estimated

aortic BP from peripheral BP waveforms. Altogether, these studies substantially advance understanding of the strengths and limitations of current BP measurement methods. Novel reasons for measurement inaccuracy have been identified that may lead to tangible improvements in the accuracy of BP measurement.

Keywords

Aorta, blood pressure determination, brachial artery, cardiac catheterization, haemodynamics, hypertension, pulse wave analysis, prehypertension, sphygmomanometers

List of abbreviations

Pressure indices or related terms

Amp, amplification

BP, blood pressure

DINAMAP, device for indirect non-invasive mean arterial pressure

DBP, diastolic blood pressure

HTN, hypertension

MAP, mean arterial pressure

preHTN, prehypertension

PP, pulse pressure

SBP, systolic blood pressure

SBPamp, systolic blood pressure amplification

SPRINT, Systolic Blood Pressure Intervention Trial

Organisations

AAMI, Association for the Advancement of Medical Instrumentation

ESH, European Society of Hypertension

FDA, Food and Drug Authority

JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Statistical, measurement or reporting

ANOVA, Analysis of variance

CI, confidence interval

cm, centimeter

kg, kilogram

m, metre

mm Hg, millimetre of mercury

n, number of subjects

PRISMA-IPD, Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data

RR, risk ratio

Miscellaneous

EF, ejection fraction

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Preface

High blood pressure (BP) is the foremost risk factor for cardiovascular disease.[1] Over 1.1 billion people (1 in 5 adults) worldwide have high BP.[2] Treatment to reduce high BP lowers the risk of mortality and other poor clinical outcomes.[3 4, 5] Upper arm cuff BP measurements are used to guide decisions on diagnosis and treatment of high BP. However, there are many reasons cuff measurements may not accurately reflect true BP.[6, 7] Of note, the standard cuff method used in daily clinical practice has changed very little in over 100 years, despite fundamental problems with accuracy being known for over half a century.[8] Moreover, the definite reasons for cuff inaccuracy are not yet known. Newer devices that purport to improve non-invasive BP measurement by estimating aortic BP also have accuracy problems. These issues appear to be related to the way peripheral BP waveforms are calibrated (scaled) in the measurement process, however, further clarification of the best scaling method is required.

Cuff BP inaccuracy may have important clinical implications,[9] but several key questions remain unanswered. For example, there is evidence that cuff BP underestimates intra-arterial brachial SBP and overestimates intra-arterial brachial DBP.[10, 11] This is the prevailing dogma on cuff accuracy, yet whether cuff BP also underestimates aortic SBP and overestimates aortic DBP is unclear, but some evidence suggests this may not be the case.[12, 13] Indeed, results from several small studies suggest the difference between intra-arterial brachial and aortic SBP is highly variable.[14-16] Clarifying the relationships between cuff BP and intra-arterial brachial and aortic BP is an important goal, particularly because of the physiological expectation that aortic BP should better represent the pressure loading on the vital organs than peripheral brachial BP. The first aim of this thesis was dedicated to resolving these questions around the accuracy of cuff measured BP compared with brachial and aortic intra-arterial BP.

Reasons for inaccuracy of cuff measured BP compared with intra-arterial BP remain unclear.[8] There have been many different hypotheses on this issue,[17-19] but never a definitive breakthrough that could be translated to substantially improve BP accuracy. Cuff BP measurements are based on signals measured at the upper arm via standard ‘one size fits all’ approaches that measure BP the same way in every single person.[20, 21] But, evidence of sizeable individual variability in BP transmission through the large arteries suggests different BP phenotypes could exist,[14, 15, 22] however, this idea has never been interrogated with relation to the influence on cuff BP accuracy. The second aim of the thesis examined variability in intra-arterial BP transmission from the central-to-peripheral arteries to determine if BP phenotypes

exist, and if so, whether these could be discriminated by standard cuff BP used in daily clinical practice.

In recent years specialist devices that estimate aortic BP non-invasively have become available. The devices were developed due to both increasing knowledge of distinct differences between aortic and brachial BP, [23] and importantly, the expectation of greater clinical relevance from aortic BP.[22, 23] These devices were expected to markedly improve BP measurement methods compared to the standard cuff by precisely estimating aortic BP and BP waveform features, and thereby predicting clinical outcomes above and beyond cuff BP. But, instead debate on the accuracy of estimated aortic BP devices has been ongoing for many years.[24-28]

The primary limitation to the accuracy of these devices appears to be the calibration (scaling) of peripheral BP waveforms with inaccurate cuff BP. The calibration is performed with either cuff systolic BP/ diastolic BP (DBP) or mean arterial pressure/DBP and the latter may produce more accurate results.[29] An important question that remains unanswered is whether accurate measurement of BP using cuff methods would improve the accuracy of estimated aortic SBP due to more accurate calibration. Therefore, the third aim of the thesis was to determine the best peripheral BP waveform calibration for estimation of aortic BP, and to determine additional arterial variables (e.g. central-to-peripheral BP transmission) that may influence accuracy.

This thesis consists of individual studies and manuscripts that have been published, submitted or are in final preparation for submission to peer-reviewed scientific journals. Chapters 2, 3 and 4 contain separate studies that are largely presented in the final published or submitted format. Only slight modifications to writing style and grammar, which do not alter the results and conclusions of the individual study have been made for clarity and consistency of presentation throughout the thesis. Select tables and figures published as peer-reviewed supplemental material have been added to the main results (Chapter 2 and Chapter 4) for easier interpretation. The contribution of each study to the thesis aims is outlined at the end of each chapter.

Thesis Aims

Aim 1

To determine the accuracy of cuff measured BP compared with intra-arterial brachial and aortic BP.

Aim 2

To determine if distinctive BP phenotypes exist that relate to BP transmission from the central-to-peripheral arteries and whether these could be discriminated by cuff measured BP.

Aim 3

To determine the best peripheral BP waveform calibration method for accurate estimation of aortic BP.

Chapter 1 Review of literature

1.2 Overview

Cardiovascular disease is the number one cause of mortality worldwide.[30, 31] High blood pressure (BP), which affects 1.1 billion humans worldwide, is the foremost risk factor for cardiovascular disease.[1, 2] Treatment to reduce BP lowers the risk of adverse clinical outcomes,[3] and for all these reasons, BP measurement is among the most important of all medical tests. Accuracy of the readings is critical,[7] however, there are many reasons that standard BP measurement performed with upper arm cuff devices may be inaccurate.[6] Whilst many causes of inaccuracy can be controlled, there are fundamental problems in the ability of cuff BP devices to predict gold standard intra-arterial BP. This issue has been known for decades,[8] but a comprehensive analysis to address this has never been conducted. Furthermore, there has never been a definitive breakthrough in understanding why cuff BP may be inaccurate. Newer, specialised devices that estimate aortic BP non-invasively also have problems with accuracy. The following review aims to summarise the pertinent literature on these issues and highlight areas that require further research.

1.3 What is blood pressure and why is it important?

BP is defined as the perpendicular strain or force exerted on the arterial walls.[32] Clinicians measure BP to estimate the pressure load that the vital organs may be exposed to and therefore the potential risk of sub-clinical organ damage or serious adverse events. Several different pressure indices can be obtained from BP measurements (Figure 1.1). First, the highest pressure in the arteries is systolic BP (SBP). This is the pressure the heart must generate to eject blood from the left ventricle into the systemic circulation. Second, diastolic BP (DBP) is the lowest pressure in the arteries, and is observed at the end of the diastole phase of the cardiac cycle. Third, mean arterial pressure (MAP), which represents the average pressure over a single cardiac cycle. Last, pulse pressure (PP), which is calculated as SBP – DBP and represents the maximal pulsatile load on the arteries. Clinicians place most attention on SBP and DBP because these two parameters are the strongest predictors of clinical outcomes.[4, 5]

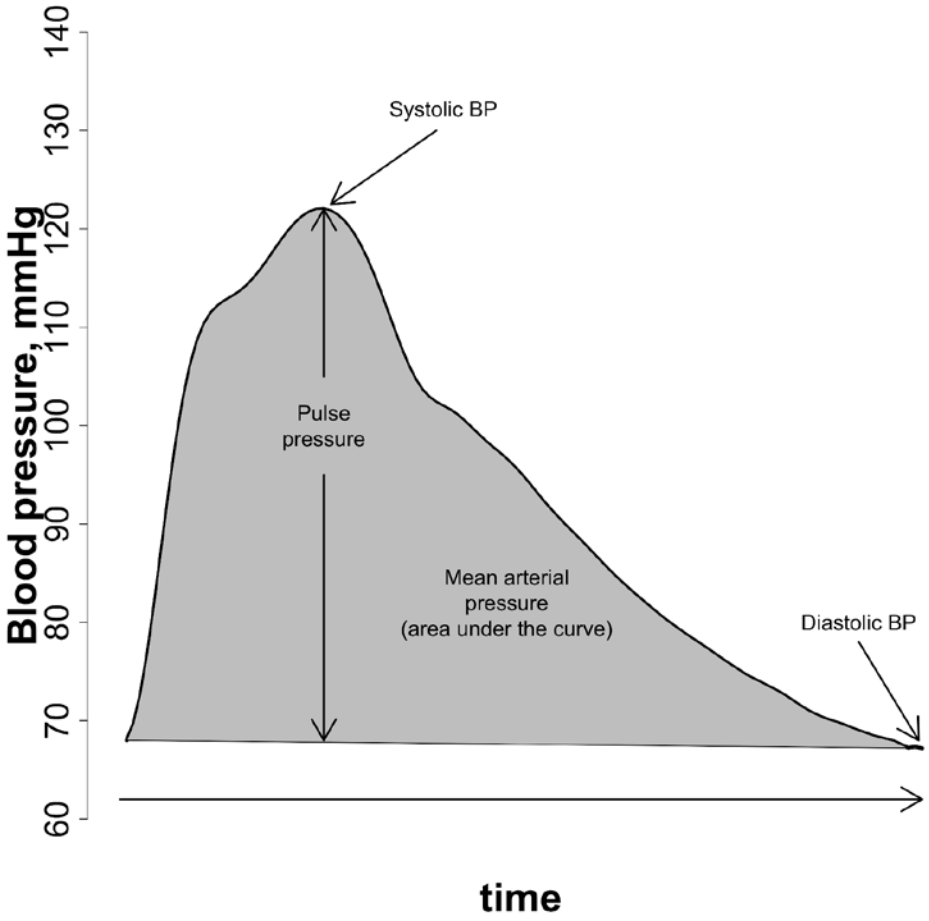

Figure 1.1 Representative example of an intra-arterial aortic blood pressure waveform illustrating the most common pressure parameters.

Systolic blood pressure (BP) is the peak pressure in the arterial system and coincides with peak cardiac contraction. Diastolic BP is the lowest pressure, observed at the end of the relaxation phase (diastole) of the heart. Mean arterial pressure represents the average pressure in the arteries and pulse pressure is the maximal pulsatile load in the arteries. This example represents the measurement of BP from an intra-arterial BP waveform, but other methods (e.g. oscillometric cuff devices, use different methods to obtain pressure parameters).

Globally, high BP is one of the leading risk factors for mortality, and is the number one risk factor for cardiovascular disease.[33] Worldwide 1.1 billion people have high BP, and this equates to 1 in 5 adults.[2] The prevalence in Australia is consistent with the rest of the world, except for the state of Tasmania, where nearly 1 in 3 people have high BP.[34] This is a major public health concern given high BP is such a strong risk factor for cardiovascular disease. The strength of BP as a risk factor was shown in an individual participant data meta-analysis of more than one million people where clear log-linear associations were observed for both SBP and DBP with ischemic (coronary) heart disease, stroke (Figure 1.2), and other vascular mortality.[35] BP is also strongly associated with subclinical organ damage that often precedes major cardiovascular events (e.g. left ventricular hypertrophy, aortic stiffness and white matter lesions).[36-41]

Since the 1970s the worldwide prevalence of cardiovascular disease mortality has declined concomitant with the prevalence of high BP. Indeed, it is well established that accurate diagnosis and subsequent treatment of high BP is vital to reduce cardiovascular risk. A comprehensive meta-analysis of 123 randomised controlled trials of BP lowering drugs recently confirmed this, showing a reduction in SBP by 10 mm Hg lowered the risk of coronary heart disease, stroke, heart failure and even all-cause mortality by between 13-28% (Figure 1.3).[3] Treating high BP effectively is clearly vital for the health of patients, but also to limit the costs of suboptimal BP, which may be in excess of $370 billion USD annually across the world.[42]

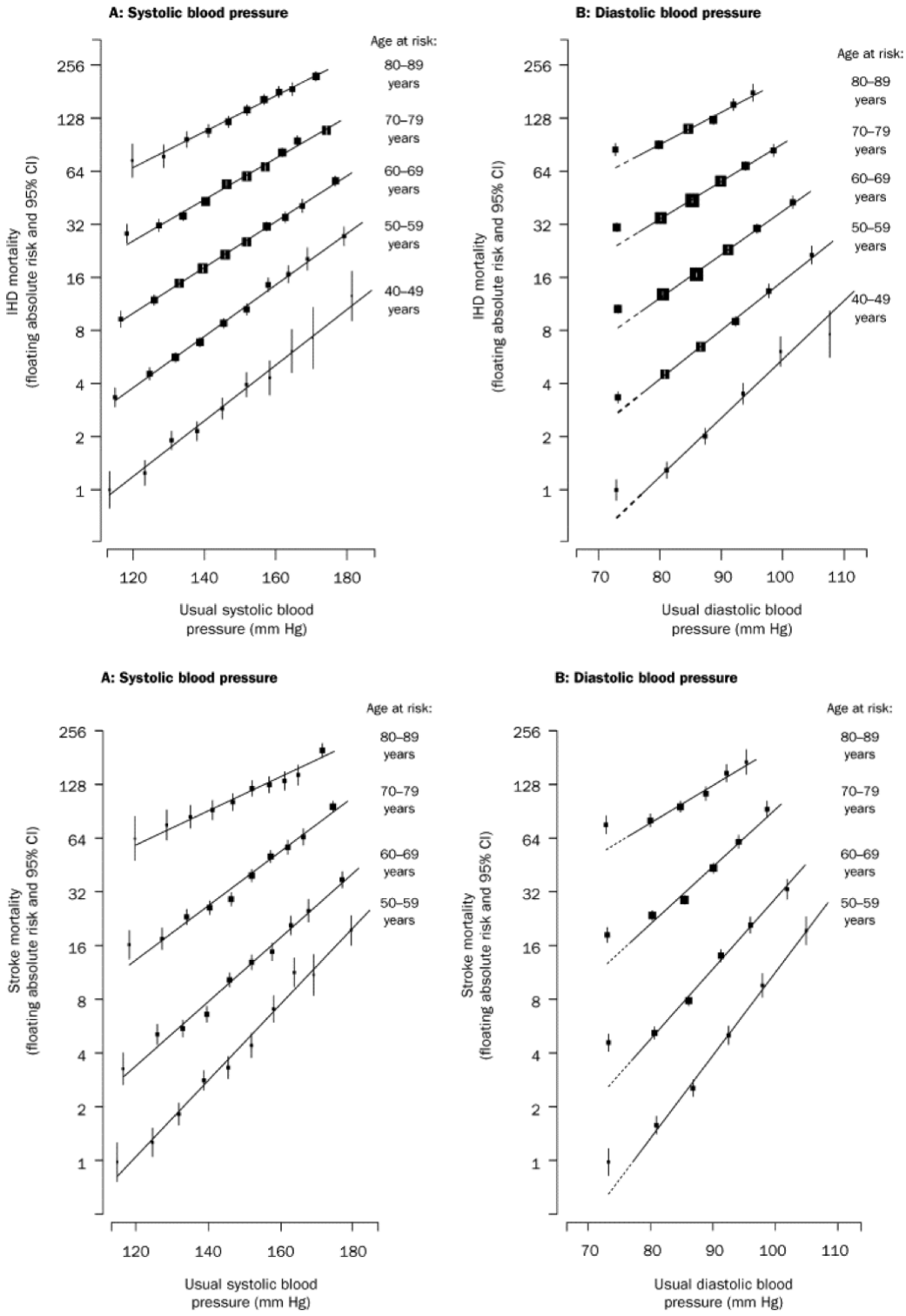

Figure 1.2 Risk of ischemic heart disease and stroke associated blood pressure.

Mortality risk due to ischemic heart disease (y-axis; top panel) and stroke (y-axis, bottom panel) is presented on a logarithmic scale according to usual systolic blood pressure (x-axis; left panel) and diastolic blood pressure (x-axis; right panel). Results are presented across ten-year age increments. Figure from Lewington et al, 2002.[35]

	Studies	Intervention		Control		RR (95% CI) per 10 mm Hg reduction in systolic blood pressure
		Events	Participants	Events	Participants	
Major cardiovascular events	55	13209	137319	14068	128259	0·80 (0·77–0·83)
Coronary heart disease	56	4862	136986	5301	128548	0·83 (0·78–0·88)
Stroke	54	4635	136682	5378	128641	0·73 (0·68–0·77)
Heart failure	43	3284	115411	3760	107440	0·72 (0·67–0·78)
Renal failure	16	890	39888	834	39043	0·95 (0·84–1·07)
All-cause mortality	57	9775	138298	9998	129700	0·87 (0·84–0·91)

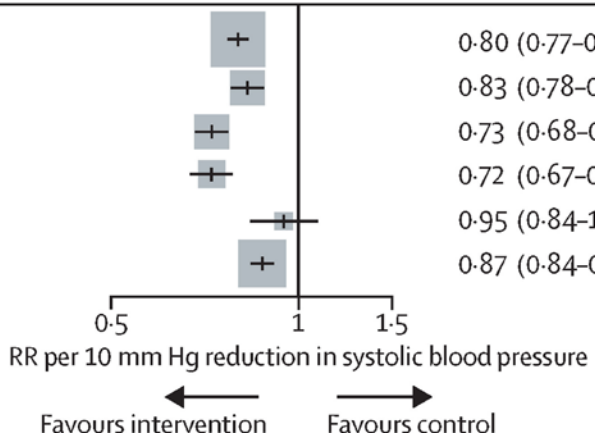

Figure 1.3 Meta-analysis data on the effect of antihypertensive therapy on cardiovascular, renal and all-cause mortality.

The risk ratio (RR) represents the level of risk associated with a 10 mm Hg reduction in systolic blood pressure. Lowering blood pressure reduced risk in all end-points except renal failure in the intervention arm of the trials (antihypertensive treatment group). Figure from Ettehad et al, 2016.[3]

1.4 Importance of accurate blood pressure measurement.

Relatively small inaccuracies in BP measurement could result in misclassification and therefore mismanagement of BP in millions of people.[9] Inaccuracy could manifest as underestimation of true risk related to BP, potentially leaving patients exposed to unnecessary cardiovascular risk.[3, 35] If underestimation of BP resulted in either undertreatment of BP or people completely missing treatment,[42] this could lead to a higher prevalence of major cardiovascular events. On the other hand, overestimation of BP could lead to treatment that is too intensive or unwarranted, potentially causing side effects such as falls,[43] hypotension, syncope and acute kidney injury or renal failure in the worst cases.[44] Overestimation of BP could also lead to additional costs due to unnecessary treatment.[9]

The traditional cut point to initiate antihypertensive therapy is ≥140/90 mm Hg (Table 1.1). However, patients with BP measured in the "prehypertension" range (120-139/80-89 mm Hg) are at increased risk of cardiovascular disease.[45, 46] Published studies, whether randomised controlled trials or observational studies, report conflicting results on the optimal level of BP for the lowest risk of adverse clinical outcomes.[47] The Systolic Blood Pressure Intervention Trial (SPRINT)[44] found reducing SBP to below 120 mm Hg (compared to standard <140/90 mm Hg) was associated with a 25% risk reduction for the primary composite cardiovascular outcome in participants with high cardiovascular risk, but without diabetes mellitus. SPRINT created many questions for the scientific community because of the automated unobserved office BP protocol used in the study, which is different to all other randomised clinical trials. This protocol reduces the white-coat effect and may explain why the BP target was so low. The Action to Control Cardiovascular Risk in Diabetes BP trial tested the reduction of BP to the same intensive target as SPRINT, but used a traditional office BP measurement protocol. The intensive BP lowering in this study did not reduce events compared to standard BP lowering. Other analyses suggest the relationship between BP and clinical outcomes can be described by U-shaped,[48] or J-shaped[49, 50] curves, suggesting lower BP could be harmful in some patients. These complex issues are the subject of ongoing debate and apparent confusion in the field that are beyond the focus of this thesis.[47, 51-53]

Table 1.1 Classifications of clinic measured blood pressure.

ESH 2013[4]	**Systolic**		**Diastolic**	**JNC7**[5]	**Systolic**		**Diastolic**
Optimal	<120	and	<80	Normal	<120	and	<80
Normal	120 – 129	and/or	80-84	Pre-hypertension	120-139	or	80-89
High normal	130-139	and/or	85-89				
Grade 1 hypertension	140-159	and/or	90-99	Stage 1 hypertension	140-159	or	90-99
Grade 2 hypertension	160-179	and/or	100-109	Stage 2 hypertension	≥160	or	≥100
Grade 3 hypertension	≥180	and/or	≥110				
Isolated systolic hypertension	≥140	and	<90	**N/A**			

Blood pressure classifications based on based on European Society of Hypertension (ESH) and Joint National Committee 7 (JNC7) guidelines.[4, 5]

1.5 Gold standard blood pressure measurement – intra-arterial

Intra-arterial BP measurement requires a catheter, wire or other pressure-sensing device to be temporarily inserted within an artery (e.g. aorta). This method is the most accurate way to test the true accuracy of non-invasive upper arm cuff BP devices, but it is not practical or ethical for everyday use. Whilst intra-arterial BP is considered the gold standard of BP measurement, there are potential limitations if catheters are not correctly handled. Using fluid-filled catheters, BP measurement errors can be caused by sub-optimal dynamic responses (e.g. under- or over-damping)[54] due to the length of tubing, air bubbles, the number of taps and connectors in the system. Solid-state (micromanometer tip) catheters are free of these limitations because the pressure transducer is at the tip of the catheter. But, if handled incorrectly, these catheters may also provide erroneous BP values (due to zero drift). Nevertheless, intra-arterial BP is widely regarded at the gold standard of BP, but due to clear practical limitations use of upper arm cuff devices is necessary for everyday BP screening.

1.6 Cuff blood pressure measurement methods

1.6.1 Original description of cuff measured blood pressure

Scipione Riva-Rocci was a 19th Century Italian internist who described the first pneumatic upper arm cuff for BP measurement.[55] In his thesis, he lamented that there were no accurate methods of BP measurement available for routine clinical use. He realised the potential clinical importance of BP measurement to "discover the force that blood exerts on vascular walls and thus on the surrounding tissue…"[55] Riva-Rocci's discovery, reported in 1896, provided a simple method of BP measurement compared to non-invasive devices before it.[56, 57] The method only enabled measurement of SBP (via palpation of the radial pulse whilst inflating the cuff) and Riva-Rocci theorised that this represented the "total pressure at a point quite close to the aorta or, if you wish, the pressure either in the aorta itself (if the left arm is used)."[55]

The Riva-Rocci method was refined in 1905 when Russian physician Nikolai Korotkoff reported his discovery of the eponymous arterial sounds. Korotkoff measured SBP and DBP by auscultation of the brachial artery during cuff deflation. The discovery, communicated in just 245 words,[58] was arguably one of the most influential in all of clinical medicine and remains the gold standard of non-invasive cuff BP measurement against which newer BP devices are tested for accuracy.[4, 5, 58, 59] In this thesis, the term cuff BP is used to refer to upper arm (brachial) cuff devices, which are used in daily clinical practice. Wrist cuff devices are also available and many have passed international validation protocols.[60] However, the

technical challenges that remain mean these devices are not usually recommended for use, except in patients with a very large arm circumference. [4]

1.6.2 Auscultatory method for cuff blood pressure measurement

Auscultation is the practice of listening to sounds in the body and is typically performed with a stethoscope. Brachial artery auscultation during BP cuff deflation reveals the five Korotkoff sounds (Figure 1.4). The first and fifth Korotkoff sounds are used to measure SBP and DBP respectively.[4] After Korotkoff's discovery scientists began trying to understand the cause of these arterial sounds.[61] Many theories were postulated including breaking steep wavefronts, various fluid-induced vibrations, level of blood flow to the forearm, wall movements and various pressure based phenomena, all of which have been reviewed in detail.[62, 63] In recent years with improved technology, more sophisticated studies have been performed. Benmira et al[64] recently published a detailed assessment of this topic. They studied 23 participants with electrocardiogram gated ultrasound to obtain arterial images as well as Doppler signals, wide frequency electronic recordings of the Korotkoff sounds, pulse wave velocity and arterial diameters. At the onset or just before the first Korotkoff sound a "low-frequency, high energy" Doppler signal was observed. The authors attribute this signal and therefore the first Korotkoff sound to arterial wall instability as flow returns to the occluded artery. These insights are important for understanding BP measurement via auscultation. The genesis of arterial signals measured by Benmira et al[64] appears to be the brachial artery, which supports the notion that the Korotkoff sounds should represent intra-arterial brachial BP. This is different to Riva-Rocci's theory that the cuff BP method would reflect the aortic BP.

1.6.3 Oscillometric method for cuff blood pressure measurement

Arterial wall vibrations during cuff deflation are used to measure BP via the oscillometric method. Most automated devices use this method which detects oscillations in cuff pressure to measure MAP. Arterial oscillations were first described in the 1870s, and by the early 1900s there was a good understanding of this phenomenon.[57] However, it took until the 1970s for the first automated oscillometric device to be developed, known as the device for indirect non-invasive mean arterial pressure (DINAMAP).[65] The DINAMAP measured MAP only, and determined this from the point of maximal cuff pressure using the maximum amplitude algorithm **(**Figure 1.5).

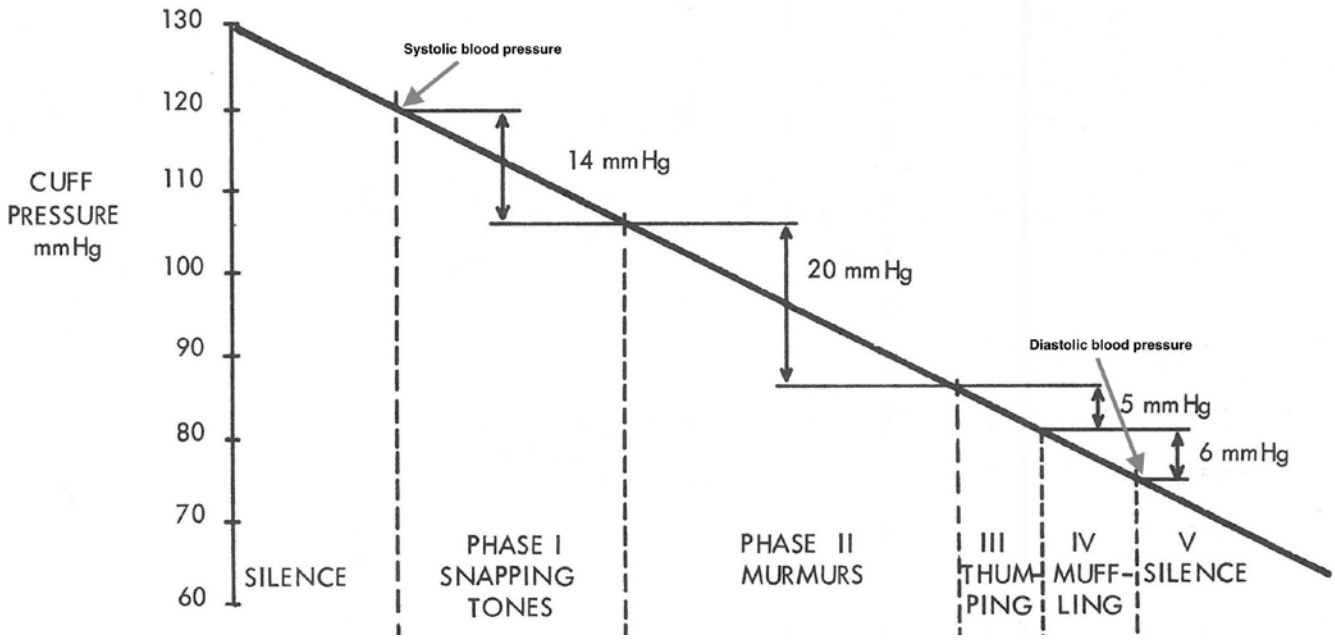

Figure 1.4. Graphical representation of the five Korotkoff sounds for the measurement of blood pressure via auscultation of the brachial artery.

As cuff pressure (y-axis) decreases the first Korotkoff sound is observed (phase I) and this corresponds to systolic blood pressure. Phase II, III and IV are observed with continued deflation before the onset of silence with the fifth Korotkoff sound (phase V). This represents diastolic blood pressure. Adapted from Geddes LA, The Direct and Indirect measurement of blood pressure, page 111, figure 2-27.[57]

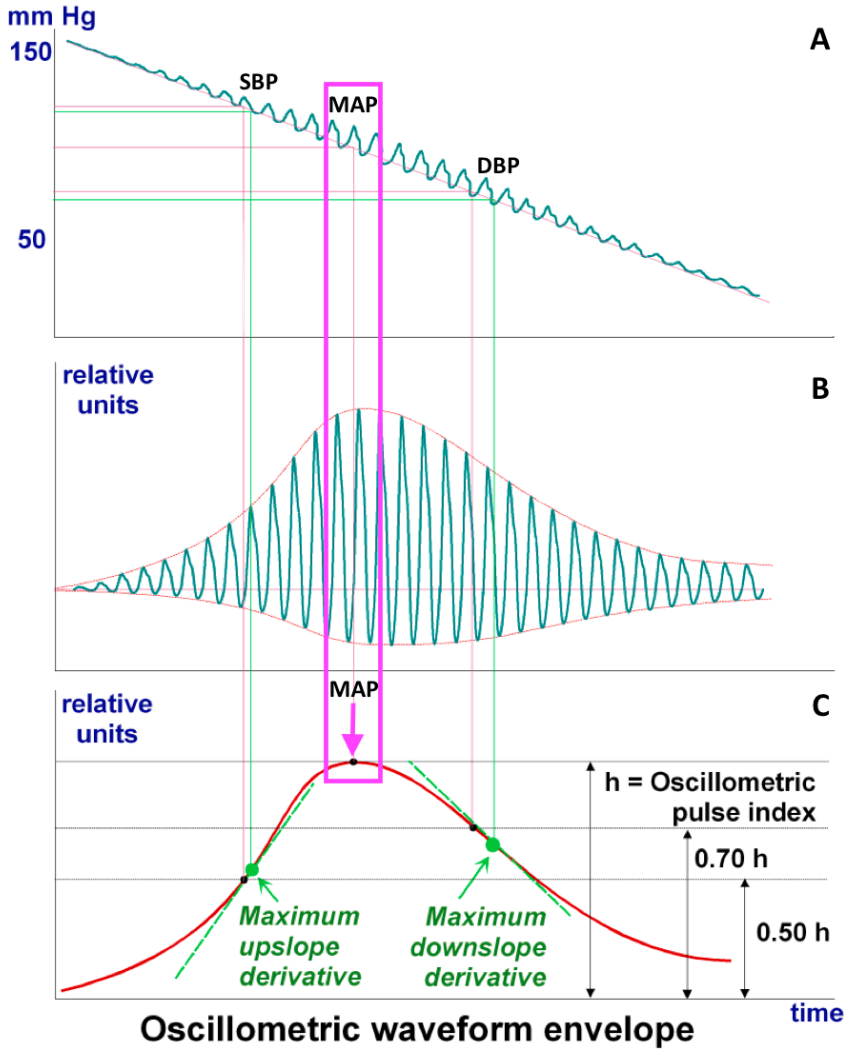

Figure 1.5 Typical method of oscillometric blood pressure measurement.

Cuff pressure deflation and the corresponding curve is depicted in panel A. The oscillometric waveform corresponding to cuff deflation is shown in panel B. The oscillometric waveform envelope is presented in panel C. The maximum amplitude algorithm method is used to detect MAP, as highlighted in panel C through to panel A. Different empirical algorithms can then be used to estimate SBP and DBP. The black dots on the upstroke and downstroke of the oscillometric waveform envelope represent the points used to define SBP and DBP via fixed ratio. The green dots and dashed green lines represent the points of SBP and DBP identification based on maximum up- and down-slopes on the waveform envelope. Figure adapted from Benmira et al, 2016[20] and Forouzanfar et al, 2015[21].

Clinical outcomes are most strongly related to SBP and DBP, thus shortly after the original DINAMAP, a revised device was developed that estimated SBP and DBP.[66] Using oscillometric devices, SBP and DBP are estimated via fixed ratios on the up- and down- slopes of the oscillometric waveform envelope or by assessing the rate of change either side of the maximal oscillation (Figure 1.5). These estimates of SBP and DBP are designed to replicate the 1st and 5th Korotkoff sounds because this is the reference standard new BP devices are validated against.[4, 5, 59] However, the confidential proprietary algorithms used to derive SBP, DBP and MAP in oscillometric devices make it difficult for anyone except the manufacturer to precisely understand the measurement methods of each device. The oscillations detected in the cuff are generated at the brachial artery level, and because the derived SBP and DBP are meant to replicate the Korotkoff sounds, it is fair to assume that oscillometric devices are also intended to measure intra-arterial brachial BP.

1.6.4 Differences between auscultation and oscillometric cuff blood pressure

Auscultation is a "direct" non-invasive measurement of SBP and DBP, via the 1st and 5th Korotkoff sounds (Figure 1.4). On the other hand, the oscillometric method uses empirical calculations to derive SBP and DBP from the oscillometric waveform envelope (Figure 1.5). These are distinct techniques with different strengths and limitations. Auscultation is a tried and tested method with decades of clinical trial data showing BP measured this way predicts risk of disease. But, auscultation is also susceptible to observer-related errors (e.g. hearing problems, digit bias) in BP measurement. An important strength of automated oscillometric devices is that the measurements are observer independent and less susceptible to the errors of auscultation. However, algorithms used in the oscillometric method may be susceptible to systematic error. Furthermore, excessive movement may disrupt the oscillometric measurement process, thus auscultatory BP measurements are recommended in certain settings (e.g. during exercise).[67] Premature ventricular contractions may also create problems for accurate oscillometric measurement of BP compared with auscultation.[66]

1.7 Issues influencing accurate cuff blood pressure measurement.

Accurate cuff BP measurements from either auscultation or automated oscillometric methods are difficult to achieve,[6] with many factors that may cause errors. Scipione Riva-Rocci made astute observations in his thesis on the importance of repeated BP measurements because of the influence of external stimuli (noise, patients reading a book) on accuracy of individual readings.[55] A recent systematic review[6] synthesised many of the factors that affect cuff BP accuracy and Table 1.2 summarises the key issues, grouped as procedure-, observer- and device-related sources of error.

The first two issues can mostly be controlled in optimal conditions and whilst important, they are not the focus of the thesis. On the other hand, device-related issues cannot be addressed without fundamental changes to the actual device or method used to measure BP. The systematic review[6] has not fully addressed this issue because the search terms were too narrow to capture all the relevant studies. Furthermore, there was no meta-analysis to fully quantify the magnitude of cuff inaccuracy. The problems with cuff BP accuracy compared to the gold standard intra-arterial BP measurement have been recognised since at least the 1950s when a report endorsed by the American Heart Association was published.[8]

Table 1.2 Factors that may influence the accuracy of cuff measured blood pressure in adults.

	SBP error (versus reference method)	DBP error (versus reference method)
Procedure-related		
Arm lower than heart level	↑	↑
Body position		
Standing	≠	↑*
Supine	≠	≠
Cuff placed over clothing	≠	↑*
Excessive pressure on stethoscope head	≠	↓
Fast cuff deflation rate	↓	↑
Incorrect choice of cuff size		
Smaller cuff	↑	↑
Larger cuff	↓	↓
Insufficient rest period	↑	↑
Legs crossed at knees	↑	↑
Reliance on a single measurement	↑	≠
Short interval between measurements	≠	≠
Stethoscope under cuff	↑	↓
Talking during measurements	↑	↑
Unsupported back	≠	↑
Unsupported arm	↑*	↑
Use of stethoscope bell (versus diaphragm)	≠	↓*
Observer-related		
Korotkoff Phase IV (versus V) for DBP	N/A	↑

Table 1.2 (continued)		
Observer hearing deficit	↓	↑
Terminal digit preference for zero	1-79% over-representation of terminal zero	3-79% over-representation of terminal zero
Device-related		
Accuracy versus invasive criterion	↓	↑
Accuracy versus non-invasive criterion	≠	≠
Device calibration error		

Adapted from: Kallioinen et al, 2017.[6] SBP, systolic blood pressure; DBP, diastolic BP; ↑, SBP or DBP higher than reference method; ↓ SBP or DBP lower than reference method; ≠ significant effects reported in each direction or no significant effects reported; * only one study reported significant effect.

1.7.1 Standard cuff blood pressure devices – lines of evidence questioning accuracy

Several lines of evidence place a question over the accuracy of cuff BP devices (device-related issues) used in daily clinical practice. Numerous studies have shown cuff BP underestimates intra-arterial brachial SBP and overestimates intra-arterial brachial DBP. This is the prevailing dogma on cuff accuracy.[10, 68, 69] However, BP values from intra-arterial aortic, brachial or radial measurements are not equivalent, and the differences may be highly variable.[14, 15, 70, 71] Cuff BP is often tested for accuracy against these intra-arterial BPs interchangeably without consideration of the physiological difference across the arterial sites. This issue was not addressed in the aforementioned systematic review.[6] Moreover, testing cuff values against BP from different intra-arterial sites may lead to confusion on what cuff BP is intended to measure. Riva-Rocci surmised cuff SBP was equivalent to intra-arterial aortic SBP.[55] Indeed, some recently published studies support this assertion.[12, 13] But, standard cuff BP methods (auscultatory and oscillometric) use signals from the brachial artery to measure BP and are expected to represent intra-arterial brachial BP. Clarifying this issue is critically important because there is a clear physiologic rationale that aortic BP is more closely related than brachial BP to the pressure load on vital organs, and thus clinical outcomes.[72, 73]

The strongest cardiovascular risk factor is BP, and therefore it is expected that inaccuracy of cuff BP could have large implications for appropriate diagnosis and management of hypertension and therefore overall cardiovascular risk.[9] Although issues of cuff accuracy compared with intra-arterial BP have been acknowledged in expert consensus documents for decades,[8] and many studies have tested this,[10, 11, 14, 16] there has never been a comprehensive analysis of all available data. This would help to resolve issues of uncertainty around the accuracy of cuff BP and in determining potential clinical ramifications of cuff inaccuracy. *The aim of Chapter 2 of this thesis was to examine the accuracy of cuff-measured BP compared with brachial and aortic intra-arterial BP.*

1.7.2 What are the reasons for cuff inaccuracy compared to intra-arterial blood pressure?

There are several hypotheses on the reasons for cuff inaccuracy, but overall this issue remains poorly understood. Increased arterial stiffness may affect the compressibility of the brachial artery and influence BP measurements,[74] as well as the ability of oscillometric algorithms to accurately detect BP.[17] A second possible cause of inaccuracy is larger arm circumference and obesity,[18, 19] which can mean the BP cuff fits poorly as well as difficulty in compression of the

artery. Data on the effect of arm circumference and obesity is equivocal,[17-19, 69, 74-76] leaving the field without a definitive understanding around this problem.

Standard cuff BP methods outlined in section 1.5 (Korotkoff sounds and oscillometry) use a standard 'one size fits all' approach to measure brachial artery signals for every measurement on every person. But, there is considerable individual variation across a range of arterial characteristics including vessel stiffness, diameter, tapering and wall thickness,[38, 70, 77-79] as well as BP transmission from central-to-peripheral arteries and BP waveform morphology.[14, 70, 71, 79] The relationship of variability in BP transmission from central-to-peripheral arteries, BP waveform characteristics and cuff BP has never been examined in detail. However, this could provide a novel explanation for inaccuracy of cuff BP measurements. *The aim of Chapter 3 of this thesis was to determine if BP phenotypes exist that are related to the transmission of BP from central-to-peripheral arteries and how these may influence cuff BP measurement accuracy compared to intra-arterial BP.*

1.8 Estimated (non-invasive) aortic blood pressure measurement methods

Brachial cuff BP is a strong predictor of cardiovascular risk.[35] However, there is a physiological expectation that aortic BP, not brachial BP should more closely associate with risk.[80] This is based on the closer proximity of the vital organs (e.g. heart, brain, kidneys) to the aortic BP load and the potential for large differences in SBP between the aorta and the brachial artery. Indeed, understanding how BP is transmitted from central-to-peripheral arteries has been of interest for many decades.[81] Distinct variability in SBP between the aorta and brachial arteries has led to the development of non-invasive methods to estimate aortic BP. [23] The only way to measure aortic BP before the invention of these devices was via intra-arterial catheterisation, a highly invasive procedure only performed during coronary angiography or coronary artery bypass surgery. This is not practical and is unethical to use for routine BP screening, thus the added impetus to develop non-invasive methods to estimate aortic BP. The first commercially available device to estimate aortic BP was SphygmoCor (AtCor Medical, North Ryde, Australia). There are now >10 different specialist devices that estimate aortic BP (and aortic BP waveform characteristics), each with methodological strengths and limitations (Table 1.3).[82]

Studies published using estimated aortic BP methods generate controversy and heated debate. Differing views about mathematical algorithms,[83-88] and waveform calibration (scaling) methods[89-91] dominate correspondence. Overall, irrespective of the important academic

discussions on this topic, the clear limitations to the accuracy of estimated aortic BP have been reproduced by multiple independent observers.[12, 13, 25, 26, 29, 92, 93] The term "central BP" is most commonly used to refer to devices that purport to estimate aortic BP. However, "central BP" has become synonymous with the perpetual arguments between investigators. The term "estimated aortic BP" will be used throughout this thesis, because of the thesis focus on the accurate measurement of BP, irrespective of whether this is at the aorta or brachial artery. Notionally, there is an expectation of greater clinical relevance of aortic BP compared to brachial BP,[80] but accuracy issues with these devices may seriously confound studies on this topic.[80]

1.8.1 Comparison between cuff brachial and central aortic blood pressure for predicting outcomes.

In 2010, Vlachopoulos et al[94] conducted a meta-analysis of all available data on aortic BP compared with brachial cuff BP for the prediction of clinical events. Pooled results from four studies in 3465 patients showed that aortic SBP did not predict clinical outcomes above and beyond brachial SBP (risk ratio (RR): 1.236 (95% CI 1.128 to 1.354) versus RR: 1.204 (95% CI 1.104 to 1.313), p=0.62). For PP, data from five studies with 4574 patients was analysed and aortic PP (RR: 1.318 (95% CI 1.221 to 1.423)) trended toward predicting clinical outcomes better than brachial PP (RR: 1.188 (95% CI 1.104 to 1.280), p=0.057). After excluding one study perceived to be methodologically flawed, aortic PP was found to be a significantly stronger predictor of clinical outcomes than brachial PP (RR: 1.338 (95% CI 1.236 to 1.448) versus 1.178 (95% CI 1.091 to 1.272), p=0.017).[95]

A recent analysis of 2183 Framingham Heart Study participants found there was no additional predictive power of estimated aortic BP beyond brachial BP.[96] Kollias et al[97] also published a meta-analysis of cuff BP versus aortic BP for prediction of target organ damage. This study found that estimated aortic SBP was modestly, but significantly more closely related to left ventricular mass index, carotid intima-media thickness and aortic stiffness (measured by pulse wave velocity) than cuff BP.[97] The modest or lack of predictive power of estimated aortic BP above and beyond brachial BP may be related to collinearity of the two BPs ($R \geq 0.96$ in the Framingham Study).[96] Brachial and aortic BP will always be correlated, but with non-invasive techniques collinearity may be greater because the BP waveform used to estimate aortic BP is calibrated (scaled) with brachial BP.

More recent data from one device (Mobil-o-graph, IEM GmbH, Stolberg, Germany), has shown estimated aortic BP from cuff oscillometric MAP/DBP calibration may improve

prediction of clinical outcomes. Indeed, estimated aortic BP from this method has been found to predict left ventricular hypertrophy in most,[36, 98] but not all available data,[99] more strongly than brachial cuff BP and estimated aortic BP from cuff SBP/DBP calibration. Additionally, other data shows cuff MAP/DBP calibration to be superior for predicting coronary atherosclerosis,[100] and mortality in a small cohort of end stage renal disease patients.[101] The oscillometric MAP/DBP calibration mode reduces collinearity of estimated aortic BP and brachial BP,[101] which potentially means the variance in clinical outcomes could have a stronger association with estimated aortic BP. However, these findings may be specific to the Mobil-o-graph device.[102] Several limitations of estimated aortic BP are commonly acknowledged, relating to mathematical algorithms and BP waveform calibration methods. These issues are usually responsible for problems with measurement accuracy.[29, 103] The heterogeneity of estimated aortic BP values between devices could explain the varying strength of associations with target organ damage, as well as the conflicting data on the clinical usefulness of estimated aortic versus brachial cuff BP.

1.9 Issues influencing accuracy of estimated aortic blood pressure.

The limitations of devices that estimate aortic BP are shown in Table 1.3. The two most commonly cited limitations are use of a generalized transfer function and methods of calibration. In these devices, transfer functions are used to express the relationship between the peripheral (brachial or radial) waveform and the aortic waveform. The transfer functions are generalized because they are averaged from a dataset of individual participant transfer functions and are intended to be applicable across the entire population. For example, the transfer function in the SphygmoCor device was developed in just 14 people,[104] but has since been validated by numerous independent groups.[105-107] The accuracy of generalized transfer functions has been the subject of continual scientific disagreement,[24, 81, 108] especially in specific populations such as patients with type 2 diabetes mellitus,[87, 109, 110] chronic kidney disease,[111, 112] and children.[113, 114] Generalized transfer functions are not the focus of this thesis, for more information refer to Chapter 26 of McDonald's Blood Flow in the Arteries textbook 5th edition[115] and Segers et al.[28]

The other primary limitation of estimated aortic BP is the calibration of peripheral BP waveforms. Calibration is performed to scale waveforms to pressure units (mm Hg). For example, the operation of the SphygmoCor involves three key steps including calibration: 1) radial waveform is recorded via applanation tonometry; 2) waveform calibration, usually with cuff SBP/DBP, or alternatively with cuff MAP/DBP and 3) radial to aortic generalized transfer

function is applied to estimate aortic BP (Figure 1.6). Issues that ignite lack of agreement around the best calibration methods to estimate aortic BP accurately include BP amplification,[15, 26, 99,] cuff accuracy,[82, 116, 117] and the actual BP values used for calibration.[12, 15, 26, 29, 85, 89, 92, 93, 103, 116-119]

Table 1.3. Critical analysis of the current methods to estimate aortic blood pressure non-invasively.

	Positive aspects	Limitations	Commercial devices available
Carotid tonometry	- Close proximity of aorta and carotid - No transfer function of mathematical modelling - Can be used in children - 3 mortality studies[120-122]	- Aortic to carotid amplification might not be negligible - Calibration to mean and diastolic pressure cuff pressure - High quality carotid tracings could be difficult to obtain	Complior Analyse (Alam Medical, France) Pulse Pen (Diatecne, Italy) SphygmoCor CVMS (AtCor, Australia)
Carotid echotracking	- Close proximity of aorta and carotid - Can be used in children or obese patients	- Calibration to mean and diastolic pressure cuff pressure - Diameter and BP waveform might differ due to non-linearity of arterial wall	ArtLab and MyLab (Esaote, Italy)
Radial tonometry + transfer function	- Radial tonometry easier than carotid tonometry - 1 mortality study [123]	- ***Calibration to cuff pressure*** - ***No correction for upper arm amplification*** - Use of generalized transfer function for the whole population	B-Pro, Caspal, CasPro (Healthstats, Singapore) SphygmoCor CVMS (AtCor, Australia)
Radial tonometry + SBP2 (+calibration correction)	- Hands-free radial tonometry - Estimation not dependent on cuff calibration error	- ***Incorrect information on aortic to brachial amplification***	Omron HEM9000-AI (Omron, Japan)

		- Difficulty to detect 2nd systolic shoulder - Limited accuracy in young healthy subjects and low BP subjects	
Brachial oscillometry	- Non operator-dependent - Ease of use - Possibility to assess central SBP over 24h for some devices - One mortality study[101]	- ***Calibration to cuff pressure*** - Based on generalized transfer function for the whole population	Arteriograph (TensioMed, Hungary) Centron cBP301 (Centron, UK) Mobil-o-graph (IEM, Germany) PulseCor (New Zealand) SphygmoCor XCEL (AtCor, Australia) Vicorder (Skidmore Medical, UK) Watch BP Office Central (Microlife, Switzerland) BPLab (BPLab, Russia)

Adapted from Millasseau and Agnoletti.[82] The limitations in ***underlined bold italics*** will be addressed in Chapter 4 of this thesis. SBP2, second systolic peak on radial BP waveform.

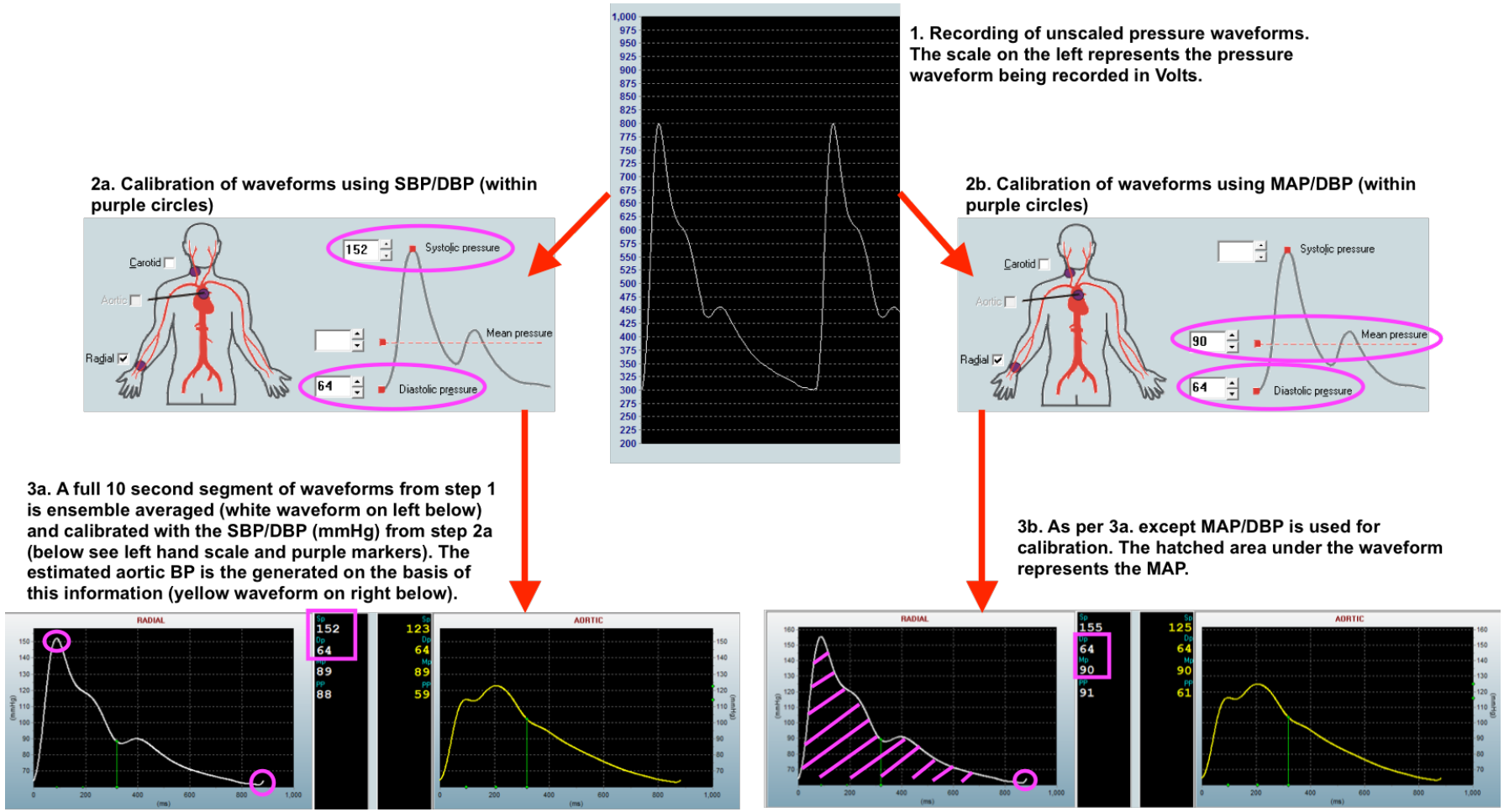

Figure 1.6 Process for estimation of aortic blood pressure using SphygmoCor CVMS

Representative figure of process to estimate aortic BP via calibration (scaling) of peripheral BP waveforms using systolic BP (SBP)/diastolic BP (DBP) calibration or mean arterial pressure/DBP with SphygmoCor CVMS (AtCor Medical. North Ryde, Australia). See figure text for details.

1.9.1 Estimated aortic blood pressure devices – lines of evidence questioning accuracy

Several lines of evidence on different aspects of the calibration process raise questions on the accuracy of estimated aortic BP. There have been several meta-analyses assessing the accuracy of estimated aortic BP compared to intra-arterial aortic BP.[13, 29, 103] The most recent, from Papaioannou et al, 2016[29] examined commercially available devices for accuracy when the two most common waveform calibrations, cuff SBP/DBP or cuff MAP/DBP were used. As expected, estimated aortic SBP from cuff SBP/DBP waveform calibration substantially and significantly underestimated intra-arterial aortic SBP (13 studies, -7.8 mm Hg, 95% CI -10.3 to -5.3). On the other hand, cuff MAP/DBP calibration still significantly underestimated aortic SBP, but by a much smaller magnitude (6 studies, -3.0 mm Hg, 95% CI -5.8 to -0.22). Ignoring brachial-to-radial SBP amplification and cuff BP error may both contribute to inaccuracy of estimated aortic BP.[26, 93, 117]

Cuff SBP/DBP has long been recommended as the optimal calibration method when radial waveforms are used to estimate aortic BP.[91, 124] This is based on the textbook assumption of negligible brachial-to-radial SBP amplification.[115] However, we and others have previously shown substantial brachial-to-radial SBP amplification in non-invasive and intra-arterial BP studies. Our previous work showed that after accounting for brachial-to-radial SBP amplification in radial waveform calibration, estimated aortic SBP was significantly increased in younger (+5±4 mm Hg) and older apparently healthy participants (+12±6 mm Hg),[26] and patients with type 2 diabetes mellitus (+9±6 mm Hg).[93] Despite some differing views,[15, 89-91, 125-128] most evidence suggests brachial-to-radial SBP amplification exists (or is at least variable between individuals),[15, 25, 26, 70, 81, 93, 129-131] and two expert consensus documents cite this as an issue affecting accurate estimation of aortic BP from radial waveforms.[102, 132] MAP/DBP is relatively stable through the large arteries,[133] therefore, calibration using this method may partly account for brachial-to-radial SBP amplification.[96] Cuff BP inaccuracy may also compound measurement error, which is also a problem for newer brachial cuff based methods.

In the past five years, the popularity of brachial cuff based devices for estimation of aortic BP has rapidly increased. These devices are more user friendly than other methods, making them more appealing in the clinical setting. Using brachial waveforms to estimate aortic BP also negates the potential for inaccurate calibration due to brachial-to-radial SBP amplification. However, because cuff BP tends to inaccurately represent intra-arterial BP,[10, 11] cuff SBP/DBP calibration of brachial waveforms still underestimates intra-arterial aortic SBP.[29] Shih et al, [117] have shown that 96% of the error in SBP is caused by cuff underestimation of intra-arterial brachial SBP. However, the authors developed the generalized transfer function on the same

participant cohort they then tested with the cuff calibration. This could inadvertently eliminate some error caused by the transfer function that would be evident if the cuff calibration was performed on an independent dataset. On the other hand, using cuff MAP/DBP calibration may produce a more accurate,[29] and clinically relevant[36, 98, 101] estimate of aortic SBP than cuff SBP/DBP calibration, although this may be device specific. To date no cuff calibration has produced an estimated aortic BP to the same level of accuracy as compared to intra-arterial aortic MAP/DBP calibration. An important question to examine is if accurate measurement of cuff SBP/DBP or cuff MAP/DBP was achieved, which of the two calibration methods would produce the best estimated aortic BP. *The aim of Chapter 4 of this thesis was to determine the best peripheral waveform calibration method for accurate estimated aortic BP and to understand arterial variables that may influence this.*

1.10 Potential benefits of improving blood pressure measurement accuracy

There are clear hints within the literature that BP measurement accuracy from standard cuff methods and estimated aortic BP may be inaccurate. This is concerning and improving BP measurement accuracy would be expected to have several benefits. First, more accurate BP measurements would lead better BP management and potentially more personalised treatments. Because even small errors in BP measurement (e.g. 5 mm Hg) could have major ramifications for BP diagnosis,[9] any small improvements in accuracy would be valuable. Second, more accurate measurements would improve the quality of research on BP, and advance knowledge on thresholds for BP management across different populations, efficacy of antihypertensive therapies and the relationship of BP with damage of different target organs. This is especially important for kidney disease, where data are still equivocal on the benefits of antihypertensive medications,[3] with the suggestion that intensive BP lowering could even accelerate declines in kidney function.[134] Finally, accurate BP measurements would allow true understanding of the clinical relevance of brachial versus estimated aortic BP. This would lead to better understanding of this issue among various populations (e.g. apparently healthy, various disease states) and different vital organs (e.g. heart, kidneys).

1.11 Summary

This review of literature has covered key issues related to the accurate measurement of BP. Overall, evidence accumulated over several decades suggests that cuff measured BP, used in daily clinical practice for diagnosis and management of high BP, may be inaccurate compared with gold standard intra-arterial BP. Important questions on the true level of cuff inaccuracy compared to intra-arterial BP from different arterial sites and potential clinical ramifications of

inaccuracy need to be resolved. Beyond quantifying the level of cuff inaccuracy, there has never been a definitive breakthrough to understand this problem. Specialist devices that estimate aortic BP non-invasively may be prone to inaccuracy due to calibration methods, and further detailed studies on this issue are required.

Chapter 2 - Accuracy of cuff measured blood pressure: systematic reviews and meta-analyses

This thesis chapter has been published and formatted according to the guidelines of *Journal of the American College of Cardiology*.

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Presentations and awards:

Australian Society of Medical Research: Medical Research Week Postgraduate student oral presentations Tasmania - 1st Prize out of 6 presentations and selected from >40 abstracts.

International Society of Hypertension congress oral presentation, Seoul, South Korea, September 2016.

ARTERY 15 congress oral presentation, Krakow, Poland, October 2015.

2.1 Abstract

Background: Hypertension (HTN) is the single greatest cardiovascular risk factor worldwide. HTN management is usually guided by brachial cuff blood pressure (BP), but questions have been raised regarding accuracy.

Objectives: We studied the accuracy of cuff BP and the consequent impact on BP classification compared with intra-arterial BP reference standards.

Methods: Three individual participant data meta-analyses were conducted among studies (from the 1950's to 2016) that measured intra-arterial aortic BP, intra-arterial brachial BP, and cuff BP.

Results: Seventy-four studies and 3,073 participants were included. Intra-arterial brachial systolic BP (SBP) was higher than aortic values (8.0 mm Hg; 95% CI 5.9 to 10.1; p <0.0001) and intra-arterial brachial diastolic BP was lower than aortic values (-1.0 mm Hg; 95% CI -2.0 to -0.1; p =0.038). Cuff BP underestimated intra-arterial brachial SBP (-5.7 mm Hg; 95% CI -8.0 to -3.5; p <0.0001) but overestimated intra-arterial diastolic BP (5.5 mm Hg, 95% CI 3.5 to 7.5, p <0.0001). Cuff and intra-arterial aortic SBP showed a small mean difference (0.3 mm Hg; 95% CI -1.5 to 2.1; p =0.77) but poor agreement (mean absolute difference 8.0 mm Hg, 95% CI 7.1 to 8.9). Concordance between BP classification using JNC7 cuff BP (normal, pre-HTN, HTN stages 1 and 2) compared with intra-arterial brachial BP was 60%, 50%, 53% and 80%, and using intra-arterial aortic BP was 79%, 57%, 52% and 76%. Using revised intra-arterial thresholds based on cuff BP percentile rank, concordance between BP classification using cuff BP compared with intra-arterial brachial BP was 71%, 66%, 52% and 76%, and using intra-arterial aortic BP was 74%, 61%, 56% and 65%.

Conclusions: Cuff BP has variable accuracy for measuring either brachial or aortic intra-arterial BP, and this adversely influences correct BP classification. These findings indicate that stronger accuracy standards for BP devices may improve cardiovascular risk management.

2.2 Introduction

Cardiovascular disease is the number one cause of mortality worldwide, with elevated blood pressure (BP) as the single largest risk factor.[33, 35, 136] Non-invasive brachial (upper arm) cuff BP is the principal method for hypertension diagnosis and management, thus, accurate BP measurement is amongst the most important medical tests performed.[7] Relatively small errors in cuff BP measurement can have major public health ramifications. An inaccuracy of 5 mm Hg estimated to result in the misclassification of BP among 48 million people each year in the United States alone (21 million related to BP underestimation, 27 million related to overestimated BP).[9] BP underestimation leads to missed therapeutic potential and unnecessary elevation of cardiovascular risk.[137] BP overestimation creates additional cost and exposure to possible adverse effects of unnecessary treatment.[9] The recognition of prehypertension as a nonbenign clinical presentation,[45] and the benefit to some patient populations of achieving low BP targets[44] further emphasizes the need for accurate cuff BP across the range of BP classifications.

Several lines of evidence place a question mark over the accuracy of cuff BP. First, many small studies indicate a possible bias for cuff BP to underestimate intra-arterial brachial systolic BP (SBP), yet overestimate intra-arterial brachial diastolic BP (DBP) and, thereby, underestimate intra-arterial pulse pressure (PP).[10, 11, 14] Second, cuff BP devices being tested for accuracy against other noninvasive measurements according to international validation protocols may perform to a "pass" standard even when clinically significant measurement errors occur among many patients.[138] Third, there is large individual variability in intra-arterial BP between the aorta and brachial artery,[14, 22, 71] and whether oscillometric or auscultatory cuff BP accurately measures either aortic or brachial BP has never been systematically determined. This is important to resolve given 1) the possibility that aortic BP is more clinically relevant than brachial BP, [22, 94, 97, 139] and 2) the burgeoning of commercial devices purporting to measure aortic BP[82] to (theoretically) better assess cardiovascular risk.[72] However, this is a controversial theory[80, 140], with some investigators asserting that there is a lack of evidence to justify departing from standard cuff BP.[140, 141] Others suggest that brachial cuff BP may already accurately measure aortic BP, eliminating the need for specialist devices.[12, 13]

These issues create uncertainty as to whether cuff BP accurately measures intra-arterial BP, either at the brachial or aortic level. Better understanding of these issues is relevant to validation protocol standards for cuff BP devices, and could lead to improved clinical management of cardiovascular risk through more accurate BP measurement and classification. We completed 3 separate but inter-related systematic reviews and individual participant data meta-analyses to

determine the accuracy of cuff BP measurement methods. We first aimed to determine the true level of intra-arterial BP agreement between the aorta and brachial artery (meta-analysis 1), and then whether cuff BP accurately measured either intra-arterial brachial BP (meta-analysis 2) or intra-arterial aortic BP (meta-analysis 3). Potential clinical consequences of cuff BP measurement error were determined by the concordance between cuff and intra-arterial BP for classifying HTN according to criteria of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). [5]

2.3 Methods

Search technique and study eligibility. The search technique, study eligibility criteria, data collection, synthesis and statistical analysis were conducted similarly across each meta-analysis, with minor differences reflecting the specific needs of each meta-analysis question. The Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) were adhered to (Appendix Table 1.1) [142]. Two reviewers (D.S.P, M.G.S) identified eligible studies by title, abstract or full-text review and performed a separate data quality assessment. All these activities were undertaken with each reviewer blinded to the other reviewer's results. Discrepancies were resolved via consensus.

Four online databases (PubMed, Scopus, Embase and Web of Knowledge) were systematically searched for eligible articles from database inception until 9 May 2016, with slight modifications for each meta-analysis (Appendix Table 1.2). Additional studies were found by searching the reference lists of identified studies and personal communication with authors. Unpublished data was accepted if sufficient methodology was provided (Appendix 1.1). Study eligibility was not restricted by subject age, language or year of publication. We included studies that measured intra-arterial BP by high-fidelity micromanometer tip or fluid-filled catheters, as well as indwelling arterial needles and cannulas. For each meta-analysis, studies were only included if the BP measurements being compared were recorded within the immediate period of each other, rather than at different times [143], due to possible hemodynamic changes between measurement periods [102]. Studies that measured BP at multiple arterial sites (e.g. brachial and radial) in the same study were included if authors were able to provide separated data. Studies that recorded data under non-basal conditions involving hemodynamic shifts (e.g. exercise or administration of vasoactive drugs that altered BP during the recording procedure) were excluded. There was some minor variability of the inclusion and exclusion criteria that were specific to the goal of each meta-analysis. These included cuff BP methods of auscultation (mercury or aneroid), and oscillometric and automatic Korotkoff sound devices for meta-analyses 2 and 3. Studies were also excluded if the goal of the work was to determine

the effect of different cuff sizes on the relationship between cuff BP and intra-arterial BP, because of the expectation of cuff BP measurement error [144]. For meta-analyses 1 and 3, studies that measured aortic BP distal to the aortic arch were excluded because potential amplification of SBP along the aorta [145] could contribute to discordance of comparison between BP measurements.

Data collection. For each eligible study, individual participant level de-identified BP data were requested from authors. PP was calculated as SBP – DBP. Clinical information including age, sex, anthropometry, medications, and disease status were also requested if available. Data in non-international system of units format were standardised to international system of units, except for pressure units. Individual data supplied by authors were checked for consistency with published aggregate data where available. If discrepancies were identified, clarification was sought from authors. If no response was received to data requests, or authors were not contactable, individual data were extracted from within published tables (Appendix 1.2), or from figure scatterplots using extraction software, when possible.[146] Data obtained from scatterplots were only included in the meta-analyses when accuracy could be verified by comparison with published summary data or correlation coefficients (Appendix Table 1.3). A quality score was applied to each study to account for important study design attributes that may have impacted on data quality (Appendix 1.3**,** Appendix Tables 1.4- 1.6). The University of Tasmania Health and Medical Human Research Ethics Committee approved the study (reference: H0015048).

Magnitude of BP differences. The proportion of cuff BP measurements that were ≥5, ≥10 or ≥15 mm Hg different from intra-arterial BP were determined as a measure of accuracy.[147]

BP classification. To determine accuracy of cuff BP for BP classification, each individual's cuff BP was classified according to JNC 7 criteria (normal BP <120/80 mm Hg, preHTN SBP 120 to 139 or DBP 80 to 89 mm Hg, stage 1 HTN SBP 140 to 159 or DBP 90 to 99 mm Hg and stage 2 HTN SBP ≥160 or DBP ≥100 mm Hg) [5], and then compared for concordance with the BP classification according to the measurement of BP by intra-arterial brachial and aortic BP. For example, for an individual with cuff BP classified as normal (<120/80 mm Hg), the corresponding intra-arterial BP for that individual was classified into the appropriate category (e.g. normal, preHTN, stage 1 or 2 HTN), and found to be concordant if also falling into the same normal BP classification (<120/80 mm Hg). This approach enabled an assessment of the potential impact of cuff BP inaccuracy on clinical practice, but also involves a level of arbitrariness with BP cut points because there is a continuous relationship between BP and cardiovascular risk. Additional analyses were also undertaken in which the risk cut points for

intra-arterial BP (both brachial and aortic) were drawn at equal percentile ranks to the traditional cuff BP cut points. Sensitivity and specificity of cuff BP for delineating HTN at a cut point of ≥140/90 mm Hg was also assessed.

Statistical analysis. BP and clinical characteristics are presented as mean and 95% confidence interval (95% CI) unless otherwise specified. BP differences were calculated as brachial artery BP minus aortic BP (meta-analysis 1) and cuff BP minus intra-arterial brachial or aortic BP (meta-analysis 2 and 3). Both 1-stage and 2-stage meta-analysis was used. The results generated from each method are considered equivalent in individual participant data meta-analysis [148]. Two-stage meta-analyses were used to analyse mean BP differences because this method allowed production of summary forest plots to illustrate the level of the BP difference across included studies. For this method, data were first analyzed study by study and then synthesized using random effects meta-analysis due to the observational nature of the data. Correlation coefficients from individual studies were used to calculate summary correlation coefficients on the relationship between BP measurements in each meta-analysis. This same method was used for sensitivity and specificity analyses for cuff BP delineating HTN based on the 140/90 mm Hg cut point. Linear mixed modelling (1-stage meta-analysis) was used to account for clustering of individuals within each study for mean absolute difference, BP classification analysis, percentile calculation for the revised intra-arterial BP thresholds and potential predictors of BP differences. Mean absolute difference was calculated as the absolute value of the BP difference at the individual participant level. In meta-analysis 3, Laugesen et al. [118] and Rossen et al. [149] were pooled for analysis, because participants were from the same population and the measurement protocols used were identical, except for the type of cuff BP device.

Sensitivity analyses were among studies that received the maximum study quality score to assess whether results were influenced by study design factors and to separately assess published data sources compared with unpublished data sources. To determine the influence on results of meta-analyses 2 and 3, sensitivity analyses were conducted for single BP measurements compared with the average of multiple cuff BP measures, as well as the type of catheter used for intra-arterial BP measurement. Analyses on linearity of relationships between cuff and intra-arterial BP were also explored. P values <0.05 were considered statistically significant. Data were synthesized and analyzed using R, version 3.1.2, R Core Team (2014), primarily using the metafor and lme4 packages and Stata 14, StataCorp (2015; metandi module). Additional statistical methods are in Appendix 1.4.

2.4 Results

Eligible studies and subject characteristics. A total of 75,071 studies were identified from the three meta-analysis searches. After review based on title and abstract, 371 studies were full-text reviewed and 152 of these were eligible for inclusion in the meta-analyses. Individual participant data were not available from 7, 49 and 23 studies for meta-analyses 1, 2 and 3 respectively. This left 13 studies,[11, 14-16, 22, 71, 150-153] 22 studies,[10, 11, 14, 16, 19, 68, 69, 152, 154-164] and 39 studies[11, 12, 14, 16, 69, 114, 118, 149, 152, 165-189] for SBP analysis, whereas 12 studies,[11, 15, 16, 22, 71, 150-153] 18 studies,[10, 11, 16, 19, 68, 69, 152, 155-162] and 36 studies[11, 16, 69, 114, 118, 149, 152, 165-179, 181-189] were available for analysis relating to DBP and PP. Systematic review flow diagrams and study characteristics for all meta-analyses are detailed in Appendix Figures 1.1-1.6 and Appendix Tables 1.7-1.12). Data were extracted from published tables in 11 studies, and from published figures in 6 studies. Data was sourced from 18 countries (Australia, New Zealand, China, Japan, Singapore, United States, Canada, England, Scotland, France, Germany, Italy, Austria, Portugal, The Netherlands, Denmark, Norway and Israel). Across the three meta-analyses, subjects were generally middle-older aged, predominately male and overweight according to body mass index (Tables 2.1-2.3). When individual participant data were checked as per guidelines,[142] no important issues, such as inconsistency with published aggregate data arose. There were minor differences between the number of subjects in some published articles and the number of subjects used in the meta-analyses (see explanation in Appendix 1.5).

Table 2.1 Subject characteristics from meta-analysis 1.

	Mean (95% CI) or n (%)	n=individual subjects, S=studies
Age (years)	58.6 (53.7 to 63.6)	n=487, S=12
Male sex	353 (72)	n=490, S=12
Height (cm)	165.5 (162.5 to 168.6)	n=382, S=7
Weight (kg)	70.9 (67.6 to 74.3)	n=382, S=7
Body mass index (kg/m^2)	26.0 (24.9 to 26.7)	n=382, S=7
Intra-arterial aortic systolic blood pressure (mm Hg)	131.8 (126.4 to 137.0)	n=515, S=13
Intra-arterial brachial systolic blood pressure (mm Hg)	140.3 (135.7 to 144.7)	n=515, S=13
Intra-arterial aortic diastolic blood pressure (mm Hg)	70.9 (68.6 to 73.1)	n=495, S=12
Intra-arterial brachial diastolic blood pressure (mm Hg)	69.9 (67.2 to 72.5)	n=495, S=12
Intra-arterial aortic pulse pressure (mm Hg)	60.3 (55.3 to 65.2)	n=495, S=12
Intra-arterial brachial pulse pressure (mm Hg)	70.3 (65.9 to 74.6)	n=495, S=12

Data are mean (95% confidence interval (CI)) or n (percentage). Subject characteristics were not available for all studies, and the numbers available are reported in the right hand column of the table. The maximum data available was n=515 from 13 studies. Subject characteristic data was derived from individual data, and when this was unavailable, aggregate data extracted from published studies.

Table 2.2 Subject characteristics from meta-analysis 2.

	Mean (95% CI) or n (%)	n=individual participants, S=studies
Age (years)	53.0 (42.7 to 63.4)	n=538, S=13
Male sex	261 (62%)	n=418, S=11
Height (cm)	164.0 (162.0 to 166.1)	n=494, S=10
Weight (kg)	73.8 (68.7 to 79.0)	n=494, S=10
Body mass index (kg/m^2)	27.3 (26.3 to 28.4)	n=494, S=10
Brachial cuff systolic blood pressure (mm Hg)	141.5 (133.4 to 149.3)	n=735, S=22
Intra-arterial brachial systolic blood pressure (mm Hg)	147.5 (139.4 to 155.5)	n=735, S=22
Brachial cuff diastolic blood pressure (mm Hg)	78.8 (73.8 to 83.6)	n=668, S=18
Intra-arterial brachial diastolic blood pressure (mm Hg)	73.6 (69.6 to 77.6)	n=668, S=18
Brachial cuff pulse pressure (mm Hg)	62.8 (57.3 to 68.1)	n=668, S=18
Intra-arterial brachial pulse pressure (mm Hg)	74.6 (70.0 to 79.2)	n=668, S=18

Data are mean (95% confidence interval (CI)) or n (percentage). Subject characteristics were not available for all studies, and the numbers available are reported in the right hand column of the table. The maximum data available was n=735 from 22 studies. Subject characteristic data was derived from individual data, and when this was unavailable, aggregate data extracted from published studies.

Table 2.3 Subject characteristics from meta-analysis 3.

n=1823 subjects	Mean (95% CI) or n (%)	n=individual subjects, S=studies
Age (years)	60.4 (57.2-63.5)	n=1640, S=35
Male sex	1222 (70)	n=1751, S=35
Height (cm)	166.5 (164.7-168.4)	n=1447, S=26
Weight (kg)	76.9 (72.8-81.0)	n=1447, S=26
Body mass index (kg/m^2)	27.1 (26.2-28.1)	n=1447, S=26
Brachial cuff systolic blood pressure (mm Hg)	135.3 (132.2-138.4)	n=1823, S=39
Intra-arterial aortic systolic blood pressure (mm Hg)	135.1 (132.0-138.2)	n=1823, S=39
Brachial cuff diastolic blood pressure (mm Hg)	76.4 (74.2-78.5)	n=1676, S=36
Intra-arterial aortic diastolic blood pressure (mm Hg)	70.9 (69.3-72.4)	n=1676, S=36
Brachial cuff pulse pressure (mm Hg)	58.5 (55.8-61.1)	n=1676, S=36
Intra-arterial aortic pulse pressure (mm Hg)	63.8 (61.3-66.3)	n=1676, S=36

Data are mean (95% confidence interval (CI)) or n (percentage). Subject characteristics were not available for all studies, and the numbers available are reported in the right hand column of the table. The maximum data available was n=1823 from 39 studies. Subject characteristic data was derived from individual data, and when this was unavailable, aggregate data extracted from published studies.

Meta-analyses on BP differences.

In meta-analysis 1 brachial artery SBP was significantly higher than aortic SBP and PP ($p<0.0001$; Figures 2.1- 2.2). On the other hand, brachial DBP was marginally, but significantly lower than aortic DBP ($p=0.038$; Figure 2.3). The range of differences for SBP, DBP and PP was large (-9 to 62 mm Hg, -22 to 25 mm Hg and -17 to 62 mm Hg respectively, Figure 2.4). The pooled correlation coefficients showed strong associations between intra-arterial brachial and aortic SBP ($r=0.95$, 95% CI 0.93 to 0.97), DBP ($r=0.94$, 95% CI 0.93 to 0.96) and PP ($r=0.92$, 95% CI 0.89 to 0.94, $p<0.0001$ all, Figure 2.5).

In meta-analysis 2, brachial cuff BP methods significantly underestimated intra-arterial brachial SBP and PP, but significantly overestimated intra-arterial brachial DBP ($p<0.0001$ all, Figure 2.6 - Figure 2.8). The mean absolute difference for SBP was 7.9 mm Hg, 95% confidence interval (95% CI) 6.5 to 9.5. Intra-arterial brachial SBP was underestimated among studies that used either oscillometric or mercury sphygmomanometric techniques, albeit only of borderline significance for the latter (Table 2.4). However, both oscillometric and mercury sphygmomanometric cuff methods significantly overestimated intra-arterial brachial DBP and, therefore, also significantly underestimated intra-arterial brachial PP. Strong correlations were observed between brachial cuff and intra-arterial brachial SBP ($r=0.93$, 95% CI 0.91 to 0.95), DBP ($r=0.83$, 95% CI 0.78 to 0.88) and PP ($r=0.87$, 95% CI 0.82 to 0.91, $p<0.0001$ all, Figure 2.9)

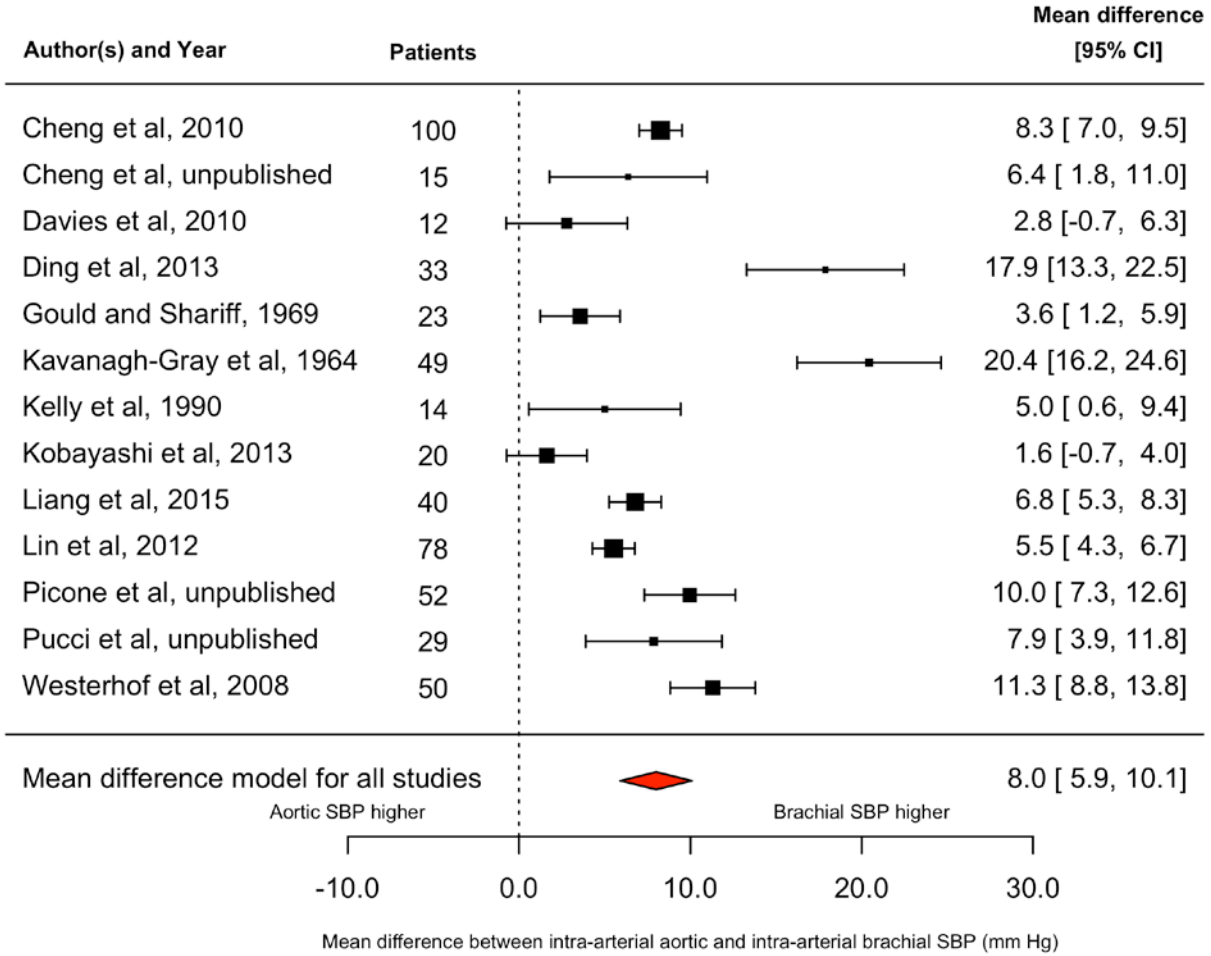


Figure 2.1 Forest plot of intra-arterial aortic and brachial systolic blood pressure difference.

Pooled mean difference and 95% confidence interval for meta-analysis 1, the comparison of intra-arterial aortic and brachial systolic blood pressure.

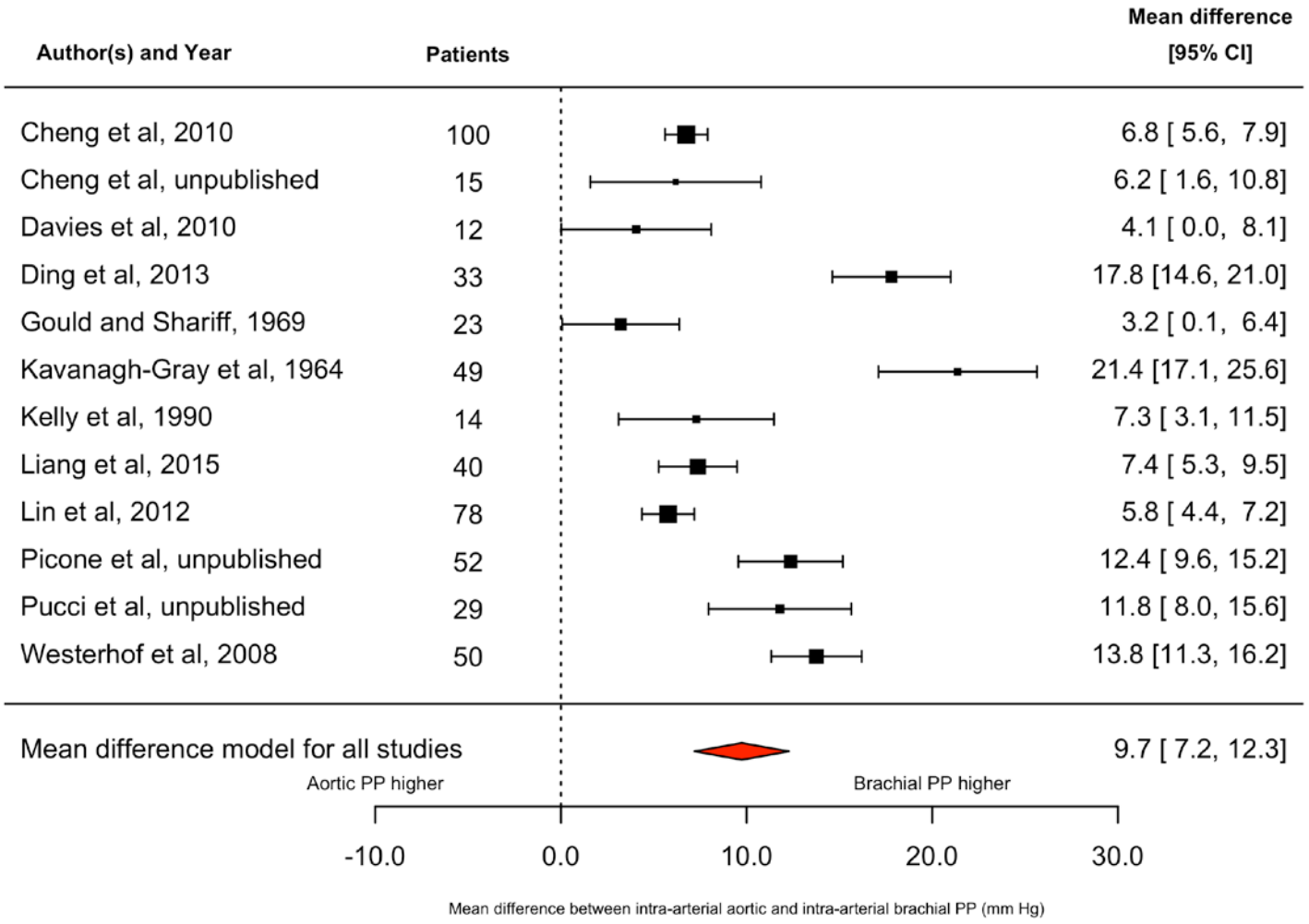


Figure 2.2 Forest plot of intra-arterial aortic and brachial pulse pressure difference.

Pooled mean difference and 95% confidence interval for meta-analysis 1, the comparison of intra-arterial aortic and brachial pulse pressure.

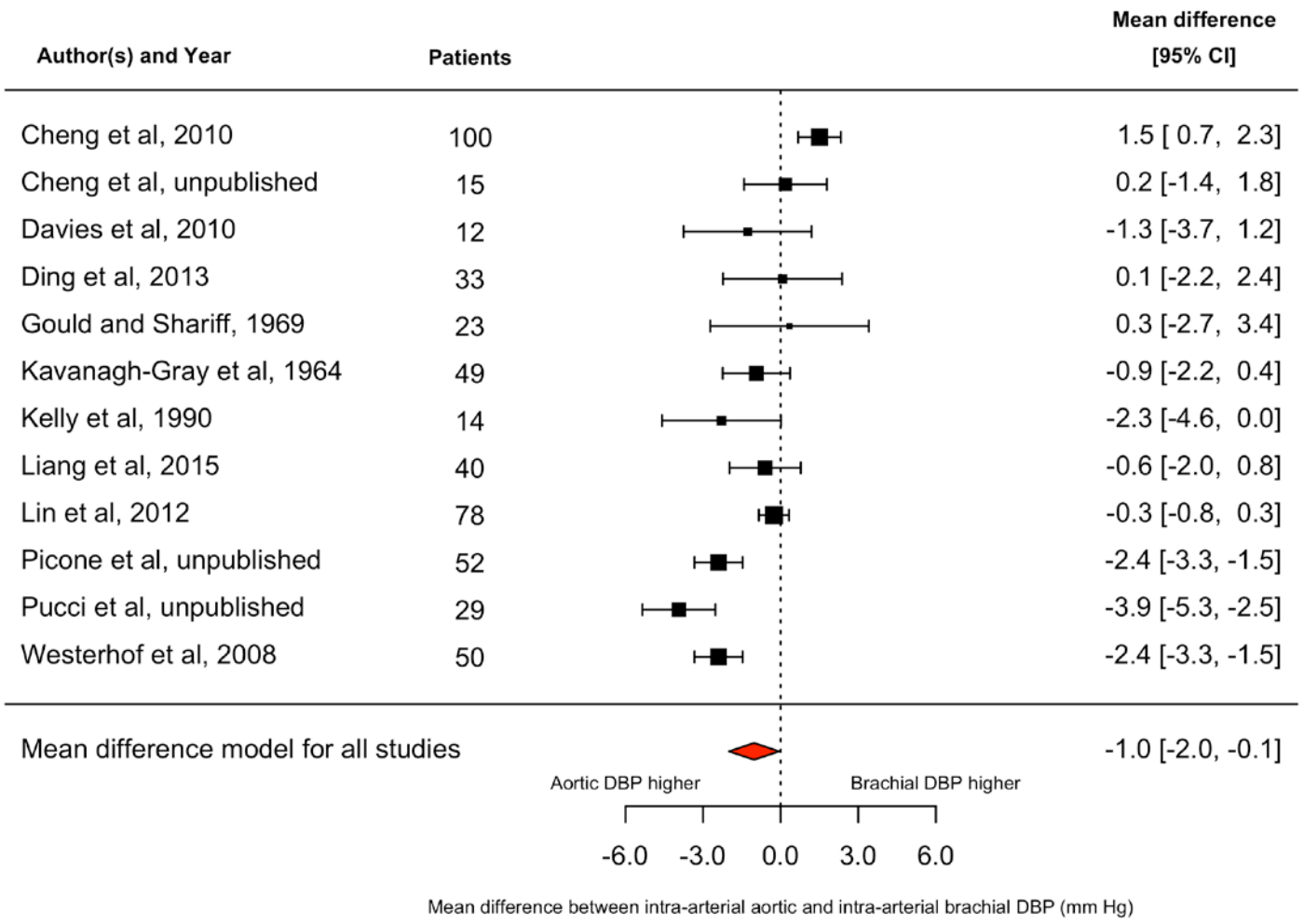


Figure 2.3 Forest plot of intra-arterial aortic and brachial diastolic blood pressure difference.

Pooled mean difference and 95% confidence interval for meta-analysis 1, the comparison of intra-arterial aortic and brachial diastolic blood pressure.

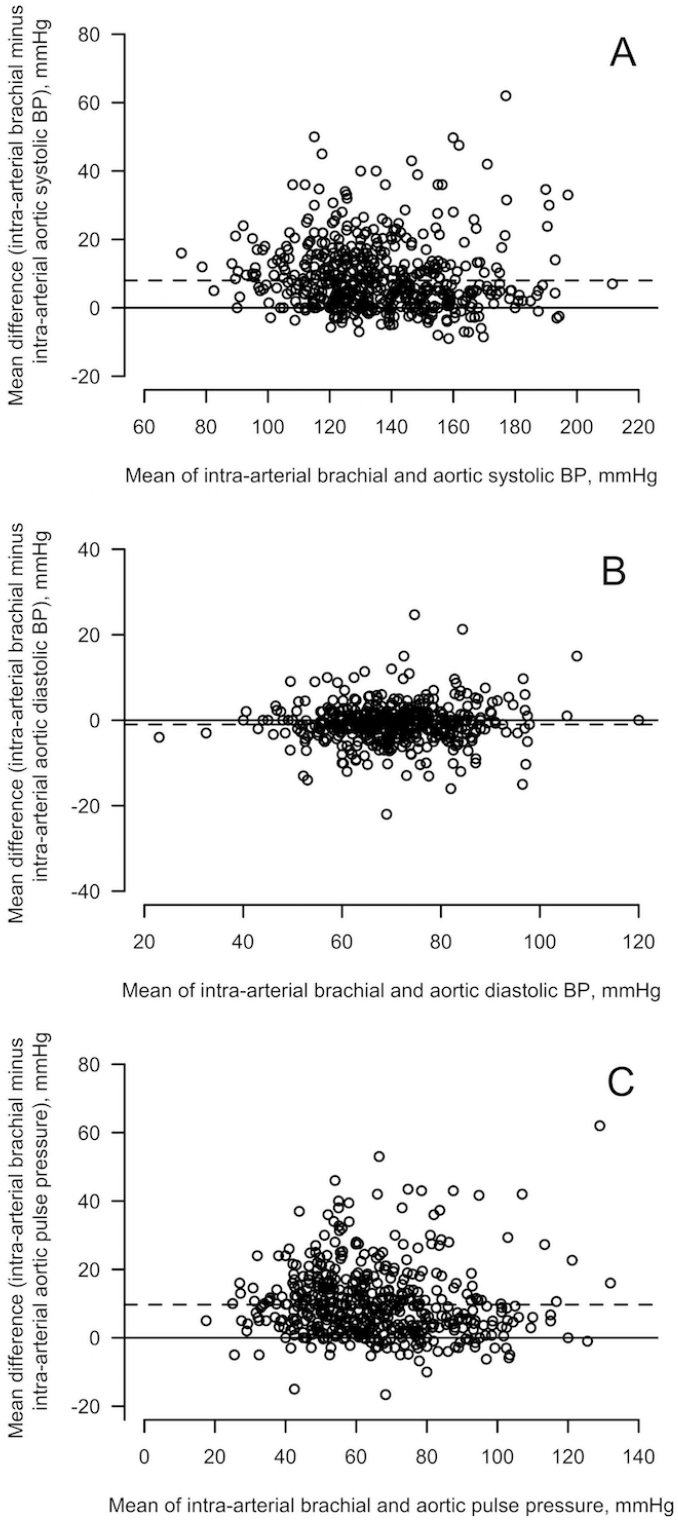


Figure 2.4 Agreement plots for blood pressure results in meta-analysis 1.

The mean of intra-arterial brachial and aortic BP is presented on the x-axis and the mean difference between intra-arterial brachial minus intra-arterial aortic blood pressure (BP) is on the y-axis. Systolic BP (SBP), diastolic BP (DBP) and pulse pressure are presented in panels A-C respectively.

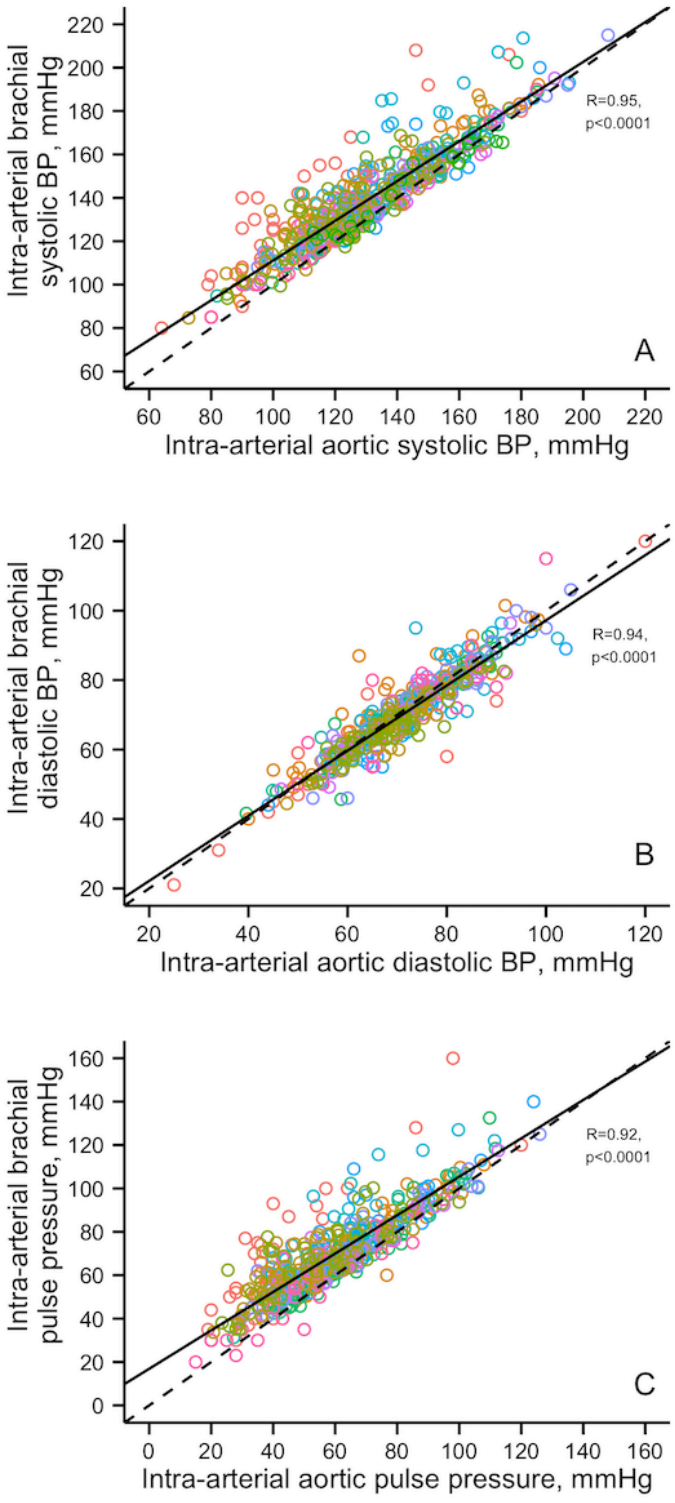


Figure 2.5 Association between intra-arterial aortic and brachial blood pressure.

Systolic BP (SBP), diastolic BP (DBP) and pulse pressure (panels A-C respectively) for meta-analysis 1. The differently coloured circles each represent a separate study from the meta-analysis. The solid line in each plot represents the regression line for the pooled associations and the dotted line is the line of identity.

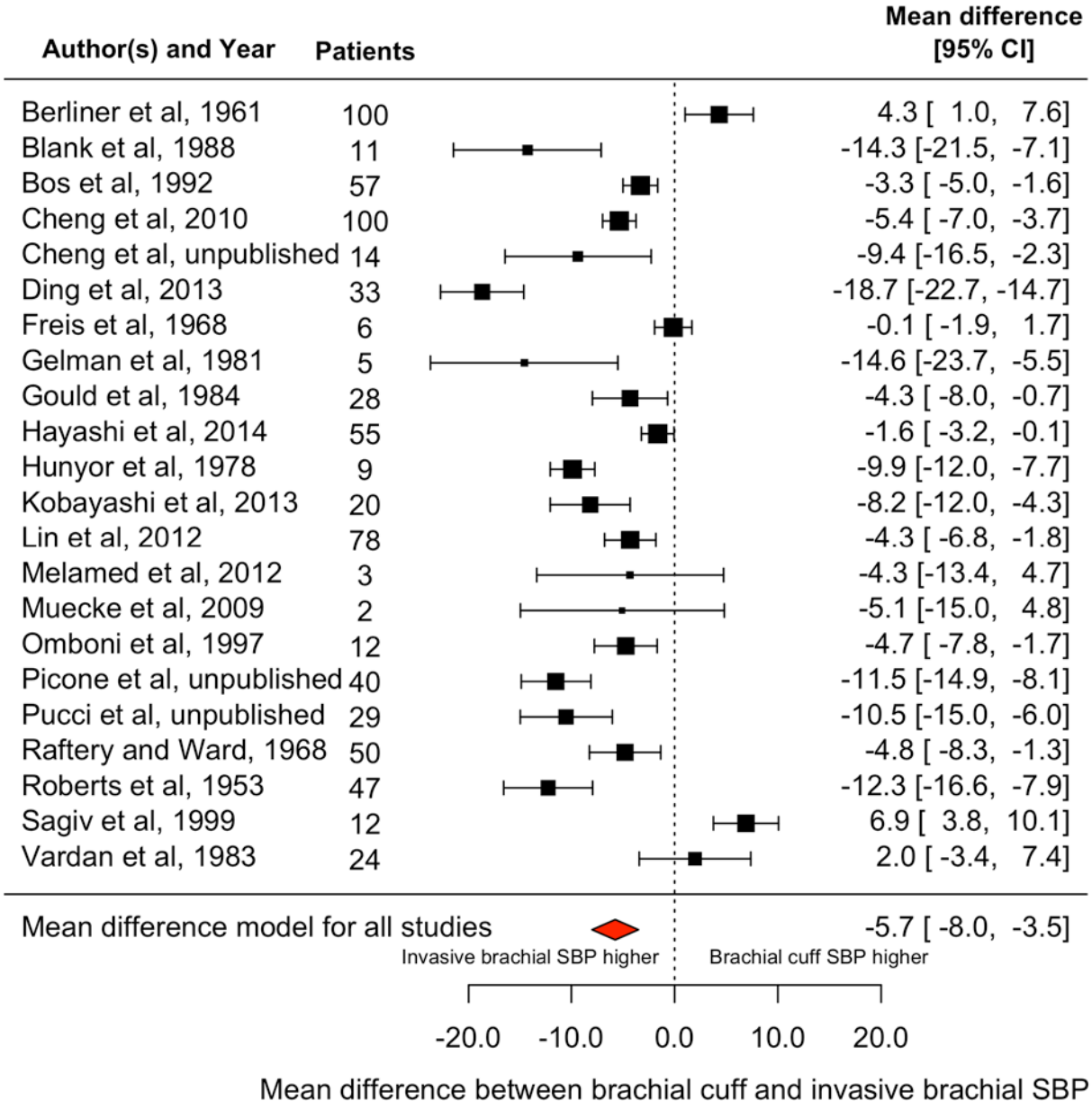


Figure 2.6 Forest plot of brachial cuff and intra-arterial brachial systolic blood pressure difference.

Pooled mean difference and 95% confidence interval for meta-analysis 2, the comparison of brachial cuff and intra-arterial brachial systolic blood pressure.

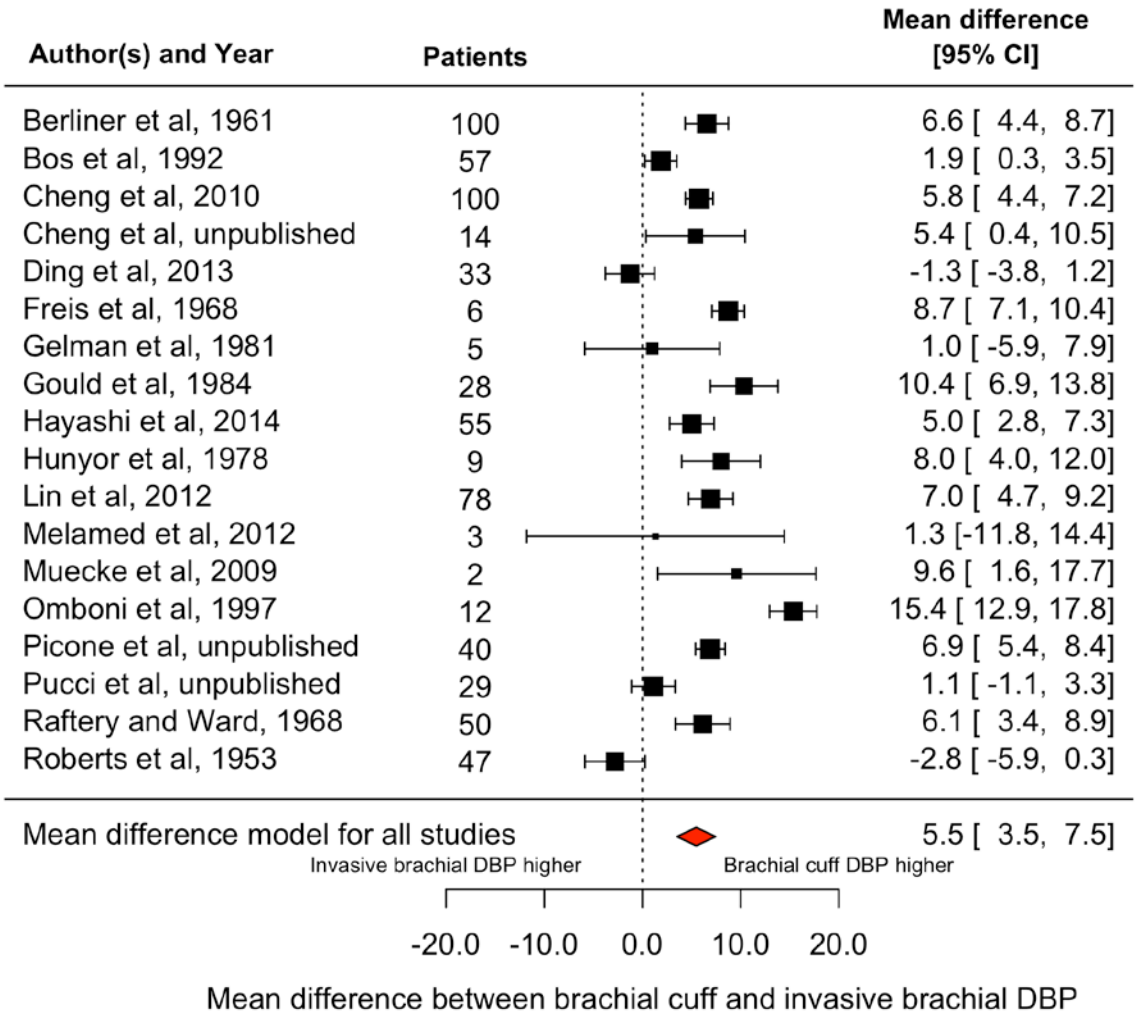


Figure 2.7 Forest plot of brachial cuff and intra-arterial brachial diastolic blood pressure difference.

Pooled mean difference and 95% confidence interval for meta-analysis 2, the comparison of brachial cuff and intra-arterial brachial diastolic blood pressure.

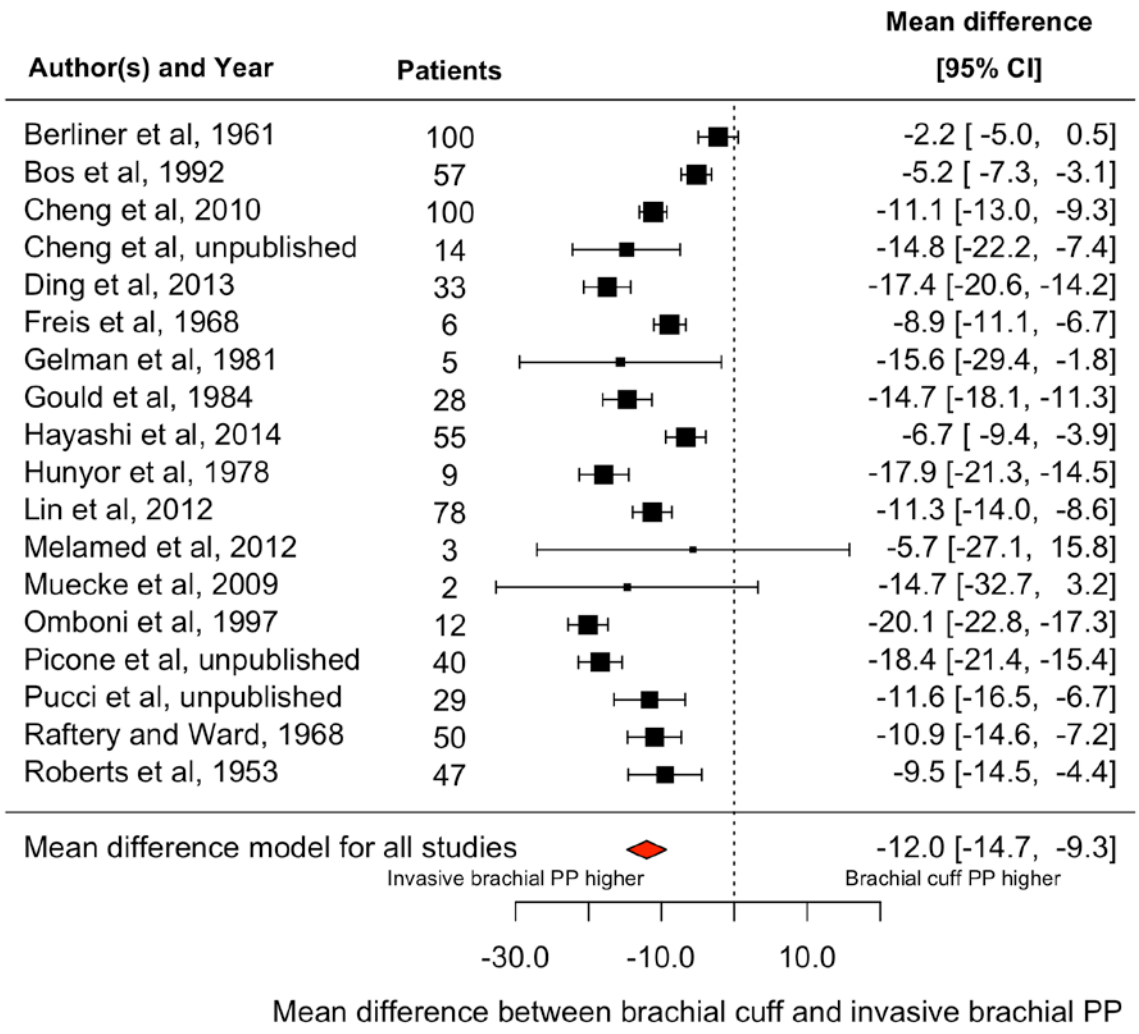


Figure 2.8 Forest plot of brachial cuff and intra-arterial brachial pulse pressure difference.

Pooled mean difference and 95% confidence interval for meta-analysis 2, the comparison of brachial cuff and intra-arterial brachial pulse pressure.

Table 2.4. Sub-analysis comparing oscillometric versus mercury sphygmomanometry for accuracy compared to intra-arterial brachial BP.

		Mean difference	Mean absolute difference	Range of difference	I^2
Oscillometric devices	Brachial cuff – intra-arterial brachial SBP, mm Hg (n=374, 10 studies)	-8.0 (-11.1 to -4.8)*	8.1 (5.8 to 10.8)	-67 to 36	89.4*
	Brachial cuff – intra-arterial brachial DBP, mm Hg (n=354, 9 studies)	4.5 (2.4 to 6.6)*	6.1 (5.3 to 7.0)	-32 to 41	83.2*
	Brachial cuff – intra-arterial brachial PP, mm Hg (n=354, 9 studies)	-12.8 (-15.9 to -9.7)*	12.4 (10.3 to 14.6)	-47 to 38	82.2*
Mercury sphygmomanometry	Brachial cuff – intra-arterial brachial SBP, mm Hg (n=356, 11 studies)	-3.4 (-6.9 to -0.2)^	7.5 (5.7 to 9.6)	-46 to 62	93.1*
	Brachial cuff – intra-arterial brachial DBP, mm Hg (n=309, 8 studies)	6.3 (2.8 to 9.8)*	8.4 (6.5 to 10.5)	-36 to 43	94.0*
	Brachial cuff – intra-arterial brachial PP, mm Hg (n=309, 8 studies)	-11.4 (-15.7 to -7.1)*	11.8 (9.1 to 14.7)	-52 to 34	94.0*

SBP, systolic blood pressure, DBP, diastolic BP, PP, pulse pressure. Data are mean (95% confidence intervals), range (minimum – maximum) or I^2 statistic. *$p<0.0001$, ^$p=0.0637$. Gelman et al[156] (n=5) not included in this analysis because it was not clear the specific type of cuff BP device used in that study.

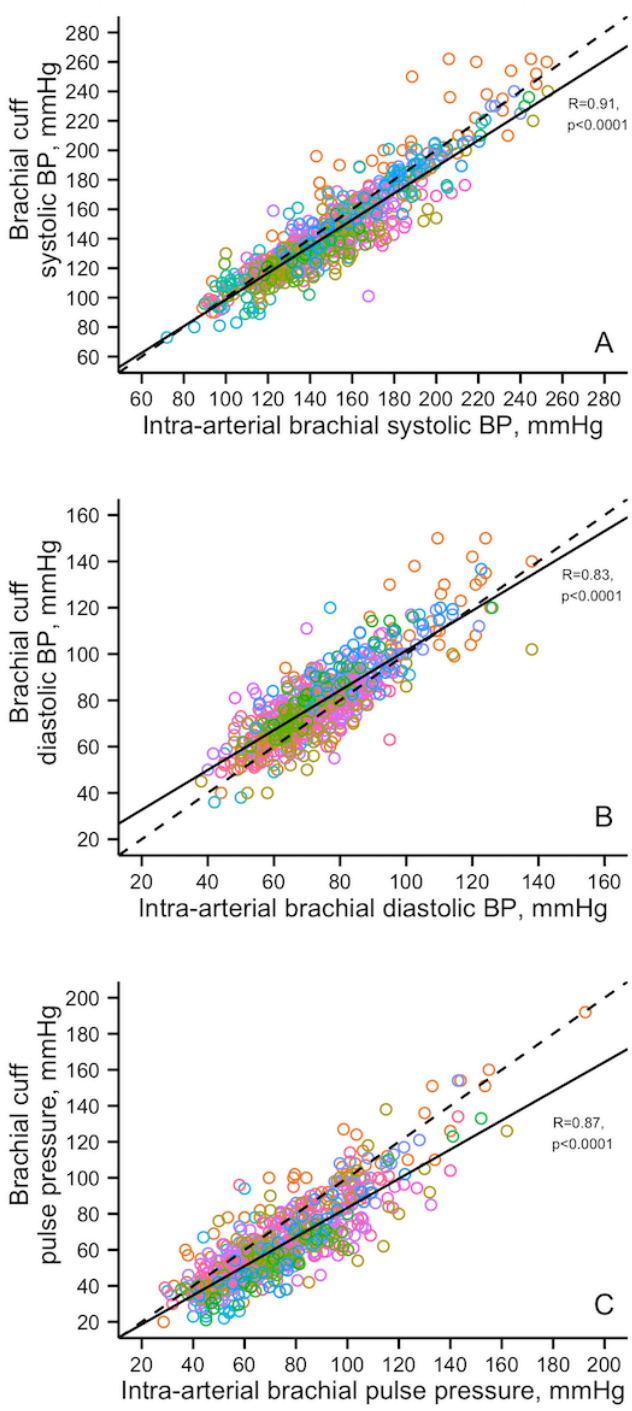


Figure 2.9 Association between brachial cuff and intra-arterial brachial blood pressure.

Scatter plots for brachial cuff and intra-arterial brachial systolic blood pressure (SBP), diastolic BP (DBP) and pulse pressure (panels A-C respectively) for meta-analysis 2. The differently coloured circles each represent a separate study from the meta-analysis. The solid line in each plot represents the regression line for the pooled associations and the dotted line is the line of identity.

In meta-analysis 3, there was no significant difference between brachial cuff and intra-arterial aortic SBP (Figure 2.11, p=0.77), however, this was due to a relative balance in the number of studies reporting either significant overestimation (7 studies) or significant underestimation (7 studies) of intra-arterial aortic SBP by cuff SBP. Indeed, the mean absolute difference was 8.0 mm Hg (95% CI) 7.1 to 8.9. Brachial cuff methods significantly overestimated intra-arterial aortic DBP and, thus, significantly underestimated intra-arterial aortic PP (Figures 2.11- Figure 2.12, p<0.0001 both). Oscillometric and mercury sphygmomanometric cuff methods were not analysed separately like meta-analysis 2, because the mercury method was only used in 2 studies, totalling 21 individuals. There were strong relationships between brachial cuff and intra-arterial aortic SBP based on the pooled correlation coefficients (r=0.90, 95% CI 0.88 to 0.92), DBP (r=0.79, 95% CI 0.76 to 0.84) and PP (r=0.84, 95% CI 0.81 to 0.87, p<0.0001 all, Figure 2.13). In all three meta-analyses there was significant heterogeneity between studies for the SBP, DBP and PP analyses (I^2>86%, p<0.0001 all).

BP classification based on brachial cuff BP compared with intra-arterial BP. Among individuals with BP classified as either preHTN or stage 1 HTN, only 50 to 60% of brachial cuff BP measures were concordant with intra-arterial BP measures. Underestimation of BP classification was the predominant issue for brachial cuff comparisons with intra-arterial brachial BP, whereas intra-arterial aortic BP classifications were similarly overestimated and underestimated. On the other hand, there was reasonable concordance between brachial cuff BP and intra-arterial BP (brachial or aortic) values measured among individuals with stage 2 HTN (≥160/100 mm Hg) according to intra-arterial BP. There was also reasonable concordance between cuff BP and intra-arterial aortic BP for BP classification in the normal range (<120/80 mm Hg, Table 2.5). There were similar findings when BP classification was only based on SBP thresholds (Appendix Table 1.13).

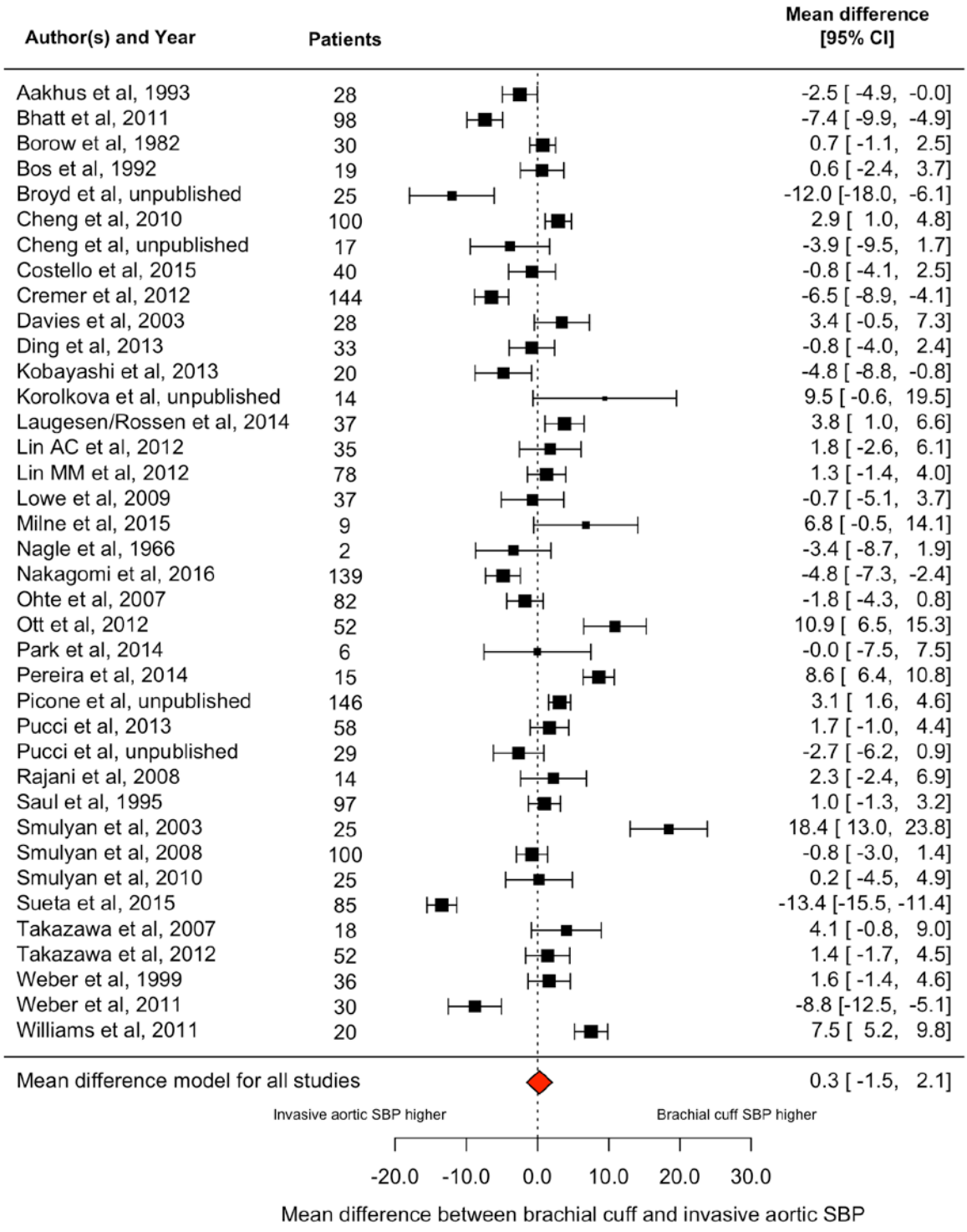


Figure 2.10 Forest plot of brachial cuff and intra-arterial aortic systolic blood pressure difference.

Pooled mean difference and 95% confidence interval for meta-analysis 3, the comparison of brachial cuff and intra-arterial aortic systolic blood pressure.

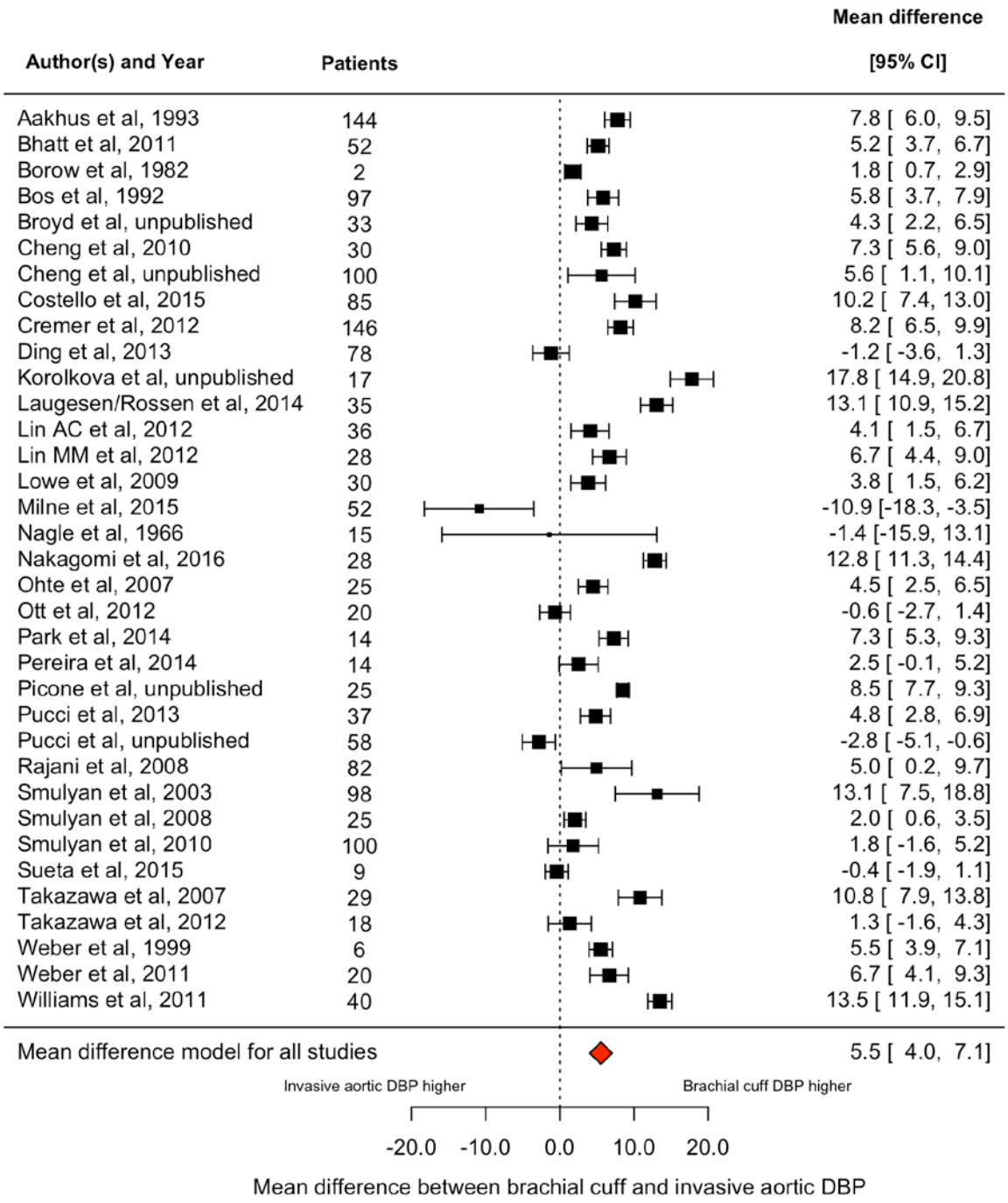


Figure 2.11 Forest plot of brachial cuff and intra-arterial aortic diastolic blood pressure difference.

Pooled mean difference and 95% confidence interval for meta-analysis 3, the comparison of brachial cuff and intra-arterial aortic diastolic blood pressure.

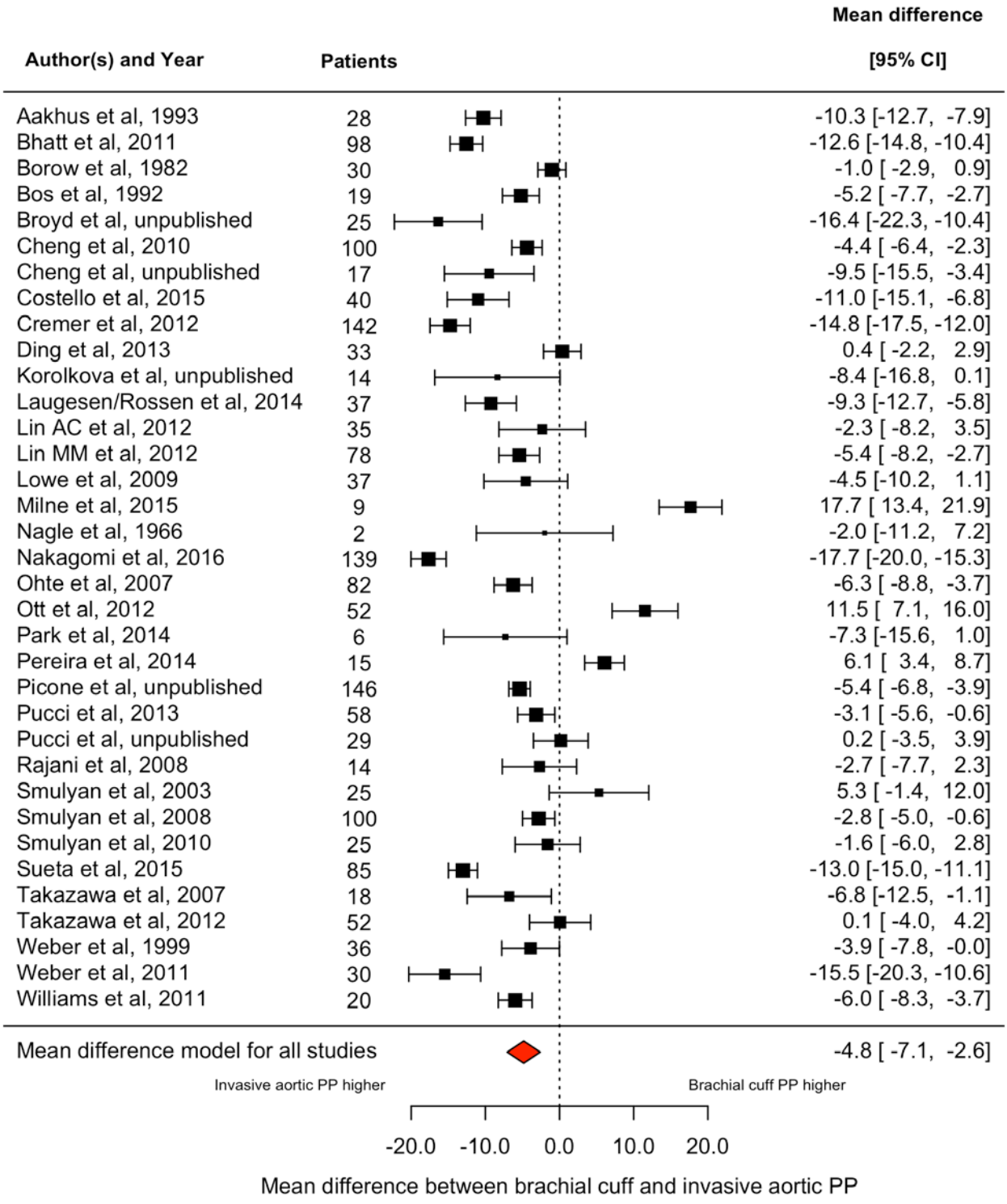


Figure 2.12 Forest plot of brachial cuff and intra-arterial aortic pulse pressure difference.

Pooled mean difference and 95% confidence interval for meta-analysis 3, the comparison of brachial cuff and intra-arterial aortic pulse pressure.

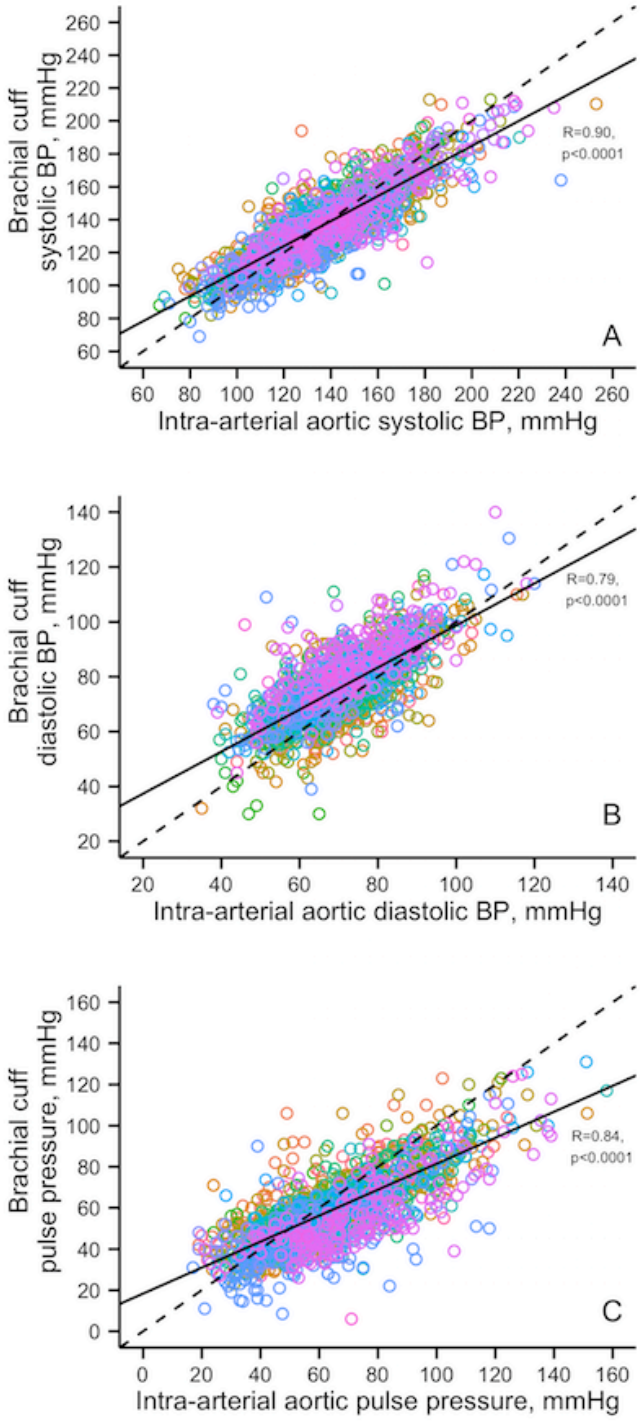


Figure 2.13 Association between brachial cuff and intra-arterial aortic blood pressure. Scatter plots for brachial cuff and intra-arterial aortic systolic blood pressure (SBP), diastolic BP (DBP) and pulse pressure (panels A-C respectively) for meta-analysis 3. The differently coloured circles each represent a separate study from the meta-analysis. The solid line in each plot represents the regression line for the pooled associations and the dotted line is the line of identity.

Table 2.5 Concordance of blood pressure classification using guideline based thresholds. Number of subjects and percentage concordance between brachial cuff and intra-arterial brachial (panel A) and aortic (panel B) systolic and diastolic BP for classification of BP control.

A	**Intra-arterial brachial blood pressure**			
n=668	**Normal**	**Prehypertension**	**Stage 1 hypertension**	**Stage 2 hypertension**
Cuff blood pressure	SBP <120 and DBP<80	SBP 120-139 and/or DBP 80 – 89	SBP 140-159 and/or DBP 90 – 99	SBP≥160 or DBP≥100
Normal SBP <120 and DBP<80	80 (60)	41 (35)	4 (4)	1 (1)
Prehypertension SBP 120-139 and/or DBP 80 – 89	22 (9)	124 (50)	71 (36)	7 (5)
Stage 1 hypertension SBP 140-159 and/or DBP 90 – 99	1 (2)	20 (13)	79 (53)	43 (32)
Stage 2 hypertension SBP≥160 or DBP≥100	0 (0)	1 (1)	31 (19)	143 (80)
Prehypertension and stage 1 hypertension combined SBP 120-159 and/or DBP 80 – 99	23(6)	294 (78)		50 (16)
B	**Intra-arterial aortic blood pressure**			
N=1676	**Normal**	**Prehypertension**	**Stage 1 hypertension**	**Stage 2 hypertension**
Cuff blood pressure	SBP <120 and DBP<80	SBP 120-139 and/or DBP 80 – 89	SBP 140-159 and/or DBP 90 – 99	SBP≥160 or DBP≥100
Normal SBP <120 and DBP<80	322 (79)	78 (19)	4 (1)	2 (1)

Prehypertension SBP 120-139 and/or DBP 80 – 89	112 (19)	341 (57)	130 (22)	13 (2)
Stage 1 hypertension SBP 140-159 and/or DBP 90 – 99	16 (4)	103 (24)	221 (52)	94 (20)
Stage 2 hypertension SBP ≥160 or DBP ≥100	0 (0)	7 (3)	48 (21)	185 (76)
Prehypertension and stage 1 hypertension combined SBP 120-159 and/or DBP 80 – 99	128 (12)	795 (78)		107 (10)

Data are presented as n (%) and each row adds to 100%. Linear mixed modelling was used to account for clustering of subjects within studies. Brachial cuff BP measurements were classified based on JNC 7 guidelines, and compared for concordance by applying the same cut points to the intra-arterial brachial (panel A) and aortic (panel B) systolic and diastolic BP. The proportion of intra-arterial brachial or aortic measurements concordant with brachial cuff BP is reported as a percentage. A value of 100% within the shaded boxes is equal to complete concordance of BP classification. Prehypertension and stage 1 hypertension were merged as a combined category to explore the possible clinical implication of cuff BP accuracy at this BP level.

When revised percentile rank intra-arterial BP thresholds were used, there was an improvement in concordance compared with the traditional threshold analysis in some BP categories (for example, in meta-analysis 2, normal and preHTN categories changed from 60% to 71% and from 50% to 66%). However, concordance remained similar or was reduced among other categories (Table 2.6). The revised thresholds shifted the systematic underestimation of risk using cuff BP compared with intra-arterial brachial BP among the categories of preHTN and stage 1 HTN to a more even distribution of over- and under-estimation of the correct BP classification category. For example, in the category of cuff BP preHTN, the percentage of intra-arterial brachial BP cases that were in the stage 1 HTN category was reduced from 36% to 17% (cuff underestimation). However, in the category of cuff BP preHTN, the percentage of intra-arterial brachial BP in the normal category increased from 9% to 13% (cuff overestimation). Similarly, in the category of cuff BP stage 1 HTN, the percentage of intra-arterial brachial BP cases that were either in stage 2 HTN or preHTN categories changed from 32% to 20% (cuff underestimation) and from 13% to 26% (cuff overestimation), respectively. With respect to delineating HTN at the traditional cut-off of 140/90 mm Hg, in meta-analysis 2 the sensitivity was 78.5% (95% CI 66.8 to 87.0), while specificity was 95.2% (95% CI 86.5 to 98.4%). In meta-analysis 3, sensitivity was 81.7% (95% CI 74.9 to 87.0%) and specificity was 88.5% (95% CI 83.4 to 92.2%).

Magnitude of difference between cuff and intra-arterial BP. Brachial cuff BP readings were ≥5, ≥10 or ≥15 mm Hg different from intra-arterial brachial SBP in 465 (67%), 275 (41%) and 173 (26%) of subjects of meta-analyses 2 (Figure 2.14A). Similarly, when compared with intra-arterial aortic BP, brachial cuff SBP was ≥5, ≥10 or ≥15 mm Hg different in 1236 (67%), 748 (40%) and 411 (22%) of subjects of meta-analyses 3 (Figure 2.14B). Results were similar for DBP differences, although there was better agreement for DBP differences ≥15 mm Hg (Appendix Figure 1.7).

Clinical and demographic correlates of brachial cuff and intra-arterial BP differences. Older age and higher body mass index were related in univariable analysis to less underestimation of intra-arterial brachial and aortic SBP and PP by brachial cuff SBP and PP (Appendix Tables 1.14 and 1.15). In multivariable analysis age and body mass index both remained significantly related to the difference in PP, but age was not significantly related to the difference between brachial cuff and intra-arterial brachial SBP, whilst body mass index was not significantly related to the difference between brachial cuff and intra-arterial aortic SBP. There were no consistent associations observed for brachial cuff DBP versus intra-arterial DBP.

Table 2.6 Concordance of blood pressure classification based on revised intra-arterial thresholds. Number of subjects and percentage concordance between brachial cuff and intra-arterial brachial (panel A) and aortic (panel B) systolic and diastolic blood pressure (BP) for classification of BP control.

A		**Intra-arterial brachial blood pressure**			
n=668 **Cuff blood pressure**		**Normal** SBP <124.5 and DBP <74	**Prehypertension** SBP 124.5- <150 and/or DBP 74– <85	**Stage 1 hypertension** SBP 150- <167 and/or DBP 85– <91	**Stage 2 hypertension** SBP ≥167 or DBP ≥91
	Centiles	<19th	19th – <54th	54th - <76th	≥76th
Normal SBP <120 and DBP<80	<19th	93 (71)	31 (27)	1 (1)	1 (1)
Prehypertension SBP 120-139 and/or DBP 80 – 89	19th – <54th	28 (13)	156 (66)	34 (17)	6 (4)
Stage 1 hypertension SBP 140-159 and/or DBP 90 – 99	54th - <76th	3 (2)	38 (26)	73 (52)	29 (20)
Stage 2 hypertension SBP≥160 or DBP≥100	≥76th	0 (0)	6(3)	31 (21)	138 (76)
Prehypertension and stage 1 hypertension combined SBP 120-159 and/or DBP 80 – 99	19th – <76th	31 (9)	301 (81)		35 (10)

B			**Intra-arterial aortic blood pressure**			
n=1676			**Normal**	**Prehypertension**	**Stage 1 hypertension**	**Stage 2 hypertension**
Cuff blood pressure			SBP <119.1 and DBP <74	SBP 119.1-141.8 and/or DBP 74 – 83.5	SBP 141.8-165.1 and/or DBP 83.5–93.1	SBP ≥ 165.1 or DBP ≥ 93.1
		Centiles	<24th	24th - <59th	59th – 86th	≥86th
Normal <120 and DBP<80	SBP	<24th	302 (74)	97 (25)	6 (1)	1 (0)
Prehypertension 120-139 and/or DBP 80 – 89	SBP	24th - <59th	89 (15)	364 (61)	133 (22)	10 (2)
Stage 1 hypertension 140-159 and/or DBP 90 – 99	SBP	59th – <86th	14 (3)	108 (27)	245 (56)	67 (14)
Stage 2 hypertension ≥160 or DBP ≥100	SBP	≥86th	0 (0)	8 (5)	66 (30)	166 (65)
Prehypertension and stage 1 hypertension combined SBP 120-159 and/or DBP 80 – 99		24th - <86th	103 (10)	850 (83)		77(7)

Data are presented as n (%) and each row adds to 100%. Linear mixed modelling was used to account for clustering of subjects within studies. Brachial cuff BP measurements were classified based on JNC 7 guidelines, and compared for concordance with classification of the corresponding intra-arterial brachial (panel A) and aortic (panel B) systolic and diastolic BP. The proportion of intra-arterial brachial or aortic measurements concordant with brachial cuff BP is reported as a percentage. A value of 100% within the shaded boxes is equal to complete concordance of BP classification. Modified intra-arterial thresholds have been calculated from the equivalent percentile rank of cuff BP thresholds. Prehypertension and stage 1 hypertension were merged as a combined category to explore the possible clinical implication of cuff BP accuracy at this BP level.

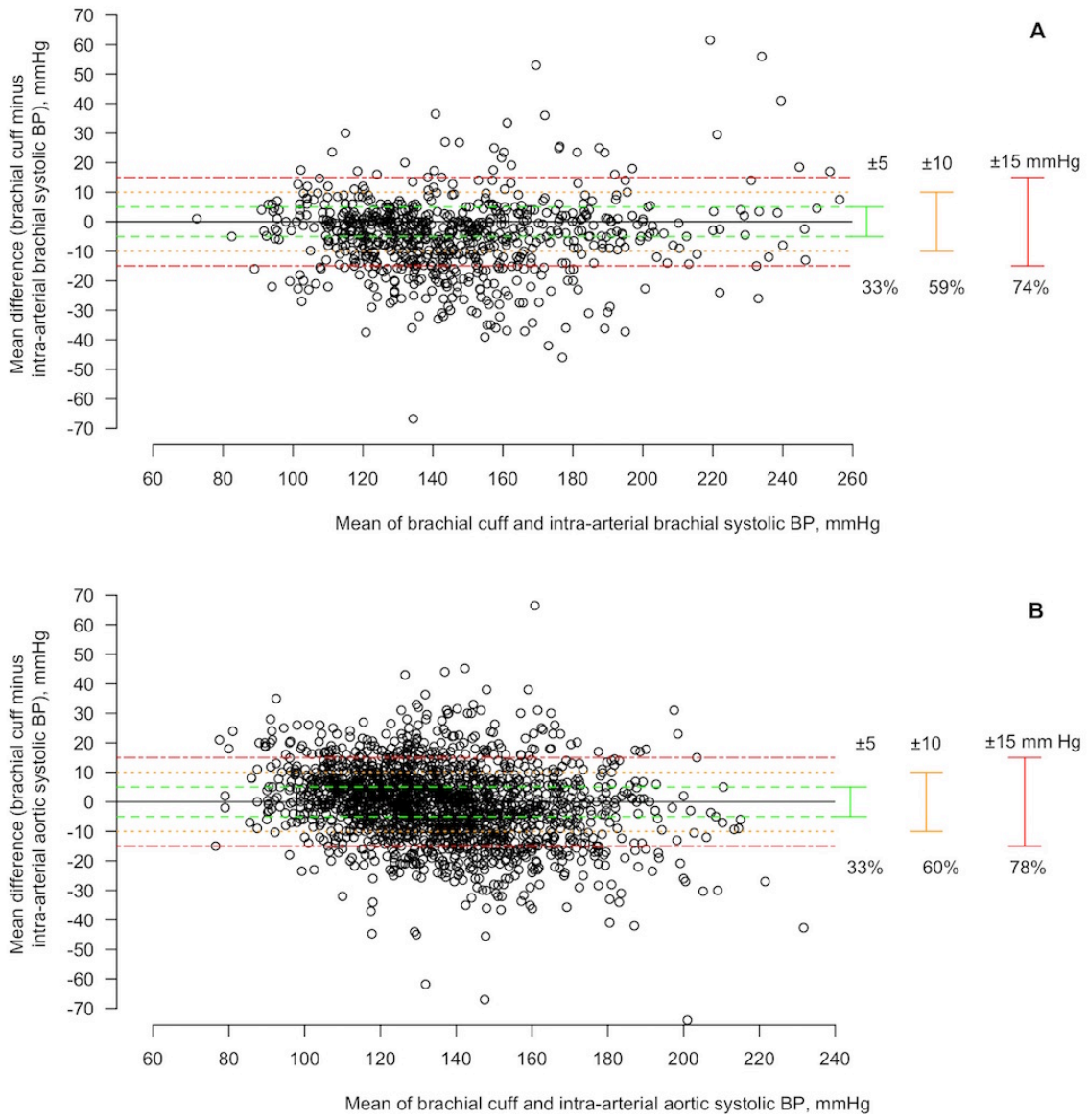


Figure 2.14 Individual brachial cuff and intra-arterial blood pressure differences.

Plots of brachial cuff and intra-arterial brachial (panel A), as well as brachial cuff and intra-arterial aortic (panel B) systolic blood pressure (BP). The mean of the brachial cuff systolic BP and intra-arterial systolic BP is on the x-axis and the mean difference between brachial cuff systolic BP and the intra-arterial systolic BP is on the y-axis. The proportion of brachial cuff systolic BP values within ±5 mm Hg of the intra-arterial systolic BP measures is represented by the dashed line (green), and reported under the ±5 bar. The same presentation is provided for cuff systolic BP values within ±10 mm Hg (dotted line [orange]) and ±15 mm Hg (dot-dashed line [red]). The solid black horizontal line represents the mean SBP difference calculated as brachial cuff minus intra-arterial BP.

Sensitivity analysis. Participants were significantly older and had higher intra-arterial brachial SBP and intra-arterial aortic PP in the maximum rated compared to the non-maximum rated studies in meta-analysis 1. There were significantly more males in the maximum rated studies in meta-analyses 2 and 3. There were no other significant differences between the maximum rated and non-maximum rated studies ($p>0.05$ all, Appendix Tables 1.16- 1.18). There were no significant differences in BP values for published versus unpublished data ($p>0.05$, Appendix Tables 1.19- 1.21). We did not have a direct measure of ethnicity, however, BP differences were not significantly influenced by the country of data origin. The relationship between the difference in cuff and intra-arterial brachial SBP and the average of cuff and intra-arterial brachial SBP (Figure 2.14) was non-linear (U-shaped). However, this appeared to be driven by five outlying data points, because removal of these data resulted in linear estimates that were similar to non-linear modelling (linear=-24.8, 95% CI -48.7 to -0.72, $p=0.044$; non linear 26.9, 95% CI 4.9 to 49.2, $p=0.017$). The relationship between cuff and intra-arterial aortic SBP data was linear.

2.5 Discussion

With HTN as the single major risk factor for global disease burden [33], the accuracy of clinic BP methods is critical. Our study had several key findings. First, we confirmed the expectation that intra-arterial brachial SBP was higher than intra-arterial aortic SBP, and also that there was little difference in DBP between the central and peripheral arterial sites. However, there was extreme individual variability in the magnitude of central-to-peripheral differences for both SBP and DBP. Second, we found that cuff BP underestimated intra-arterial brachial SBP (and PP), but overestimated intra-arterial brachial DBP irrespective of BP technique (e.g. oscillometric or auscultation using mercury methods). This is confirmation of perceived dogma relating to oscillometric devices, but as far as we know is the first comprehensive analysis of all cuff BP methods to be reported. Third, when cuff SBP was compared with intra-arterial aortic SBP, there was a small mean difference but poor agreement between measures at the individual level, whereas cuff DBP overestimated and cuff PP underestimated intra-arterial aortic values. Finally, the observed variability in cuff BP accuracy adversely influenced correct classification of BP (compared against intra-arterial classification) across all JNC 7 categories, with particular discordance in the range from preHTN to stage 1 HTN. These data are summarized in the Central Illustration (Figure 2.15) and indicate the need to improve accuracy standards of cuff BP devices.

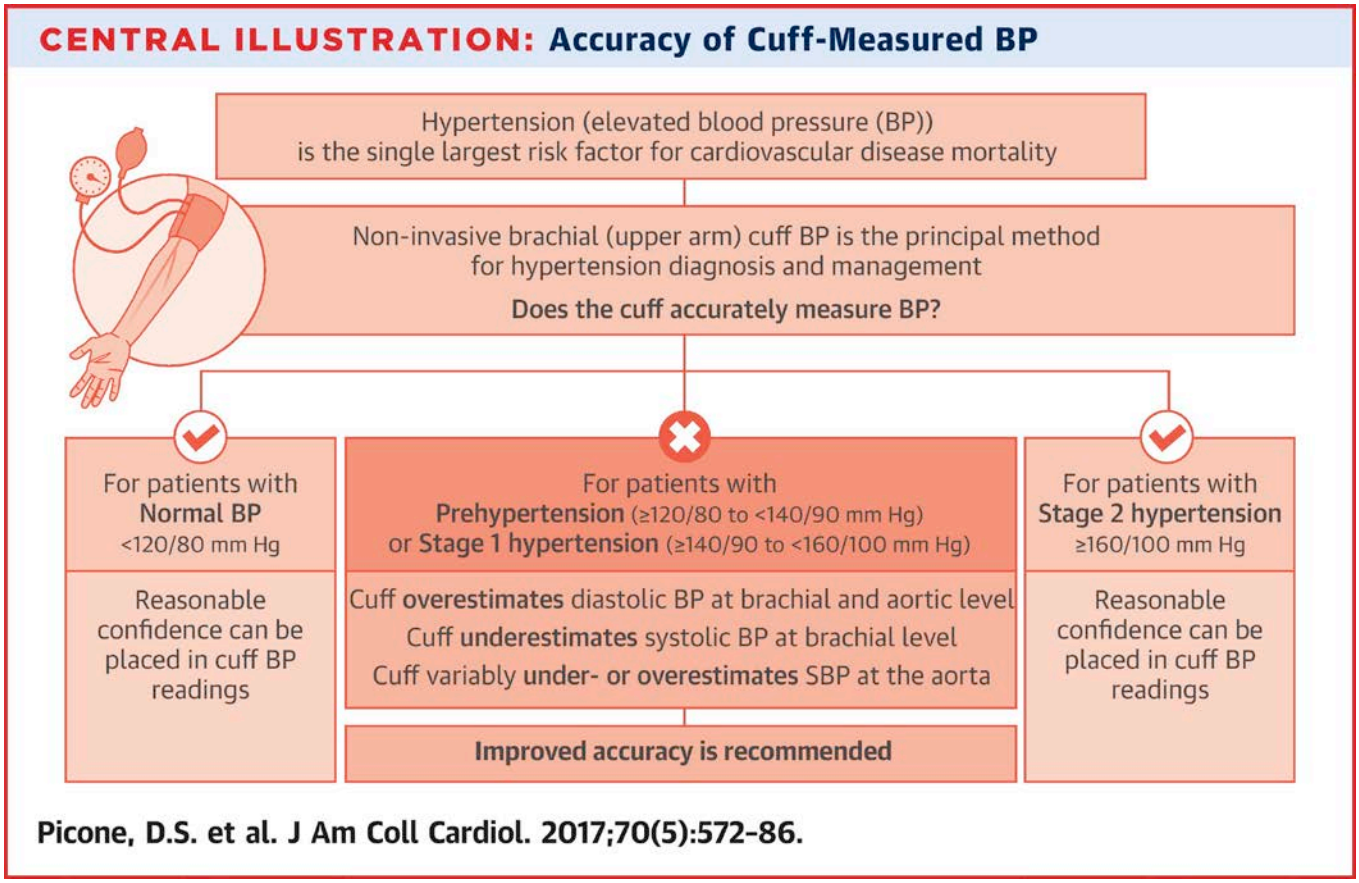


Figure 2.15 Summary findings from individual participant data meta-analyses of cuff blood pressure accuracy.

This illustration depicts BP classification based on cuff BP measurements and corresponding concordance with intra-arterial BP classification. The results are calculated using all available individual participant data from the 1950s to 2016. Reasonable confidence can be placed in cuff BP readings <120/80 mm Hg or ≥160/100 mm Hg to predict intra-arterial brachial or aortic BP. Improved accuracy is recommended in the BP range from pre-hypertension (≥120/80 mm Hg to <140/90 mm Hg) to stage 1 hypertension (≥140/90 mm Hg to <160/100 mm Hg), where concordance with intra-arterial BP was not strong. SBP=systolic blood pressure.

Clinical implications. A key problem in addressing the global burden of disease related to high BP is improving the diagnosis and characterization of the hypertensive phenotype [190]. A fundamental problem with BP accuracy was identified in our study that affects most (but not all) cuff BP devices. Despite strong correlations between cuff BP and intra-arterial BP, 16 out of 22 cuff BP devices examined significantly underestimated intra-arterial brachial SBP (Figure 2.6, panel A) and 15 out of 18 significantly underestimated pulse pressure (Figure 2.6, panel C). The mean difference in the magnitude of the underestimation often exceeded 10 mm Hg. Translating these error margins to the traditional classification of BP based on intra-arterial SBP readings, cuff BP correctly identified preHTN and stage 1 HTN in only about half the participants, whether based on intra-arterial brachial or aortic SBP (Table 2.5). Concordance with revised intra-arterial brachial BP thresholds (based on cuff BP percentile rank) was improved from 50% to 66% in the preHTN range (Table 2.6). This analysis also resulted in reduced systematic underestimation of risk using cuff BP among the categories of preHTN and stage 1 HTN. Instead, a relatively even distribution was observed towards both over- and under-estimation of correct classification of intra-arterial BP. The true implications of these findings with respect to identification of risk related to BP in clinical practice will require future studies.

It could be argued that our findings are not a major clinical problem because HTN thresholds have been derived from well conducted clinical trial data using the same (or similar) cuff BP methods to that analyzed in this current work. Thus, whether cuff BP is measuring the intra-arterial BP could be largely irrelevant if risk can still be gauged relative to the BP methods employed in the clinical trials. This contention would be valid if there were consistent systematic error(s), but in fact there was wide inter-device variability with respect to SBP, DBP and PP accuracy. To clarify the issue, separate analysis on the accuracy of BP devices used in all the seminal clinical trials would be required. In any case, a reasonable degree of confidence that cuff BP is representative of intra-arterial brachial or aortic SBP is associated with readings <120/80 mm Hg or ≥160/100 mm Hg (Tables 2.5- 2.6).

Cuff BP validation standards. Guidance on validation protocols for cuff BP devices is provided by several scientific bodies [147, 191-195], however there are many procedural differences between guidelines on features such as sample size, acceptable margin of error and pass criteria [59]. Work is currently underway to achieve a universal validation protocol for cuff BP devices.[196] When comparing BP device performance with the reference standard (which can be intra-arterial BP or, most often, mercury sphygmomanometry), differences of 0 to 5 mm Hg are considered to be “very accurate,” whereas differences >15 mm Hg are “very inaccurate” [193]. Although there are many ways to determine “pass” criteria for BP devices, the British

Hypertension Society provide the highest grade pass (A) if 60% of differences fall within 5 mm Hg and only 5% of differences fall outside 15 mm Hg [147]. The analysis we have conducted cannot be directly compared with results of validation studies assessing the performance of individual BP devices. However, it is of note that only 33% of cuff SBP readings fell within 0 to 5 mm Hg, and >20% were >15 mm Hg from intra-arterial SBP (Figure 2.14). That would equate to a grade D (fail) device performance. From the available data, weak associations between age, body mass index and cuff BP differences were observed in meta-analyses 2 and 3, but we were unable to determine clear-cut reasons for the disparity between cuff and intra-arterial BP. Speculatively, the relationships between body mass index and cuff BP accuracy could be explained by differences in arm circumference or related cuff size (which correlates with body mass index),[197] however this specific data was unavailable from most studies.

A novel finding with respect to the use of mercury sphygmomanometry as a reference standard in BP validation protocols is that this method demonstrated sizable imprecision. In comparison to intra-arterial brachial BP, the mercury method performed better than oscillometric BP with respect to the level of SBP underestimation, but significant overestimation of DBP and underestimation of pulse pressure was still observed (Table 2.4). There was insufficient data on mercury BP to compare this method with oscillometric BP for accuracy compared to intra-arterial aortic BP. Overall the analyses cast some doubt on the robustness of mercury sphygmomanometry as the standard against which BP device performance is gauged (possibly due to influences of operator error), albeit acknowledging that it is the best non-invasive option currently available. Intra-arterial BP measured under rigorous criteria has the strongest level of BP accuracy and may be a better choice as the comparator for BP device validation. But it is less practical and is not ethical to use among some populations. In any case, our observation of significant differences (and marked variability) between intra-arterial aortic and brachial BP clearly shows that it is not acceptable to assume peripheral BP is representative of central BP. This finding is applicable to BP device validation protocols in which cuff BP is compared against intra-arterial BP at the radial [198], brachial [10], or aortic [174] level. Improvement of BP device accuracy standards is desirable [102].

Strengths and limitations. Individual level data were acquired from a wide variety of studies employing high-quality techniques and spanning several decades of investigations, all together comprising relatively large sample sizes for each meta-analysis. However, this also probably contributed to the observed statistical heterogeneity, indicating excess variation among experimental protocols and a degree of uncertainty regarding effect estimates. Although intra-arterial BP is the reference standard measurement of BP [132, 199], inaccurate BP is possible due

to numerous sources of error: 1) if operators do not follow appropriate techniques (e.g. catheter handling and dynamic response) [54], 2) variability in BP between the recording of cuff and intra-arterial measurements, 3) if measures being compared are recorded sequentially rather than simultaneously, or 4) if measures are being compared within contralateral rather than ipsilateral arterial sites. Reassuringly, sensitivity analyses showed no significant difference between the studies that received the maximum quality rating for experimental design taking into consideration these sources of error, versus those that did not. Availability of repeated data would have helped address this issue further, but this was unavailable in most studies. Finally, the study populations were generally typical of patients presenting with clinical indications for coronary artery catheterization and therefore there was bias towards overweight, middle-to-older-aged men, and the findings cannot be widely generalized.

2.6 Conclusions

Cuff BP is the cornerstone measurement in HTN management. The most important finding of the present study was the inaccuracy of cuff BP when compared with intra-arterial brachial BP and aortic BP. These deviations substantially influenced BP classification according to clinical guideline criteria. The inadequacies of cuff BP identified within this work could be improved with better non-invasive cuff BP methods to estimate brachial or aortic BP. This should then lead to enhanced clinical diagnosis and management of HTN.

2.7 Perspectives

2.7.1 Competency in medical knowledge

Measurement of BP with pneumatic cuff devices is subject to considerable variability that affects correlations with direct intra-arterial brachial and aortic pressure measurements. When compared with intra-arterial pressures, brachial cuff sphygmomanometry generally underestimates systolic and overestimates diastolic BP.

2.7.2 Translational outlook

New methods of non-invasive BP measurement should undergo robust validation to ensure accuracy before they are employed in patient care or population health studies.

2.8 Contribution of Chapter 2 to thesis aims

Fundamental issues on the accuracy of cuff BP have been acknowledged since at least the 1950s. Yet, there has never been a comprehensive analysis of cuff BP accuracy compared with gold standard intra-arterial BP. Chapter 2 of this thesis comprised a compendium of three

individual participant data meta-analyses and for the first time, quantified the extent of cuff BP inaccuracy across all available studies and examined possible clinical implications. There were several important findings.

As per physiological expectations, in meta-analysis one intra-arterial brachial SBP was significantly higher than intra-arterial aortic SBP and PP. The key novel finding from this analysis was the large individual variability of the difference. Such variability could have important clinical relevance, with some data suggesting aortic BP predicts clinical outcomes above and beyond brachial BP.[36, 200] Second, in confirmation of existing theory,[201] cuff BP underestimated intra-arterial brachial SBP and PP and overestimated brachial DBP. This was observed from the gold standard cuff method mercury auscultation and newer oscillometric methods. Third, an important novel finding was that whilst cuff SBP was not significantly different to intra-arterial aortic SBP, there was poor agreement (considerable over- and under-estimation). Fourth, the novel BP classification analysis based on cuff BP compared to intra-arterial BP revealed cuff methods had variable accuracy for measuring intra-arterial BP, particularly in prehypertension (120-139/80-89 mm Hg) and stage 1 hypertension (140-159/90-99 mm Hg), indicating there could be substantial clinical implications of cuff inaccuracy (e.g. undertreatment or unnecessary treatment).

A systematic analysis of cuff BP accuracy was performed for the first time in Chapter 2. However, the specific reasons for cuff BP inaccuracy remain unclear. The high level of variability in the meta-analysis between intra-arterial brachial and aortic BP is not unexpected given there is large variability between individuals in arterial characteristics. [38, 70, 77-79] Despite this variability, standard cuff BP methods use ‘one size fits all’ approaches based on signals from the brachial artery. Whether cuff BP methods can detect and account for this variability in arterial characteristics, which can affect BP and central-to-peripheral artery BP transmission is unknown. Such variability in BP transmission could suggest that distinct BP phenotypes exist. In Chapter 3 we hypothesized that the presence of distinct BP phenotypes would not be discriminated by cuff BP methods used in daily clinical practice.

Chapter 3 - Discovery of new blood pressure phenotypes and relation to accuracy of cuff devices used in daily clinical practice

This thesis chapter has been accepted and is formatted according to the guidelines of *Hypertension*.

Picone DS, Schultz MG, Peng X, Black JA, Dwyer N, Roberts-Thomson P, Chen C-H, Cheng H-M, Pucci G, Wang J, Sharman JE. Discovery of new blood pressure phenotypes and relation to accuracy of cuff devices used in daily clinical practice. *Hypertension,* 2018; 71(6): 1239-47.

Citations: 1

Presentations and awards:

ARTERY16 conference: 1st Prize Young Investigator oral presentation session, selected from nine presentations, October 2016.

High Blood Pressure Research Council of Australia annual scientific meeting oral presentation, Hobart, Australia, December 2016.

Novel blood pressure phenotypes identified from invasive aortic-to-peripheral amplification: impact on accuracy of brachial cuff measurement. Moderated Poster, Pulse of Asia 2016, Seoul, South Korea, September 2016.

3.1 Abstract

Cuff blood pressure (BP) is the reference standard for management of high BP, but the method is inaccurate and can lead to BP misclassification. The aims of this study were to determine if distinctive BP phenotypes exist based on BP transmission (amplification) variability from central-to-peripheral arteries and whether applying one standard cuff BP measurement approach (e.g. oscillometry) to all people could discriminate the BP phenotypes. Intra-arterial BP was measured at the ascending aorta, brachial and radial arteries in 126 participants (61±10 years, 69% male) following coronary angiography. Central-to-peripheral systolic BP (SBP) transmission (SBP-amplification) was defined by ≥5 mmHg SBP increase between the aorta-to-brachial or brachial-to-radial arteries. Standard cuff BP was measured four different times using three different devices. Three independent investigators also provided data (n=255 from four studies) using another three separate cuff BP devices. Four distinct BP phenotypes were discovered based on variability in SBP amplification: phenotype 1) both aortic-to-brachial and brachial-to-radial SBP-amplification; phenotype 2) only aortic-to-brachial SBP-amplification; phenotype 3) only brachial-to-radial SBP-amplification; phenotype 4) neither aortic-to-brachial nor brachial-to-radial SBP-amplification. Aortic SBP was significantly higher among phenotypes 3 and 4 compared to phenotypes 1 and 2 (p=0.00074), but this was not discriminated using any standard cuff BP measures (p=0.31). Data from independent investigators confirmed the key findings. This is the first in-human discovery of BP phenotypes that have significantly different BPs, but which are not discriminated by standard cuff BP devices used in daily clinical practice. Improved BP device accuracy may be achieved by considering individual phenotypic BP differences.

3.2 Introduction

Cardiovascular disease is the global number one cause of mortality.[202] The foremost risk factor is high blood pressure (BP), which affects over 1.1 billion people worldwide.[2, 203] Treatment to reduce high BP lowers cardiovascular risk,[3] and for these reasons, accurate cuff BP is regarded as "one of the most important measurements in all of clinical medicine."[7] Surprisingly, standard upper arm cuff BP measurement methods have barely changed in more than 100 years, even though fundamental issues with cuff BP accuracy have been known since the 1950s.[8] The extent of this problem was only recently exposed via individual participant data meta-analyses of all available data on cuff BP accuracy.[77] Compared with intra-arterial (invasive) BP, it was found that cuff BP had minimal accuracy for measuring either the BP in the arm (brachial artery) or at the central aorta, particularly in the systolic BP (SBP) range of 120 – 159 mmHg, and this had major implications for correct diagnosis of BP according to guidelines.[77]

Standard cuff BP methods, whether oscillometric or manual (Korotkoff sounds), measure BP from arterial signals at the brachial artery during cuff deflation or in some cases, inflation.[64, 204] However, there may be large individual variation in arterial characteristics (i.e. stiffness, diameter, flow dynamics) and BP transmission along the length of the arterial tree.[77-79, 205, 206] The variation in central-to-peripheral BP could be hard for cuff BP to detect, since it measures signals at an isolated peripheral artery with a generic, 'one size fits all' method (either oscillometric algorithms or Korotkoff sounds). These methods potentially overlook subtle but distinct phenotypic differences in the way that BP is transmitted from central-to-peripheral arteries (e.g. possibly increased SBP transmission in some people, but not in others). Indeed, there are other clues to the presence of distinct BP phenotypes. For example, among people with renal disease, cuff BP becomes increasingly inaccurate as the severity of disease and vascular dysfunction (aortic stiffness) increases.[111] Also, people with apparently normal clinic cuff BP can still have signs of organ damage related to high BP, suggesting that a sizeable element of BP risk is missed by the cuff BP method.[207]

This current study was performed to determine if distinct BP phenotypes exist in the way that BP is transmitted from the central-to-peripheral arteries. Of most relevance are the changes in SBP and pulse pressure (PP) since only minimal changes occur in diastolic BP (DBP) and mean arterial pressure.[132] The contributors to individual differences in BP transmission (amplification) are multifactorial, with influential haemodynamic and non-haemodynamic factors at the heart (e.g. left ventricular output), aorta (e.g. compliance) and distal vasculature (e.g. structural and functional characteristics).[205, 208-210] We sought to assess variability in BP amplification by careful examination of the relationships between arterial BP

waveforms measured invasively within the aorta, brachial (upper arm) and radial (wrist) arteries and hypothesized that there would be several distinctive BP phenotypes based on variability in central-to-peripheral artery BP amplification. Secondly, we sought to determine whether distinct BP phenotypes could be discriminated by applying a standard cuff BP measurement approach (e.g. oscillometry), using several cuff BP devices recorded at different time points. We hypothesized that the distinctive BP phenotypes would not be discriminated by any of the cuff BP measures used in daily clinical practice.

3.3 Methods

Participants. Patients with a clinical indication for coronary angiography at the Royal Hobart Hospital (Hobart, Australia) were studied. We excluded patients with the following characteristics that may introduce error in the measurement of intra-arterial BP: atrial fibrillation or aortic stenosis (n=10); a cuff inter-arm difference >5 mmHg for SBP and/or DBP; or unable to measure cuff BP in both arms (e.g. due to injury, lymph node removal; n=17); or use of femoral artery for intra-arterial access (due to inaccessibility to the peripheral limb arteries; n=11). We also excluded patients where medical (n=34, e.g. radial artery spasm, n=2) or technical (n=9) issues arose that prevented the research measures or adversely affected the quality of the waveforms that were recorded. Additionally, n=4 did not provide consent. Therefore, from a total of 211 people we completed studies in 126 continuous people. The University of Tasmania Human Research Ethics Committee approved the study (reference H0010566) and each participant provided signed informed consent.

Intra-arterial BP measurements. Participants were studied under stable haemodynamic conditions, without moving or talking and were clear of drugs inducing acute vasoactive responses, as per ARTERY guidelines.[102] The right radial artery was used for catheter access. After the clinical procedure, intra-arterial BP was recorded with a fluid-filled system using 5Fr (48% of cases) or 6Fr (52% of cases) catheters including 5-6Fr Judkins Left (Cordis, NJ), 5-6Fr multipurpose (Cordis), and 5Fr TIG (Terumo, NJ). Intra-arterial BP measurements began with the catheter in the proximal ascending aorta. The catheter was then pulled back to the upper arm (mid-humerus) for brachial waveform measurement. Finally, the catheter was pulled back to the wrist, and the sheath was partially removed to allow the most distal radial waveform measurement possible. Fluoroscopy was used to confirm the catheter position at each arterial site and the catheter was flushed before all waveform recordings. Stable pressure waveforms were recorded for a minimum of 20 seconds at each arterial site to reduce the influence of respiratory variation. Waveforms were recorded via analogue-to-digital signal converter at a frequency of 1000 Hz (LabChart 7, AD Instruments, Bella Vista, Australia). The dynamic

response of the fluid-filled catheter system was assessed by performing 'pop-tests' and confirmed in the appropriate range outlined by Gardner[54] (natural frequency >18 Hz and the damping coefficient >0.3).

Cuff BP measurements. Since BP can change over time and, because cuff BP values may vary between BP devices (owing to different operating functions)[211] external validity was addressed by measuring standard cuff BP using three different device models and four different individual devices (independently validated or Food and Drug Authority (FDA) cleared) at four different time points: First, during the angiography pre-assessment visit, typically the day prior to the angiogram, a single seated BP was measured by a nurse (WelchAllyn Spot Vital Signs (5200-103Z), Skaneateles Falls, NY, USA).[212] Second, prior to the catheterization, whilst in the waiting room, cuff BP was measured simultaneously on both arms, using two identical devices (UA767, A&D Medical, Tokyo, Japan), with participants either supine or seated.[213, 214] Third, before commencing the coronary angiogram, duplicate cuff BP measurements were taken whilst the participant was supine in the catheterization laboratory (SphgymoCor Xcel, AtCor Medical, West Ryde, Australia). SphygmoCor Xcel uses the Suntech Advantage Model 2 series non-invasive BP module to measure brachial cuff BP. Fourth, after the clinical procedure, cuff BP was measured once simultaneous with intra-arterial brachial BP (SphygmoCor Xcel). For all cuff measurements, participants were asked to remain still and quiet throughout the recordings. For cuff and intra-arterial measurements, PP was calculated as SBP – DBP.

Defining BP phenotypes. The magnitude of SBP increase (SBP amplification) between the aorta-to-brachial and brachial-to-radial arteries was used to define the BP phenotypes. When SBP increased by ≥5 mmHg between the aortic-to-brachial or brachial-to-radial arteries, this was defined as SBP amplification. The threshold of 5 mmHg was chosen because it represents a difference in BP generally greater than could be attributed to measurement variability.[192, 215] SBP increases of <5 mmHg between the aortic-to-brachial or brachial-to-radial arteries were defined as no SBP amplification. Phenotypic differences in SBP were of most interest because SBP is more closely associated with cardiovascular disease and events compared to other BP indices.[35, 216] Moreover, there is little variability in DBP between the central-to-peripheral arteries.[77]

Pressure waveform analysis. Commercially available software (SphgymoCor CVMS, AtCor Medical) was used to perform offline waveform analysis. Each intra-arterial waveform was entered into the system in 'simulation' mode. The output provided detailed analysis of BP waveform parameters including the first and second systolic peaks. From these and PP, we calculated the following waveform parameters:

1. Augmentation pressure = second – first systolic waveform peak.
2. Aortic augmentation index = augmentation pressure / PP * 100.
3. Radial augmentation index = second / first systolic waveform peak *100.

Clinical information. Participant clinical characteristics including anthropometry and clinical history were recorded at the angiography pre-assessment (usually one day prior to the procedure) by nursing staff. Other clinical information was extracted from the Royal Hobart Hospital digitized medical records system.

Independent confirmation of major findings. As far as we know, this is the first study to record standard cuff BP as well as intra-arterial aortic, brachial and radial BP. However, from our systematic review,[77] we identified six independent studies (one unpublished) that measured intra-arterial aortic and brachial BP, along with cuff BP,[11, 16, 152, 217, 218] thus providing an opportunity for separate confirmation of the findings relating to aortic-to-brachial SBP amplification. The authors of all studies were contacted, and four (three from Taiwan and China[11, 16, 152] and one from Italy [Pucci et al unpublished]) provided individual participant data with a total of 255 participants. We compared people with ≥5 mmHg aortic-to-brachial SBP amplification to those with no aortic-to-brachial SBP amplification (<5 mmHg). In each study, data was collected in patients undergoing coronary angiography. All studies performed aortic and brachial intra-arterial measurements sequentially, except Lin et al[152], which used a dual sensor catheter to perform simultaneous measurements. Two of the confirmation studies used Omron HEM 9000AI cuff devices, Pucci et al, unpublished and Ding et al, 2013[16], whilst the other studies used VP-2000 (Colin Corporation, Komaki, Japan)[11] and WatchBP Office (Microlife, Widnau, Switzerland)[152] devices. These devices have all been validated according to international guidelines or FDA cleared for brachial BP measurement.[219, 220] In all studies, cuff BP was measured on the arm contralateral to the intra-arterial BP measures. Full methods for the published studies are available,[11, 16, 152]and for Pucci et al, unpublished, see Appendix 2.1 for details.

Statistical analysis. Differences in continuous variables between phenotypes were assessed via one-way analysis of variance. Tukey honest significant difference tests were used to determine where significant differences were between phenotypes, adjusting for multiple comparisons. In the analysis of aortic-to-brachial SBP amplification versus no aortic-to-brachial SBP amplification for each individual study, differences in BP measures were determined using T-tests and when the confirmation studies were pooled, linear mixed modelling was performed (to account for within study clustering of individuals). Suspected confounders of the phenotypic differences in BP were assessed using analysis of covariance (four phenotypes), linear

regression (aortic-to-brachial phenotypes only) and linear mixed modelling (pooled independent confirmation studies). A sub-analysis of patients with available data on use of antihypertensive and statin therapies was performed. Between-arm cuff SBP difference (left minus right arm, taken in the catheterisation waiting room) was added to each model to account for potential confounding due to different BP values in the left and right arms. A sensitivity analysis of patients with heart rate differences <5 beats/minute between the aorta-to-brachial, brachial-to-radial or aorta-to-radial arteries was also conducted. Influence of arm circumference on the relationship between cuff and intra-arterial BP was tested in a sensitivity analysis of 62 patients. Patients were stratified based on an arm circumference ≤32cm (n=34) versus > 32 cm (n=28). We also analysed differences across the BP phenotypes in PP, a particularly relevant cardiovascular risk measure among older people.[221] P<0.05 was considered statistically significant. Data were synthesised and analysed using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

3.4 Results

Participant characteristics. Overall, participant characteristics were typical of patients undergoing coronary angiography: middle-older aged, predominately male and overweight according to body mass index (Table 3.1). Furthermore, most patients had a history of hypertension, a family history of cardiovascular disease and at least one diseased coronary vessel.

Discovery of BP phenotypes. Four distinct BP phenotypes were observed based on the magnitude of aortic-to-brachial and brachial-to-radial SBP amplification (Figure 3.1)

1) both aortic-to-brachial and brachial-to-radial SBP amplification (≥5 mm Hg), among 32 participants (25%; Figure 3.2A); 2) aortic-to-brachial SBP amplification, but no brachial-to-radial SBP amplification, among 41 participants (33%; Figure 3.2B); 3) no aortic-to-brachial SBP amplification, but brachial-to-radial SBP amplification, among 29 participants (23%; Figure 3.2C) and; 4) neither aortic-to-brachial nor brachial-to-radial SBP amplification, among 24 participants (19%; Figure 3.2D). The BP waveforms from each phenotype are overlaid in Figure 3.3.

Table 3.1 Clinical characteristics across the four blood pressure phenotypes.

Variable	All	Phenotype 1 (both SBPamp)	Phenotype 2 (aortic-brachial SBPamp only)	Phenotype 3 (brachial-radial SBPamp only)	Phenotype 4 (no SBPamp)	P value
Number of cases (%)	126 (100)	32 (25)	41 (33)	29 (23)	24 (19)	-
Age, years	61±10	58±10	58±11	66±9	64±8	0.0027
Male sex, n (%)	87 (69)	27 (84)	28 (68)	16 (55)	16 (67)	0.10
Height, cm	171±10	176±8	172±10	168±10	168±9	0.0025
Weight, kg	86.8±20.2	91.3±17	91.0±25	79.8±15	82.3±18	0.045
Body mass index, kg/m^2	29.5±5.6	29.3±5.1	30.8±5.9	28.3±5.7	29.1±5.2	0.31
Heart rate, beats/min	69±13	69±12	72±15	69±15	64±9	0.14
>1 coronary vessel stenosed, n (% yes)	73 (59)^	22 (69)	21 (51)	19 (66)	11 (50)	0.32
eGFR, $mL/min/1.73m^2$	82±20	83±21	87±18	74±23	81±18	0.075
Hypertension, n (% yes)	101 (82)$^{\%}$	26 (81)	36 (88)	21 (75)*	18 (82)	0.60
Type 2 diabetes, n (% yes)	30 (26)$^{\$}$	12 (38)	11 (27)	2 (7)^	5 (21)	0.036
History of cardiovascular disease, n (% yes)	54 (45)**	11 (38)	16 (41)	17 (61)*	10 (43)	0.30
Family history of cardiovascular disease, n (% yes)	81 (68)^^	17 (57)	28 (72)	18 (64)	18 (78)	0.35

SBPamp, systolic blood pressure amplification. Data are mean±standard deviation or n (%). P-values from continuous data were calculated using analysis of variance and from categorical data using Chi-square tests. *n=1 missing data; ^n=2 missing data; $^{\%}$n=3 missing data; ^^ n=6 missing data;**n=7 missing data; $^{\$}$ n=10 missing data

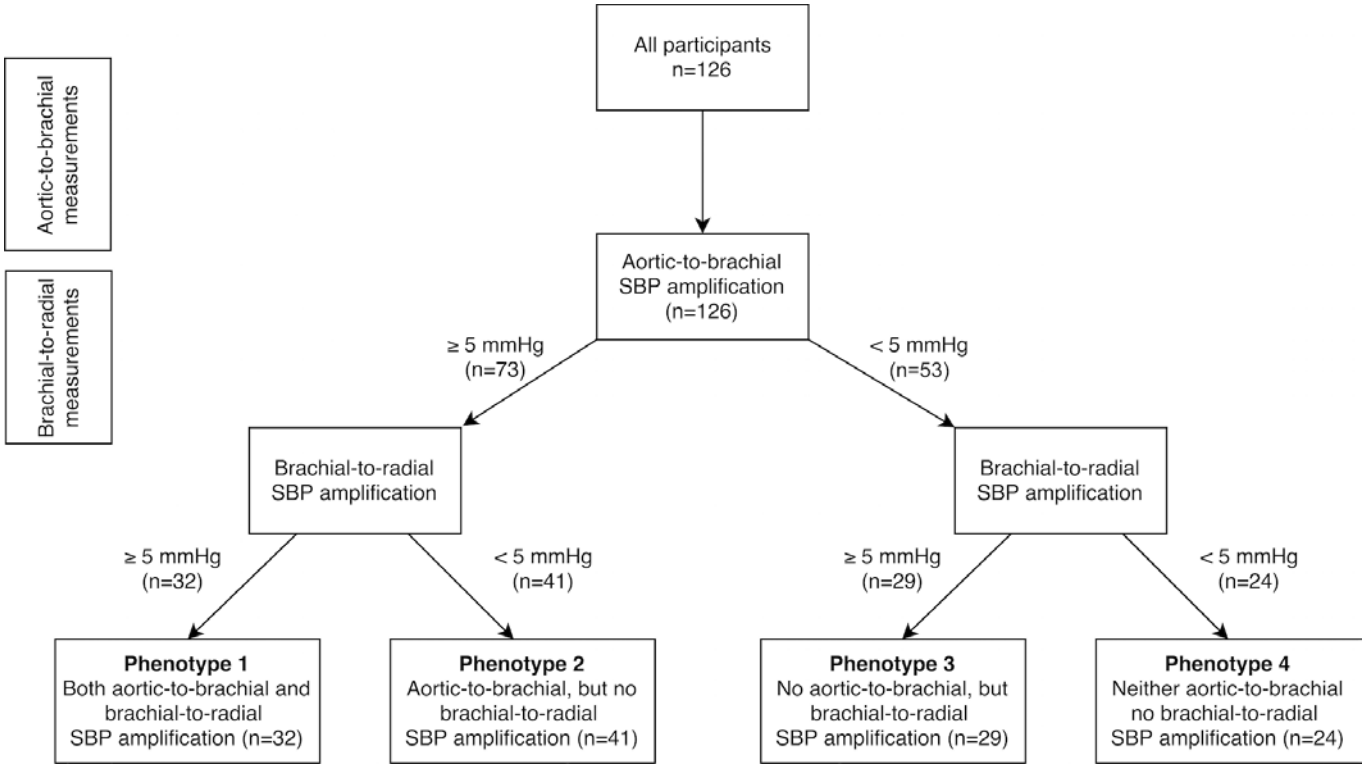


Figure 3.1 Flow of identification of the four blood pressure phenotypes.

Intra-arterial blood pressure (BP) measurements were performed in the aortic, brachial and radial arteries via catheter pullback. The first step was measurements in the ascending aorta and then pullback to the brachial artery where the next measurements were taken. The catheter was then withdrawn to the most distal possible radial artery position, with partial removal of the radial sheath. Systolic BP (SBP) increases from the aorta-to-brachial artery ≥5 mmHg were defined as SBP amplification. The same ≥5 mmHg threshold was used for brachial-to-radial SBP amplification. Thus, four BP phenotypes were defined from this study protocol.

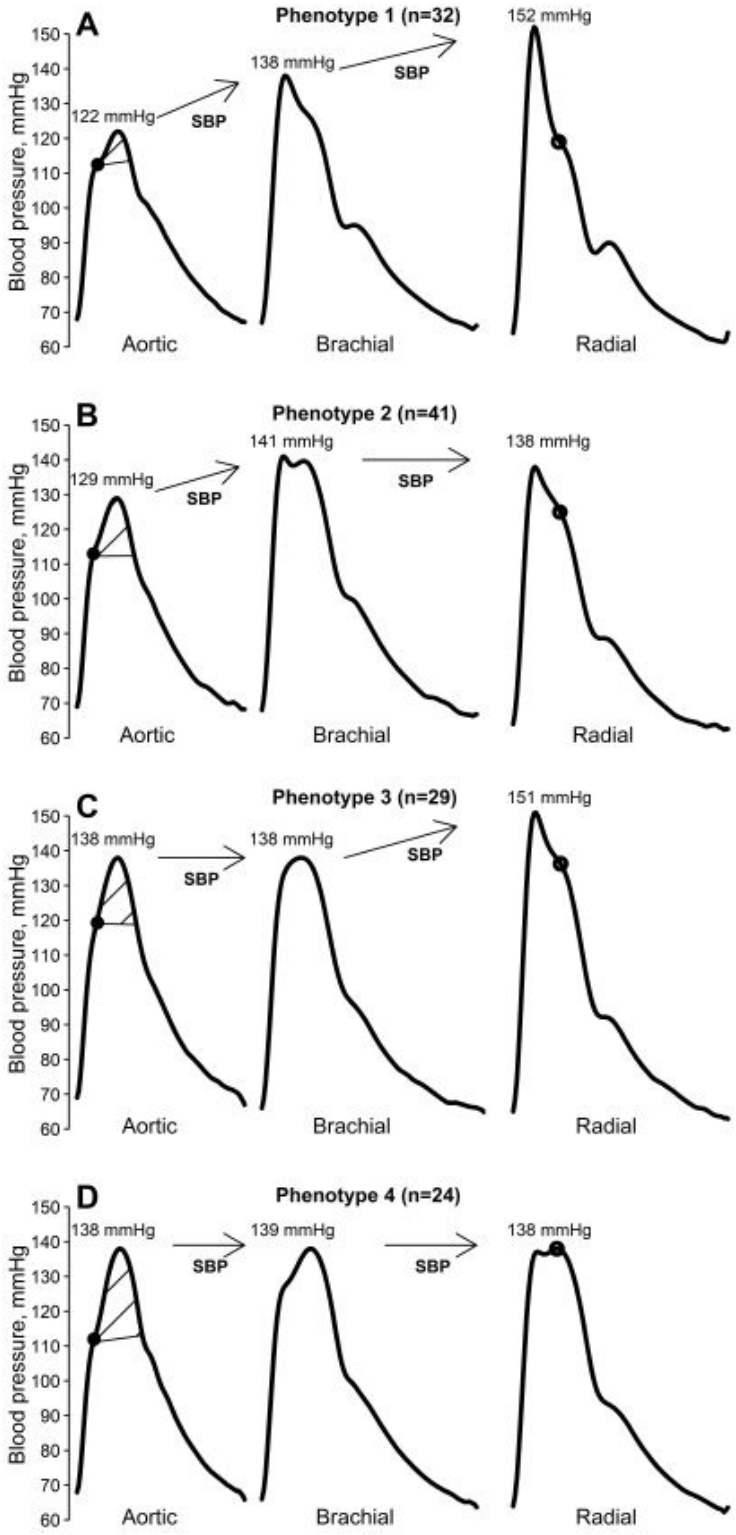


Figure 3.2 Discovery of four distinct blood pressure phenotypes.

The four blood pressure (BP) phenotypes were defined based on differences in systolic BP (SBP) amplification between the aortic-to-brachial artery and brachial-to-radial arteries. Pressure waveforms presented are the ensemble average of all participant waveforms within each BP phenotype and with the average SBP reported above the waveform. The black circles on the aortic waveforms highlight the first inflection point and the hatched areas denote the augmented pressure component. The black circle on the radial waveforms denotes the second systolic peak, which approximates aortic SBP within each BP phenotype.

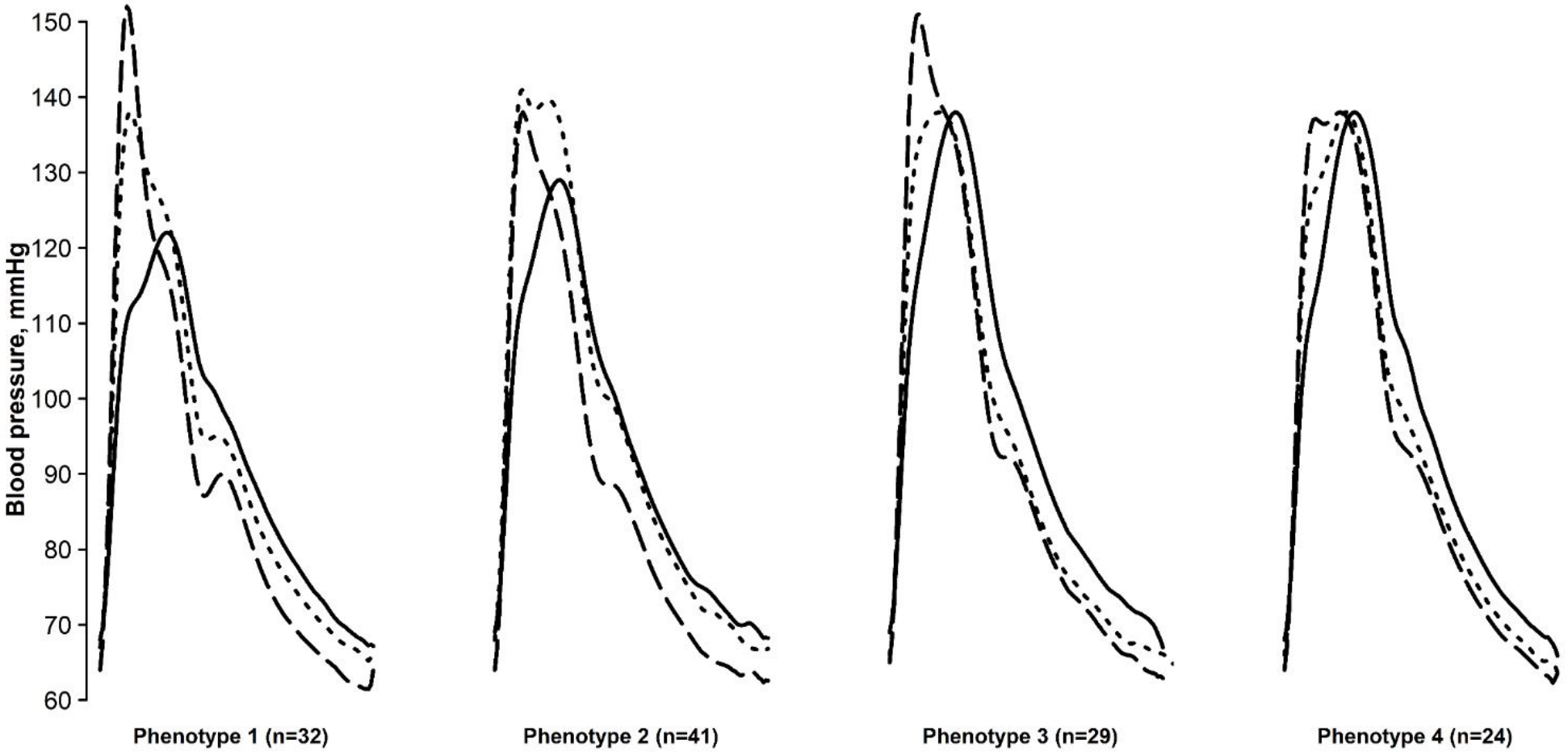


Figure 3.3 Overlaid ensemble averaged blood pressure waveforms for the four blood pressure phenotypes.

The waveforms represent the aortic (solid line), brachial (dotted line) and radial artery (dashed line) pressures.

Aortic SBP was significantly different between the phenotypes (p=0.0049), and was significantly higher in phenotypes 3 and 4 compared with phenotype 1, even after adjustment for multiple comparisons (Figure 3.4A and Table 3.2). On the other hand, brachial SBP was not different between the phenotypes (p=0.90; Figure 3.4A). Despite marked phenotypic differences in central-to-peripheral SBP amplification, and significantly increased aortic SBP among phenotypes 3 and 4, there were no significant differences in standard cuff SBP between the four phenotypes (Table 3.3). This lack of discrimination was observed for each of the four individual cuff BP devices, and across each of the four time points, as well as for the average of all cuff SBP measurements (p>0.50 all comparisons; Figure 3.4A and Table 3.3). Results for PP followed the same pattern as for SBP; aortic PP was significantly different between the phenotypes (p=0.0016), but cuff PP did not discriminate this, whether measured using different BP devices at different time points, or using the average of all cuff PP measurements (p>0.2 all comparisons; Figure 3.4B and Table 3.3).

Detailed analysis of BP waveforms, as well as demographic and clinical characteristics revealed additional differences between the BP phenotypes. AIx was significantly different across the phenotypes, and was markedly higher in phenotype 4 (Figure 3.2 and Table 3.2). We performed exploratory analyses to examine whether the uncalibrated radial AIx provided information distinct from the BP phenotypes or if it could be used as a non-invasive method (via radial tonometry) to discriminate the BP phenotypes. Analyses provided in Appendix 2.2 and Appendix Tables 2.1- 2.2 show that the BP phenotypes provide information that is separate and additive to radial AIx. People with phenotypes 3 and 4 also tended to be older and shorter (Table 3.1).

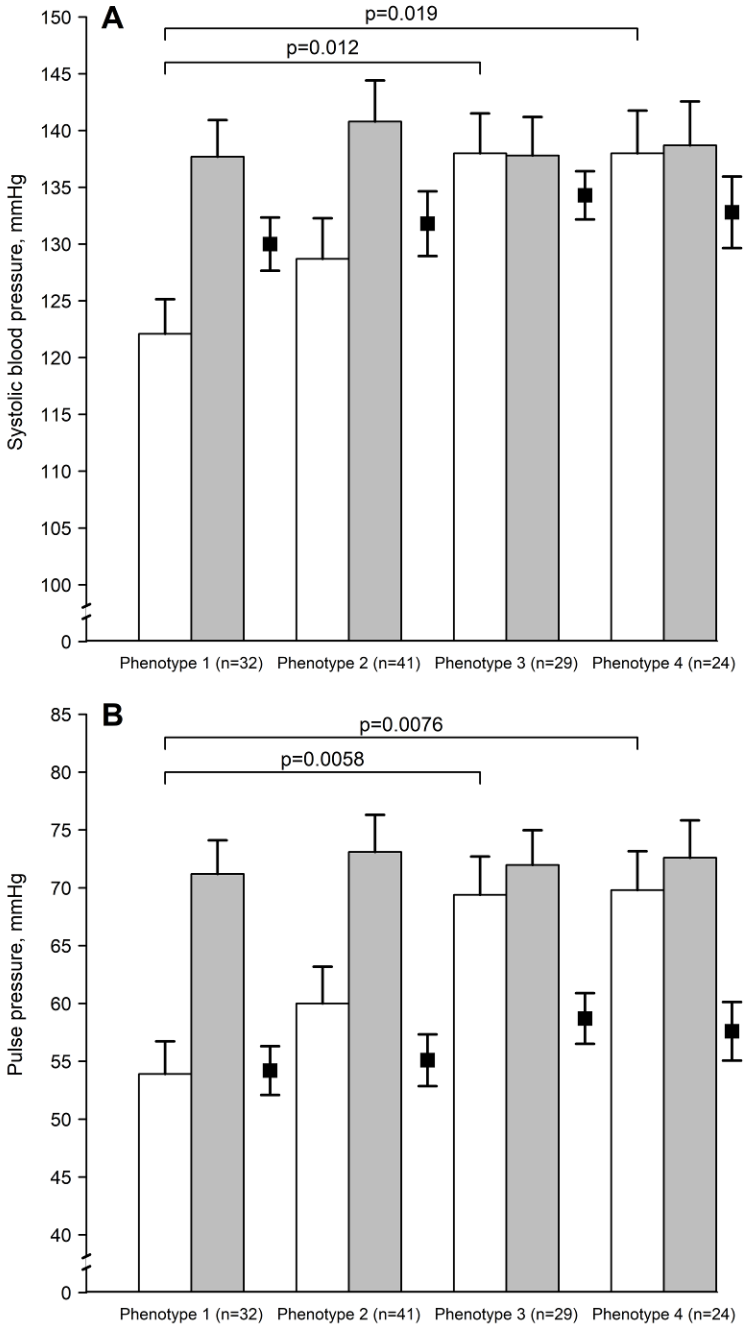


Figure 3.4 Cuff, intra-arterial aortic and brachial blood pressure across the four blood pressure phenotypes.

Systolic blood pressure (SBP) (panel A) and pulse pressure (PP) (panel B) measured at the aorta (open bars), brachial artery (closed bars) and cuff blood pressure (BP) measures (black points) across each BP phenotype. Aortic SBP and PP were significantly different between phenotypes (ANOVA p=0.0049 and p=0.0016), but not brachial SBP or cuff SBP or cuff PP (p>0.2 all). P-values on the figure represent significant differences in aortic SBP and PP between the specific phenotypes after Tukey honest significant difference analysis, which adjusts for multiple comparisons. P-value>0.05 for all other comparisons. Data are mean±standard error of the mean.

Table 3.2 Haemodynamic variables across the four blood pressure phenotypes.

Variable	Phenotype 1 (both SBPamp)	Phenotype 2 (aortic-brachial SBPamp only)	Phenotype 3 (brachial-radial SBPamp only)	Phenotype 4 (no SBPamp)	P value
Aortic SBP	122±17	129±23	138±19	138±18	0.0049
Brachial SBP	138±18	141±23	138±18	139±19	0.90
Radial SBP	152±22	138±23	151±18	138±18	0.0050
Aortic-brachial SBPamp	15.6±7.8	12.2±6.5	-0.2±3.9	0.7±3.4	<0.0001
Brachial-radial SBPamp	14.7±7.5	-3.3±6.9	12.8±6.6	-0.5±4.6	<0.0001
Aortic MAP	92±9	94±12	97±11	97±10	0.16
Aortic DBP	68±7	69±9	69±10	68±8	0.99
Aortic PP	54±16	60±20	69±18	70±16	0.0016
Brachial PP	71±16	73±21	72±16	73±16	0.97
Radial PP	88±22	73±20	86±17	74±16	0.0018
Heart rate, beats/min	69±12	72±15	69±15	64±9	0.14
Aortic augmented pressure	6.4±10	12.2±17	17.4±17	24.0±14	0.00033
Aortic augmentation index, %	11.0±20	17.9±24	22.4±21	32.3±16	0.0041
Radial augmentation index, %	80±10	93±11	91±9	100±6	<0.0001

SBP, systolic blood pressure; SBPamp, SBP amplification; MAP, mean arterial pressure, DBP, diastolic BP; PP, pulse pressure. Data are mean±standard deviation. Units are mmHg unless specified. P-values were calculated using analysis of variance.

Table 3.3 Cuff blood pressure across the four blood pressure phenotypes.

Variable	Phenotype 1 (both SBPamp)	Phenotype 2 (aortic-brachial SBPamp only)	Phenotype 3 (brachial-radial SBPamp only)	Phenotype 4 (no SBPamp)	P value
Cuff SBP (average)	130±13	132±18	134±12	133±15	0.73
Cuff SBP (pre-assessment)*	137±18	141±20	140±14	139±22	0.84
Cuff SBP (waiting room, left arm)^	132±15	135±20	135±15	129±19	0.67
Cuff SBP (waiting room, right arm)^	132±14	134±20	136±16	128±19	0.52
Cuff SBP (waiting room, average)^	132±15	134±20	135±16	128±19	0.60
Cuff SBP (pre-diagnostic procedure)$	124±13	126±18	128±15	129±18	0.71
Cuff SBP (simultaneous with intra-arterial brachial)%	127±13	130±21	133±15	132±16	0.52
Cuff PP (average)	54±12	55±14	59±12	58±12	0.50
Cuff PP (pre-assessment)*	57±16	58±18	60±15	60±16	0.80
Cuff PP (waiting room, left arm)^	53±15	57±15	57±14	54±17	0.74
Cuff PP (waiting room, right arm)^	55±16	56±16	59±15	52±17	0.59
Cuff PP (waiting room, average)^	54±15	56±15	58±14	53±17	0.70
Cuff PP (pre-diagnostic procedure) $	51±11	53±14	55±12	57±12	0.44

Cuff PP (simultaneous with intra-arterial brachial)[%]	54±10	54±15	59±12	59±12	0.23

SBP, systolic blood pressure; PP, pulse pressure; SBPamp, SBP amplification. Data are mean±standard deviation. *n=113; ^n=94; [$]n=117; [%]n=122. Units for SBP and PP are mmHg. P value calculated by analysis of variance.

Findings were not altered in a simplified analysis assessing people with aortic-to-brachial SBP amplification (phenotypes 1 and 2 combined) compared to those with no aortic-to-brachial SBP amplification (phenotypes 3 and 4 combined), whereby aortic SBP was significantly higher among people with no amplification and cuff SBP did not discriminate this variability (Figure 3.5A). The same pattern was also observed for PP (Figure 3.6A). After adjusting for age, sex, height, heart rate, diabetes status or hypertension status, the SBP findings were unchanged, but the difference in aortic PP was non-significant (Table 3.4). Adding the between-arm BP difference to the regression models did not alter the results.

A sub-analysis was also completed on 83 people who had available data on use of antihypertensive and statin therapies, both of which did not alter the phenotypic findings (Table 3.5). We also performed a sensitivity analysis, including people where heart rate differences between the aorta-to-brachial, brachial-to-radial or aorta-to-radial arteries were <5 beats/min (n=103). Findings were not altered compared to the complete analysis (data not shown). Similar differences between cuff and intra-arterial aortic SBP were found for the standard upper arm circumference (≤32cm) versus >32 cm groups (-4.6±9.1 versus -3.2±8.0 mmHg, p=0.53).

Independent confirmation of major findings. Consistent with our observations, in each independent dataset, higher aortic SBP was observed among people with no aortic-to-brachial SBP amplification compared to those with aortic-to-brachial SBP amplification (notionally representing phenotypes 3 and 4 compared with phenotypes 1 and 2). Also, consistent with our observations, cuff SBP was not different between the two SBP amplification groups in each independent dataset, or in a pooled analysis (Figure 3.5B-E). Analysis of PP revealed a similar pattern to SBP (Figure 3.6B-E). The findings were not altered when adjusted for age and sex differences between the phenotypes (Table 3.4).

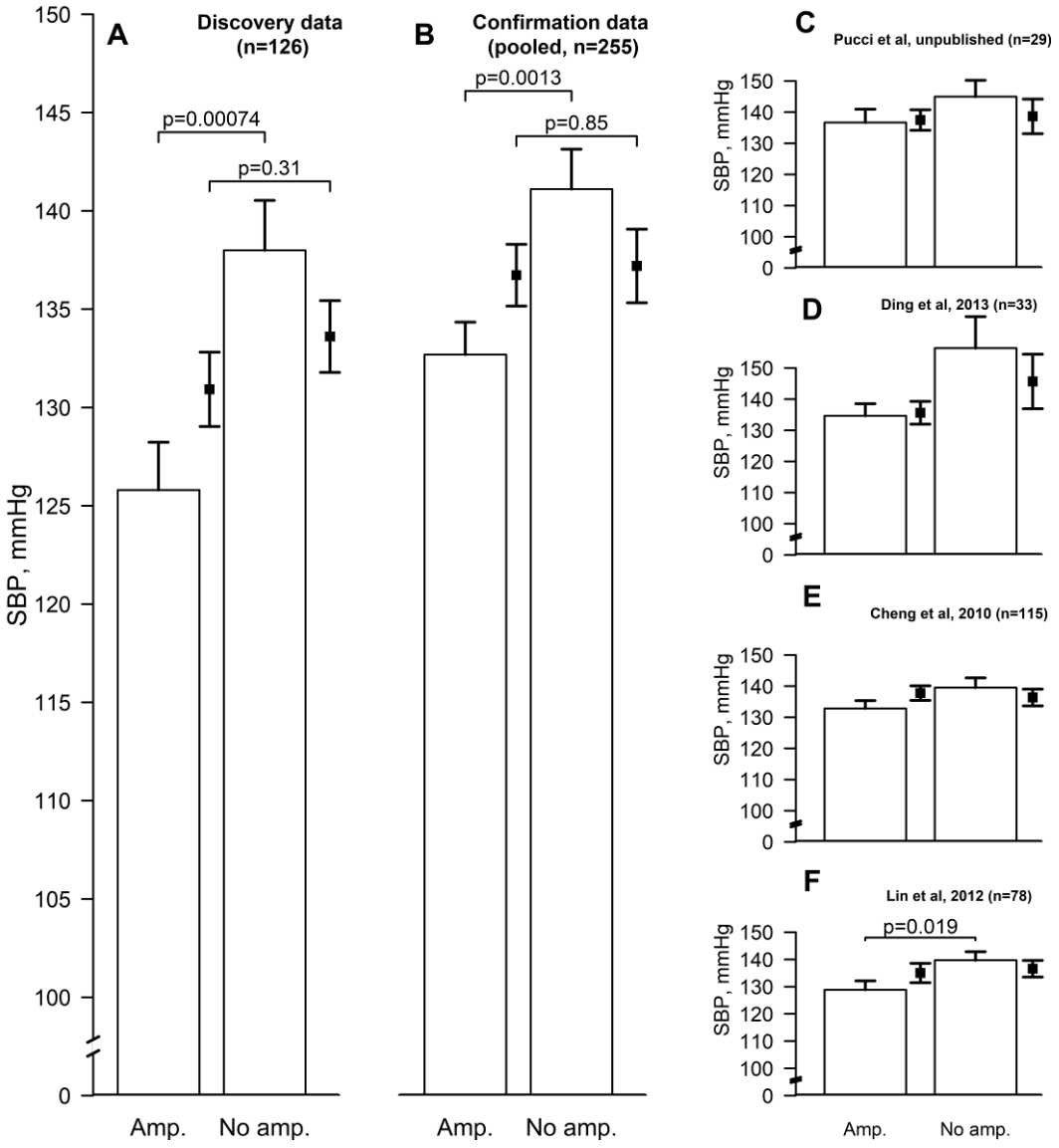


Figure 3.5 Confirmation of the blood pressure phenotype discovery using systolic blood pressure data.

Aortic systolic blood pressure (SBP; open bars) and averaged cuff SBP (black points) compared between aortic-to-brachial SBP amplification ≥5 mmHg (Amp.) and no aortic-to-brachial SBP amplification <5 mmHg (No amp.). The discovery of the distinct blood pressure phenotypes is presented in panel A. Analysis of four independent studies is presented pooled in panel B and independently in panels C-F. Data are mean±standard error of the mean.

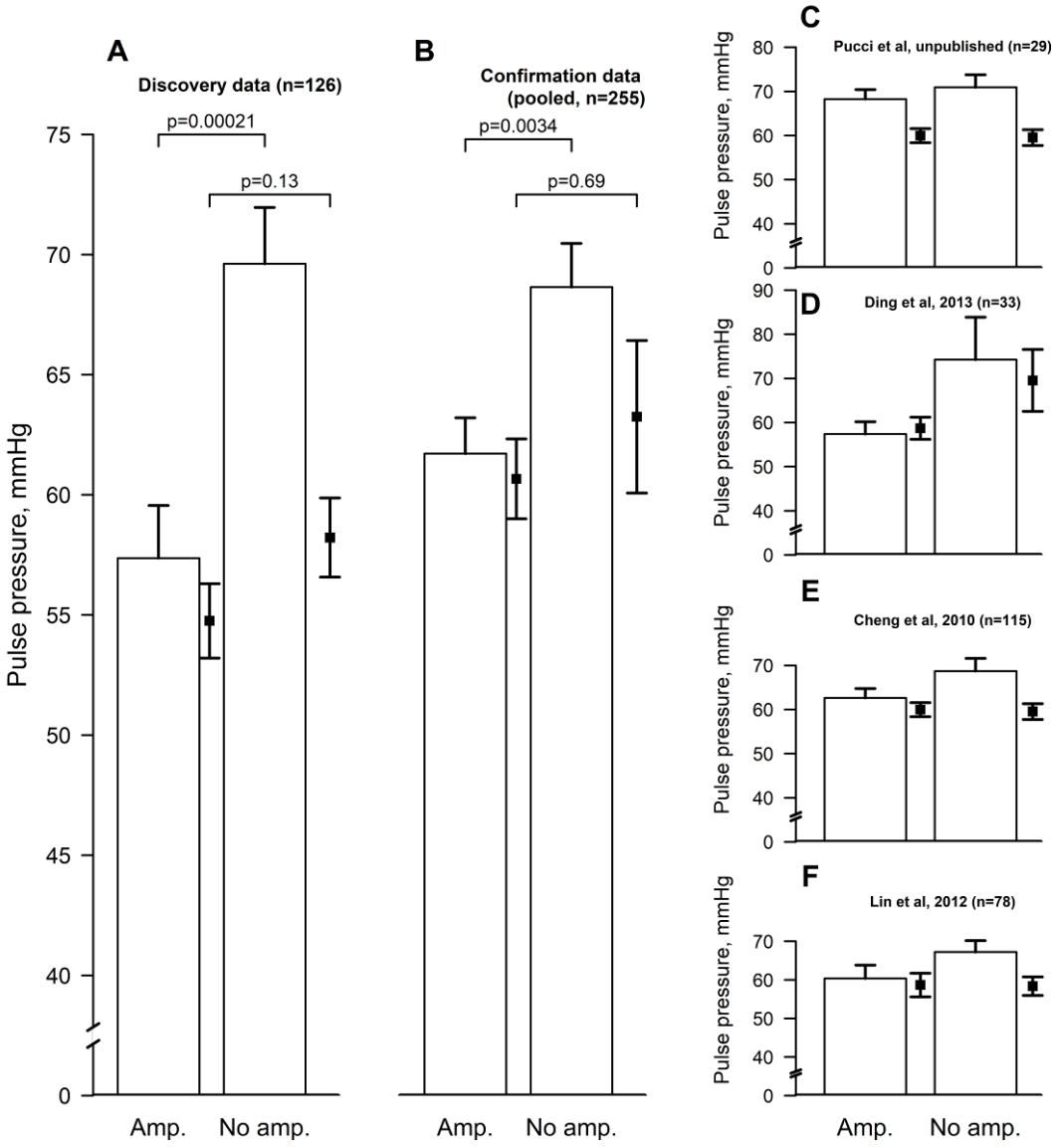


Figure 3.6. **Confirmation of the blood pressure phenotype discovery from pulse pressure data.**

Aortic pulse pressure (PP; open bars) and averaged cuff PP (black points) compared between aortic-to-brachial systolic blood pressure (SBP) amplification ≥5 mmHg (Amp.) and no aortic-to-brachial SBP amplification <5 mmHg (No amp.). The discovery data is presented in panel A. Analysis of four independent studies is presented pooled in panel B and independently in panels C-F. Data are mean±standard error of the mean.

Table 3.4 Aortic systolic blood pressure and pulse pressure differences between the blood pressure phenotypes after controlling for potential confounders.

Discovery data					
Four blood pressure phenotypes	F value	P value	Presence of aortic-brachial SBP amplification	Unstandardized beta (95% CI)	P value
Dependent: Aortic SBP, mm Hg			**Dependent: Aortic SBP, mm Hg**		
Phenotypes	4.26	0.0071	Aortic-brachial SBPamp ≥5 mm Hg (1=no)	8.73 (0.56 to 16.7)	0.039
Age, years	9.45	0.0027	Age, years	0.54 (0.17 to 0.91)	0.0049
Sex (1=male)	0.11	0.74	Sex (1=male)	-5.51 (-15.2 to 3.99)	0.27
Height, cm	0.62	0.43	Height, cm	0.21 (-0.26 to 0.67)	0.39
Heart rate, beats/min	1.90	0.17	Heart rate, beats/min	-0.16 (-0.43 to 0.11)	0.26
Hypertension status, (1=yes)	0.90	0.35	Hypertension status, (1=yes)	3.41 (-6.20 to 12.8)	0.49
Type 2 diabetes status, (1=yes)	1.87	0.17	Type 2 diabetes status, (1=yes)	4.96 (-3.71 to 13.4)	0.26
Dependent: Aortic PP, mm Hg			**Dependent: Aortic PP, mm Hg**		
Phenotypes	6.22	0.00065	Aortic-brachial SBPamp ≥5 mm Hg (1=no)	4.87 (-1.98 to 11.6)	0.17
Age, years	29.2	<0.0001	Age, years	0.78 (0.47 to 1.08)	<0.0001
Sex (1=male)	3.72	0.057	Sex (1=male)	-7.03 (-15.2 to 0.94)	0.094
Height, cm	0.34	0.56	Height, cm	-0.10 (-0.50 to 0.28)	0.61

Table 3.4 (continued)

Heart rate, beats/min	8.23	0.0050	Heart rate, beats/min	-0.32 (-0.55 to -0.094)	0.0076
Hypertension status, (1=yes)	0.098	0.76	Hypertension status, (1=yes)	0.29 (-7.78 to 8.18)	0.94
Type 2 diabetes status, (1=yes)	2.03	0.16	Type 2 diabetes status, (1=yes)	4.51 (-2.74 to 11.6)	0.23
Independent confirmation studies (pooled)					
Dependent: Aortic SBP, mm Hg	Unstandardized beta (95% CI)	P value	**Dependent: Aortic PP, mm Hg**	Unstandardized beta (95% CI)	P value
Aortic-brachial SBP amplification ≥5 mm Hg (1=no)	7.09 (2.21 to 11.9)	0.0048	Aortic-brachial SBP amplification ≥5 mm Hg (1=no)	5.06 (1.20 to 8.83)	0.011
Age, years	0.51 (0.32 to 0.70)	<0.0001	Age, years	0.81 (0.66 to 0.96)	<0.0001
Sex (1=male)	-7.60 (-13.2 to -2.16)	0.0078	Sex (1=male)	-6.83 (-11.3 to -2.50)	0.0027

SBP, systolic blood pressure; PP, pulse pressure; SBPamp, SBP amplification. In the discovery data, differences in aortic SBP and PP between the four blood pressure phenotypes was assessed by analysis of covariance and in the presence of aortic-brachial SBPamp data by linear regression. The findings were not altered with the addition of radial augmentation index to the model. In the pooled confirmation studies, linear mixed modelling was used, to account for the clustering of individuals within each separate study. Not all the parameters from the discovery data were available in the pooled confirmation, thus this analysis was performed adjusting only for age and sex.

Table 3.5 Aortic systolic blood pressure and pulse pressure differences between the four blood pressure phenotypes after controlling for additional potential confounders in a sub-sample of participants (n=83).

Four blood pressure phenotypes	F value	P value
Dependent: Aortic SBP, mm Hg		
Phenotypes	4.83	0.0040
Age, years	7.18	0.0091
Sex (1=male)	0.10	0.75
Height, cm	0.43	0.51
Heart rate, beats/min	0.46	0.50
Type 2 diabetes status, (1=yes)	1.87	0.17
Antihypertensive medication (1=yes)	0.23	0.64
Statin medication (1=yes)	0.22	0.63
Dependent: Aortic PP, mm Hg		
Phenotypes	7.79	0.00014
Age, years	20.6	<0.0001
Sex (1=male)	5.03	0.028
Height, cm	0.42	0.52
Heart rate, beats/min	4.90	0.030
Type 2 diabetes status, (1=yes)	1.60	0.21
Antihypertensive medication (1=yes)	0.28	0.60
Statin medication (1=yes)	1.13	0.29

SBP, systolic blood pressure; PP, pulse pressure. Medication status was unavailable in n=43. Differences in aortic SBP and PP between the four blood pressure phenotypes was assessed by analysis of covariance.

3.5 Discussion

This study is the first to our knowledge that examines distinct phenotypic differences in BP transmission between the central-to-peripheral arteries. The work demonstrates the discovery of four distinct BP phenotypes that are related to cuff BP inaccuracy. Most notably, significant differences in intra-arterial BP between phenotypes were not discriminated by a wide variety of standard cuff BP methods used in daily clinical practice. This has implications for hypertension management in general medicine, and indicates that improved cuff BP accuracy could be realized by moving away from using standard 'one size fits all' BP measurement methods, and instead developing more individualized approaches that give consideration to phenotypic BP differences.

As shown in our systematic reviews and meta-analyses,[77] the practical consequence of cuff BP inaccuracy is potential misclassification of risk related to BP, due to under- or over-estimation of true (intra-arterial) BP. A significant finding of this current study was the failure of cuff BP methods to recognize the marked and consistently higher aortic SBP (and PP) among phenotypes 3 and 4 – those individuals with little to no SBP amplification between the aorta and brachial arteries. Findings were highly consistent when tested across 6 different types of BP devices (8 individual machines) and four independent research teams altogether (five distinct study methods and participants). The clinical result of this failure to identify high BP using conventional cuff BP methods would be a missed opportunity to, either make lifestyle modifications, or initiate antihypertensive therapy to lower cardiovascular risk.[3]

On the basis of aortic BP having more pathophysiological relevance to hypertensive end-organ damage compared with upper arm BP,[94, 97] we speculate that cardiovascular risk would be higher among people presenting with phenotypes 3 and 4 because of marked BP underestimation and potential under treatment (or recognition) of high BP. On the other hand, reduced SBP or PP amplification could contribute to cardiovascular risk independent from the level of SBP or PP at a single arterial site (e.g. aorta), as has been reported using non-invasive BP methods among people with end stage renal disease.[120] It may also be possible that excessive BP amplification could promote organ damage at susceptible sites, but whether clinical outcomes will differ among the BP phenotypes is an issue for assessment in large scale prospective studies to determine associations with cardiovascular outcomes. Beyond this, a non-invasive means to discriminate BP phenotypes will need to be developed. This could be achieved from analysis of brachial and/or derived central BP waveforms recorded using cuff BP devices with operating features that are already familiar to doctors. Such methods would

need to discriminate BP phenotypes beyond solely focusing on features such as radial AIx, which was not an adequate substitute for the aortic waveform.

The underlying physiology explaining BP differences among the four phenotypes was not addressed in this study, but will be multifactorial and include differences in left ventricular output (e.g. stroke volume, contractility, chronotropy) as well as characteristics of the large conduit arteries (e.g. diameter, compliance) and structure and function of the small resistance vessels.[132] For example, there would be an expectation for increased SBP amplification in a relatively healthy vascular system, with left ventricular ejection of stroke volume coupled to a compliant (elastic) aorta that effectively buffers the instantaneous increase in aortic SBP.[210] As BP is transmitted to the periphery, greater arterial tapering, decreasing wall thickness, but increasing stiffness relative to the aorta, and stronger peripheral wave reflections may all contribute to increased SBP amplification.[208, 209] On the other hand, lower ventricular inotropy[208] and increased stiffening of the aorta disproportionate to the peripheral vessels,[205] would be expected to increase aortic SBP to a greater extent than peripheral SBP and cause lower SBP amplification. This is more likely with advancing age or disease adversely affecting cardiovascular structure and function.

Thus, SBP amplification is a highly complex phenomenon characterized by diverse arterial physiology, such that it is not surprising that standard cuff BP methods are less than perfect in being able to accurately measure BP using a single measurement approach (such as cuff oscillometry) among all people. The inaccuracy of cuff BP associated with SBP amplification may not be caused by SBP amplification per se, but instead is probably related to variability in arterial haemodynamics. It is important to clarify that the approach we have used to define phenotypes does not improve the accuracy of cuff BP, but instead proposes a means of distinguishing categories of people with respect to the relation of central aortic compared with the in the upper limb at the brachial and radial sites. Our findings do not undermine the clinical importance of cuff BP, but moreover suggest that improvements to cuff accuracy should lead to even better performance as a risk management tool.

The major strengths of this study were the use of high quality intra-arterial methods to identify phenotypes, and the independent verification of the main findings using data from multiple investigators. A potential limitation was the use of fluid filled rather than solid state catheters for the intra-arterial BP measurements, which may introduce error if the system is not carefully handled and does not have an appropriate dynamic response.[54] However, our methodology was conducted in accordance with expert recommendations[102] and results are entirely consistent with those of the independent investigators (Figures 3.5- 3.6), in which BP

measurements were performed using fluid-filled, as well as solid state single- and dual-sensor catheters. Nonetheless, we cannot rule out the possibility that the catheter may have impinged the arterial wall in some patients, which may be more likely in smaller arteries. Another possible limitation was that the lack of discrimination between phenotypes by standard cuff BP may not be generalizable beyond our study population, which were patients with an indication for coronary angiography. Having said this, there is no special reason that cuff BP should be particularly inaccurate among these patients, and again, findings were consistent across a wide variety of different devices measuring BP at different time points. Similarly, it is unknown whether the four distinct BP phenotypes would be observed among sample populations beyond the patient group examined in this study. For example, phenotypes might be less distinct among healthy younger people, compared to those with advancing age or disease processes affecting the vasculature, such as diabetes, but this is something that will need to be determined in future research. Other future studies should also investigate mechanisms underlying the four different phenotypes with more detailed anthropometric (e.g. upper-arm, forearm length and circumference) and hemodynamic assessments under dynamic conditions such as exercise, understanding whether the BP phenotype of an individual could be subject to visit-to-visit or diurnal variation.

Perspectives. Despite accuracy concerns known for decades[8] but only recently consolidated,[77] cuff BP measurement methods have remained virtually unchanged for over 100 years. The development of more accurate ways to measure BP is an important goal to help improve diagnosis and evaluation of hypertension.[222] Our study directly addresses this goal with the discovery of distinct BP phenotypes in which intra-arterial BPs are significantly different but standard cuff BP methods cannot discriminate this. While the phenotypes do not directly improve the accuracy of cuff BP, better quality of BP measurements may be achieved by taking individual phenotypic waveform characteristics into consideration, which should be a future research priority. Ultimately, improvements to BP measurement accuracy should lead to better hypertension management and cardiovascular risk stratification.

3.6 Novelty and Significance

What is new?

- This study has discovered distinctive BP phenotypes based on the level of systolic BP amplification between the aorta, brachial and radial arteries.

- Importantly, the BP measured invasively at the aorta was significantly different between phenotypes, but this was not discriminated by standard cuff BP devices used in daily clinical practice.

What is relevant?

- Development of more accurate ways to measure BP is an important goal to help improve diagnosis and evaluation of hypertension.
- More accurate BP measurements may be achieved by taking individual phenotypic waveform characteristics into consideration.

Summary

Although cuff BP is the reference standard for hypertension management, the method is inaccurate and this can lead to BP misclassification. This study discovered distinctive BP phenotypes that are related to cuff BP inaccuracy. This knowledge should ultimately lead to improved BP measurement accuracy and better hypertension management.

3.7 Contribution of Chapter 3 to thesis aims

Cuff measured BP used in daily clinical practice has variable accuracy for measuring intra-arterial BP. However, there has never been a definitive breakthrough in identifying the reasons for this and potential ways to improve the method. Chapter 3 presents the discovery of four BP phenotypes where distinct differences in intra-arterial aortic BP and arterial waveform characteristics were observed across the four phenotypes, but these differences were not discriminated by any of the cuff BP measures. Overall, the findings suggest improvements to standard cuff device accuracy may be realised by accounting for individual phenotypic BP differences related to differences in BP amplification and arterial waveform characteristics.

Brachial cuff BP is widely assumed to represent intra-arterial brachial BP, therefore several specialist devices that purport to estimate aortic BP have been developed. Accuracy of these devices has been closely scrutinised, with the major cause of error believed to be inaccurate cuff BP calibration (scaling) of peripheral BP waveforms. There is also some evidence that the level of SBP amplification could contribute to error in estimation of aortic BP.[25, 26, 93] This could be related to inaccurate BP waveform calibration caused by SBP amplification and the generalised algorithms used to estimate aortic BP that might not detect individual differences in SBP amplification. In Chapter 4 we aimed to determine the best calibration method to achieve accurate estimated aortic BP and the influence of SBP amplification on the estimation.

Chapter 4 - Intra-arterial analysis of the best calibration methods to estimate aortic blood pressure

At the time of thesis submission this chapter in submission. The chapter has been formatted according to the guidelines of *Journal of Hypertension.*

Picone DS, Schultz MG, Peng X, Black JA, Dwyer N, Roberts-Thomson P, Sharman JE. The best calibration methods to estimate aortic blood pressure. *Journal of Hypertension*, second invited revision, June 2018

4.1 Abstract

Objective. Estimation of aortic blood pressure (BP) requires peripheral BP waveform calibration. Mean arterial pressure (MAP)/diastolic BP (DBP) calibration is purported to estimate aortic BP more accurately than systolic BP (SBP)/DBP calibration. However, this is based on inaccurate cuff calibration. Thus, direct comparisons of each calibration method using intra-arterial BP are required to confirm this, and was the aim of this study.

Methods. Ascending aortic, brachial and radial artery intra-arterial BPs were measured among 107 patients (61.9±10.0 years, 70% male) undergoing coronary angiography. Radial waveforms were calibrated with brachial SBP/DBP and brachial MAP/DBP to directly test the accuracy of estimated aortic SBP (derived using a commercial device) from each calibration compared with intra-arterial aortic SBP. Estimated aortic BP accuracy from aortic MAP/DBP, brachial and radial SBP/DBP calibrations of peripheral waveforms was also tested (six calibration methods in total; all using intra-arterial BP).

Results. Estimated aortic SBP from brachial MAP/DBP calibration of radial waveforms had a significantly smaller mean difference than from brachial SBP/DBP calibration (-0.7±7.5 mmHg versus -6.9±7.3 mmHg, $p<0.0001$ for difference). Of the other calibration methods, estimated aortic SBP was most accurate from aortic MAP/DBP calibration of radial waveforms (-1.8±5.0 mmHg, $p=0.00023$). However, for all calibration methods, aortic-to-brachial artery and/or brachial-to-radial artery SBP amplification had a major influence on estimated aortic SBP.

Conclusions. Brachial and aortic MAP/DBP were confirmed as the best calibration methods to estimate aortic SBP. But, irrespective of calibration method, accuracy was significantly influenced by the level of SBP amplification. Thus, improved accuracy of estimated aortic SBP should be possible by closer consideration of SBP amplification or individual waveform characteristics that differ according to the level of SBP amplification.

4.2 Introduction

The purpose of blood pressure (BP) measurement is to accurately determine the pressure load at the aorta.[55, 201] Conventional upper arm cuff devices measure BP from signals detected at the brachial artery.[56, 66] A problem with this approach is that cuff measured BP has variable accuracy for determining intra-arterial BP at either the brachial artery or ascending aorta, whether measured by mercury auscultation or oscillometry.[77] We recently found that the inaccuracy of cuff BP was related to variability in the transmission of central-to-peripheral SBP (SBP amplification).[223] Intra-arterial measurement of aortic BP is unethical and not feasible for regular clinical use, and therefore specialist devices to non-invasively estimate aortic BP have been developed.[82] However, the accuracy of these devices has been called into question, [13] and this may be related to variability in the level of SBP amplification.[25, 26, 93]

A principal issue that can affect the accuracy of estimated aortic BP is the calibration of peripheral BP waveforms. Calibration is the process of scaling waveforms using units of pressure.[102] The main calibration methods are SBP/diastolic BP (DBP) or mean arterial pressure (MAP)/DBP non-invasively measured from standard cuff BP. A recent meta-analysis found that cuff MAP/DBP calibrations were more accurate for estimating central SBP,[29] albeit with substantial variability, most likely due to inaccurate cuff BP.[102] A key remaining question is whether SBP/DBP or MAP/DBP is the best calibration method for accurate estimation of aortic SBP. This issue would be most appropriately addressed using precise calibration (of peripheral intra-arterial BP waveforms) with intra-arterial SBP/DBP and MAP/DBP. We sought to undertake this for the first time in this current study. We also sought to determine the impact of intra-arterial central-to-peripheral SBP amplification on the accuracy of estimated aortic SBP.

4.3 Methods

211 consecutive patients scheduled to undergo diagnostic coronary angiography at the Royal Hobart Hospital in Hobart, Australia, were screened for inclusion. All individuals had an indication for the clinical procedure and were included irrespective of disease status, with the exception of significant arrhythmia or aortic valve disease that may have introduced error into pressure waveform recordings (n=10). Other exclusion criteria were: inter-arm difference of cuff SBP and/or DBP >5 mmHg; inability to measure cuff BP in both arms prior to the angiographic procedure (n=17); intra-arterial access via femoral artery (n=11); medical issues arising during the clinical procedure that prevented the research protocol (n=34) or; technical issues that adversely affected the quality of waveform recordings (n=9). Consent was declined by n=4, leaving 126 eligible participants. All patients provided written informed consent for the

study, which was approved by the University of Tasmania Health and Medical Human Research Ethics Committee.

Intra-arterial data acquisition. Data acquisition was carried out according to ARTERY guidelines,[102] and the methods have been previously published.[206] In brief, pressure waveform recordings were obtained at the aorta, brachial and radial arteries via catheter pullback at the end of the clinical procedure. Clinical information compiled at the time of the angiogram was obtained via review of individual patient medical records. Digitized pressure signals recorded in Volts were converted to pressure units (mmHg) as previously described.[168] From each arterial site, consistent high-quality pressure waveforms were recorded for a minimum of 20 seconds and ensemble averaged using a custom Matlab code. From 126 participants, 19 who had heart rate differences of >5 beats/min between either the aortic-to-brachial, brachial-to-radial or aortic-to-radial arterial measurement sites were excluded, leaving 107 participants for analysis.

Waveform processing and calculation of mean arterial pressure. The ensemble averaged intra-arterial pressure waveforms were down sampled from 1000 Hz to 128 Hz for compatibility with the SphygmoCor CVMS (AtCor Medical, West Ryde, Australia) software in simulation mode. The intra-arterial aortic, brachial and radial waveforms were initially processed via SphygmoCor and calibrated with the respective intra-arterial SBP and DBP (defined as the peak and nadir of the waveform). MAP for each intra-arterial waveform was calculated by SphygmoCor as the average of the calibrated ensemble averaged pressure waveform data points.

Intra-arterial calibration methods to estimate aortic BP. Estimated aortic BP from SphygmoCor is dependent on the input pressure waveform and the calibration of that waveform. Calibration of pressure waveforms with SBP/DBP or MAP/DBP would produce the same estimated aortic SBP in certain circumstances. For example, if a brachial waveform is calibrated with the exact brachial BP values from that waveform, estimated aortic BP will be identical irrespective of the calibration (i.e. SBP/DBP or MAP/DBP). On the other hand, using brachial SBP/DBP to calibrate radial waveforms (which is the standard approach for radial tonometry), could generate a different estimated aortic SBP compared to calibration with brachial MAP/DBP.

Altogether, there were six different waveform and calibration combinations tested in this study (Table 4.1). Only intra-arterial waveforms and intra-arterial calibrations were used in these six different combinations. The first two, brachial SBP/DBP and brachial MAP/DBP calibration of radial waveforms allowed for direct comparison of estimated aortic BP accuracy based on the calibration method used. The other waveform and calibration combinations tested were brachial

waveforms calibrated with aortic MAP/DBP or brachial SBP/DBP and radial waveforms calibrated with aortic MAP/DBP and radial SBP/DBP. For all six waveform and calibration combinations, the accuracy of estimated aortic BP was calculated as the difference between estimated aortic BP minus measured (intra-arterial) aortic BP (Figure 4.1).

SBP amplification. The increase in SBP across the aorta-to-brachial and brachial-to-radial arterial segments was defined as SBP amplification and calculated from the intra-arterial BP recordings. SBP amplification was a variable of interest based on previous studies that suggest it may be associated with the accuracy of estimated aortic BP.[25, 26, 93, 111]

Table 4.1 Calibration methods of intra-arterial brachial and radial blood pressure waveforms used to estimate aortic blood pressure.

Blood pressures used for calibration	Rationale
Radial waveforms	
Brachial SBP/DBP	Simulation of non-invasive brachial cuff SBP/DBP calibration.[188]
Brachial MAP/DBP	Simulation of non-invasive brachial cuff MAP/DBP calibration. [188]
Other waveform and calibration methods	
Brachial waveforms	
Aortic MAP/DBP	Previously used to test generalised transfer functions.[117, 188]
Brachial SBP/DBP	Simulation of non-invasive brachial cuff SBP/DBP calibration.[188] *Calibration with brachial MAP/DBP produces an identical result.*
Radial waveforms	
Aortic MAP/DBP	Previously used to test generalised transfer functions.[105, 188]
Radial SBP/DBP	Accounting for brachial-to-radial SBP amplification in waveform calibration. *Calibration with radial MAP/DBP produces an identical result.*

MAP, mean arterial pressure; DBP, diastolic blood pressure; SBP, systolic BP. All calibration BPs were from intra-arterial recordings.

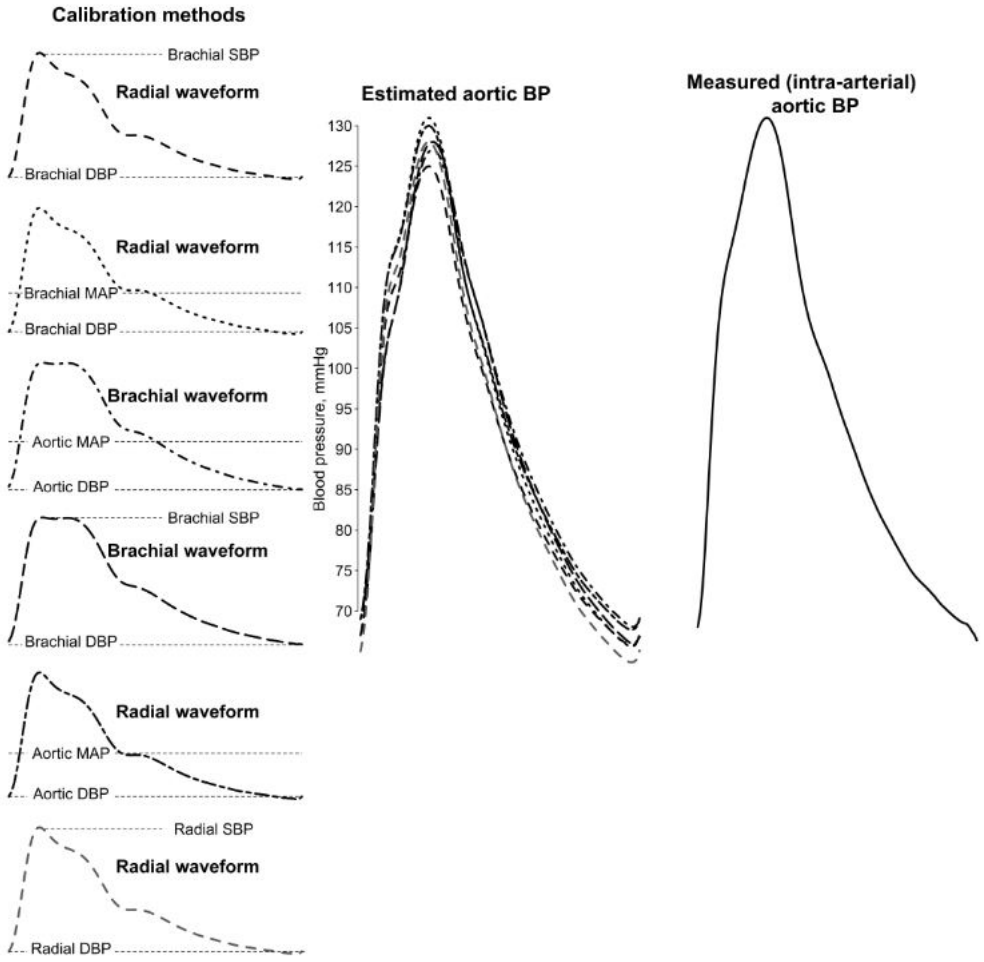


Figure 4.1 Overview of the six intra-arterial waveform and calibration methods. The left panel shows each of the waveform and calibration methods, where the bold font represents the intra-arterial blood pressure (BP) waveform measurement site (brachial or radial), and the non-emboldened font represents the intra-arterial BP calibration method. The middle panel represents an overlay of the estimated aortic BP waveforms synthesised from the six waveform calibration methods. The right panel represents the measured (intra-arterial) aortic BP waveform. The accuracy of each estimated aortic BP was compared against this intra-arterial aortic BP waveform. Only intra-arterial recordings were used for waveform calibration.

Justification for estimation of aortic BP using brachial waveforms and a radial-to-aortic transfer function. In two of the six intra-arterial waveform and calibration combinations (described in Table 4.1), we estimated aortic BP from intra-arterial brachial waveforms with a radial-to-aortic generalized transfer function. For this purpose, a brachial-to-aortic generalized transfer function may be expected to be most appropriate, but this was not available for retrospective waveform processing. Therefore, to determine if processing the intra-arterial brachial waveforms with a radial-to-aortic generalized transfer function may contribute to error in estimated aortic blood pressure compared with a brachial-to-aortic transfer function we undertook additional analysis on non-invasive SphymoCor Xcel brachial waveforms collected on 98 of the participants. Estimated aortic BP was derived from the Xcel device with a brachial-to-aortic transfer function and the non-invasive brachial waveforms were then retrospectively processed with SphygmoCor CVMS to generate estimated aortic BP using a radial-to-aortic transfer function. This method allowed the comparison of the accuracy of estimated aortic BP from brachial waveforms processed with either transfer function. This was the only analysis in which non-invasive BP measurements were used.

Statistical analysis. Continuous data are presented as mean±standard deviation, categorical variables as the number of observations and percentage. Paired T-tests were used to assess the mean difference between estimated aortic and intra-arterial aortic BP as well as for differences in estimated aortic BP from brachial SBP/DBP versus brachial MAP/DBP calibration of radial waveforms. Root mean square error (RMSE) and mean absolute difference were also calculated to determine directionless error between estimated and intra-arterial aortic BP. Pearson correlations were used to assess univariable relationships between accuracy of estimated aortic BP and SBP amplification. Linear regression models were developed to test univariable associations after adjustment for known or potential confounders. P values <0.05 were regarded as statistically significant. All data were synthesized and analyzed using R, version 3.4.0, R Core Team (2014).

4.4 Results

Clinical characteristics. The clinical characteristics of the study population were typical of patients undergoing coronary angiography. Patients were predominantly middle-older aged (61.9±10.0 years) and male (70%), with body mass index in the overweight range (29.3±5.1 kg/m^2). Most patients had a history of hypertension (84%), type 2 diabetes was present in 24% and 60% had at least one coronary artery stenosis. Intra-arterial BP and heart rate data are presented in Table 4.2.

Table 4.2 Intra-arterial blood pressure, systolic blood pressure amplification and heart rate among study participants

Variable	Mean±SD	95% CI
Aortic systolic BP, mmHg	131±21	127 to 135
Brachial systolic BP, mmHg	139±20	136 to 143
Radial systolic BP, mmHg	145±22	141 to 149
Aortic mean arterial pressure, mmHg	93±11	91 to 95
Brachial mean arterial pressure, mmHg	90±12	88 to 92
Radial mean arterial pressure, mmHg	90±11	88 to 92
Aortic diastolic BP, mmHg	68±9	67 to 70
Brachial diastolic BP, mmHg	67±8	65 to 68
Radial diastolic BP, mmHg	65±8	63 to 66
Aortic-brachial systolic BP amplification, mmHg	8.0±9.3	6.2 to 9.8
Brachial-radial systolic BP amplification, mmHg	5.9±10.3	3.9 to 7.9
Heart rate, beats/min	64±12	62 to 67

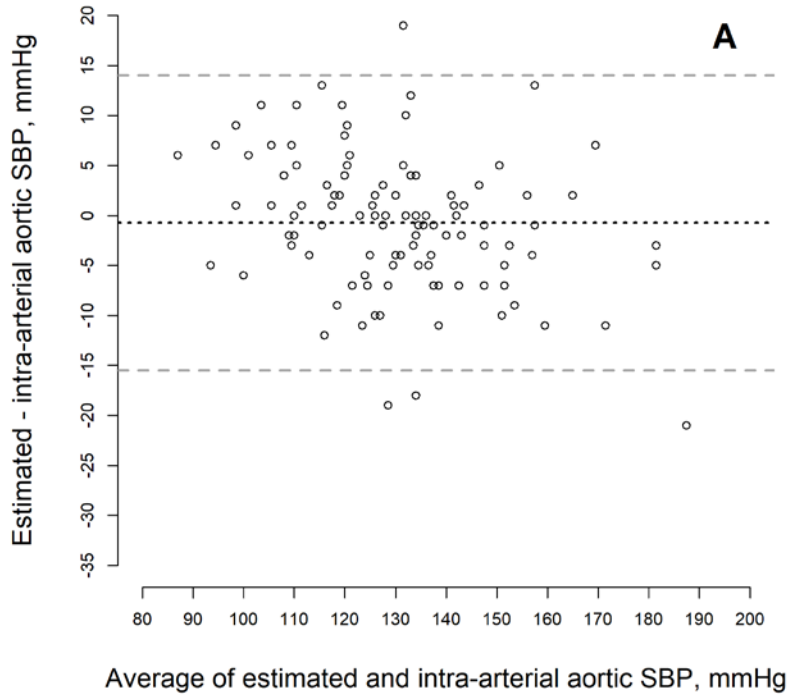
BP, blood pressure; SD, standard deviation; CI, confidence interval. n=107.

Estimated aortic BP. The best method to estimate aortic SBP was brachial MAP/DBP on radial waveforms (Figure 4.1 and Table 4.3). Estimated aortic SBP from brachial MAP/DBP calibration had a significantly smaller mean difference of the error than brachial SBP/DBP on radial waveforms (-0.7±7.5 versus -6.9±7.3 mmHg, $p<0.0001$ for difference). The RMSE and mean absolute error of the estimated aortic SBP from brachial MAP/DBP calibration was also lower than the brachial SBP/DBP calibration, however, the standard deviation was similar (Table 4.3). Further, brachial MAP/DBP calibration had a significantly smaller mean difference of the error than all other calibration methods ($p<0.001$) except aortic MAP/DBP calibration of radial waveforms ($p=0.073$ for difference). Indeed, from the other waveform and calibration combinations, aortic MAP/DBP calibration of radial waveforms produced the most accurate estimated aortic SBP (-1.8±5.0 mmHg), and had the lowest RMSE (5.27) and mean absolute error (4.13; Table 4.3). Using radial SBP/DBP instead of brachial SBP/DBP to calibrate radial waveforms significantly increased the accuracy of estimated aortic BP (based on mean difference; +3.8±7.9, $p<0.0001$). The standard deviation, RMSE and mean absolute error were similar between brachial and radial SBP/DBP calibration of radial waveforms (Table 4.3). Bland-Altman plots for all comparisons are presented in Figures 4.2- 4.3.

Table 4.3 Estimated compared with intra-arterial aortic systolic blood pressure among study participants.

Intra-arterial aortic SBP, mmHg	131±21	-	-	-	-
Waveform and calibration combination	**Estimated aortic SBP, mmHg**	**Estimated aortic - intra-arterial aortic SBP, mmHg**	**P-value**	**RMSE**	**Mean absolute error**
Radial waveforms					
Brachial SBP/DBP, mmHg	125±19	-6.9±7.3	<0.0001	10.0	7.72
Brachial MAP/DBP, mmHg	131±19	-0.7±7.5	0.32	7.53	5.64
Other waveform and calibration methods					
Brachial waveforms					
Aortic MAP/DBP, mmHg	127±18	-4.4±4.8	<0.0001	6.47	5.20
Brachial SBP/DBP, mmHg	128±19	-3.4±7.1	<0.0001	7.87	6.16
Radial waveforms					
Aortic MAP/DBP, mmHg	130±19	-1.8±5.0	0.00023	5.27	4.13
Radial SBP/DBP, mmHg	128±20	-3.1±8.4	0.00025	8.90	7.09

Data are mean±standard deviation or mean. BP, blood pressure; SBP, systolic BP; MAP, mean arterial pressure; DBP, diastolic BP; RMSE, root mean square error. P-value is for the difference between estimated – intra-arterial aortic SBP, quantified via paired T-tests. n=107.



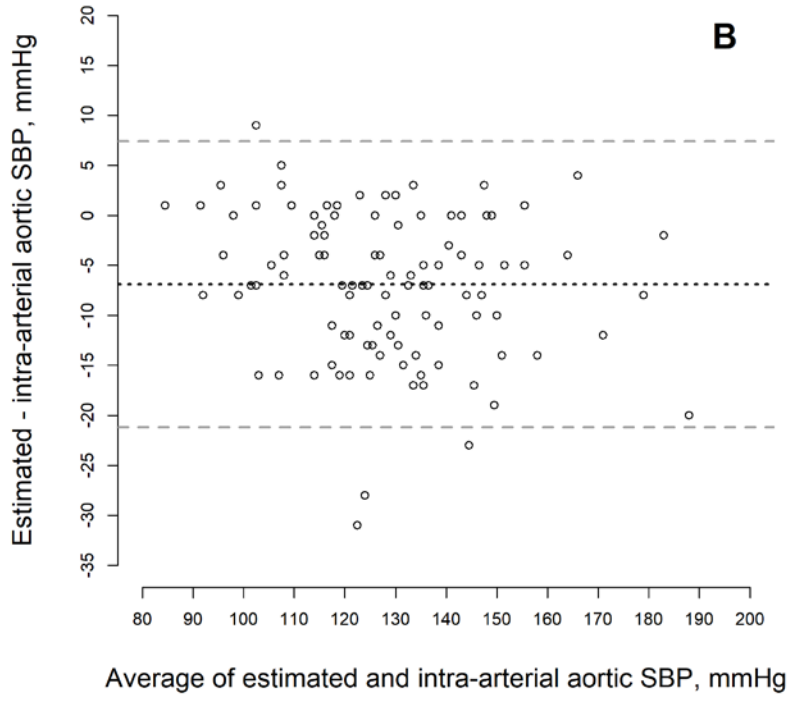


Figure 4.2 Bland-Altman plots of estimated aortic systolic blood pressure compared to intra-arterial aortic systolic blood pressure.

Estimated aortic SBP was generated from radial waveforms using intra-arterial brachial SBP/diastolic BP (DBP) calibration in panel A and intra-arterial brachial mean arterial pressure/DBP calibration in panel B.

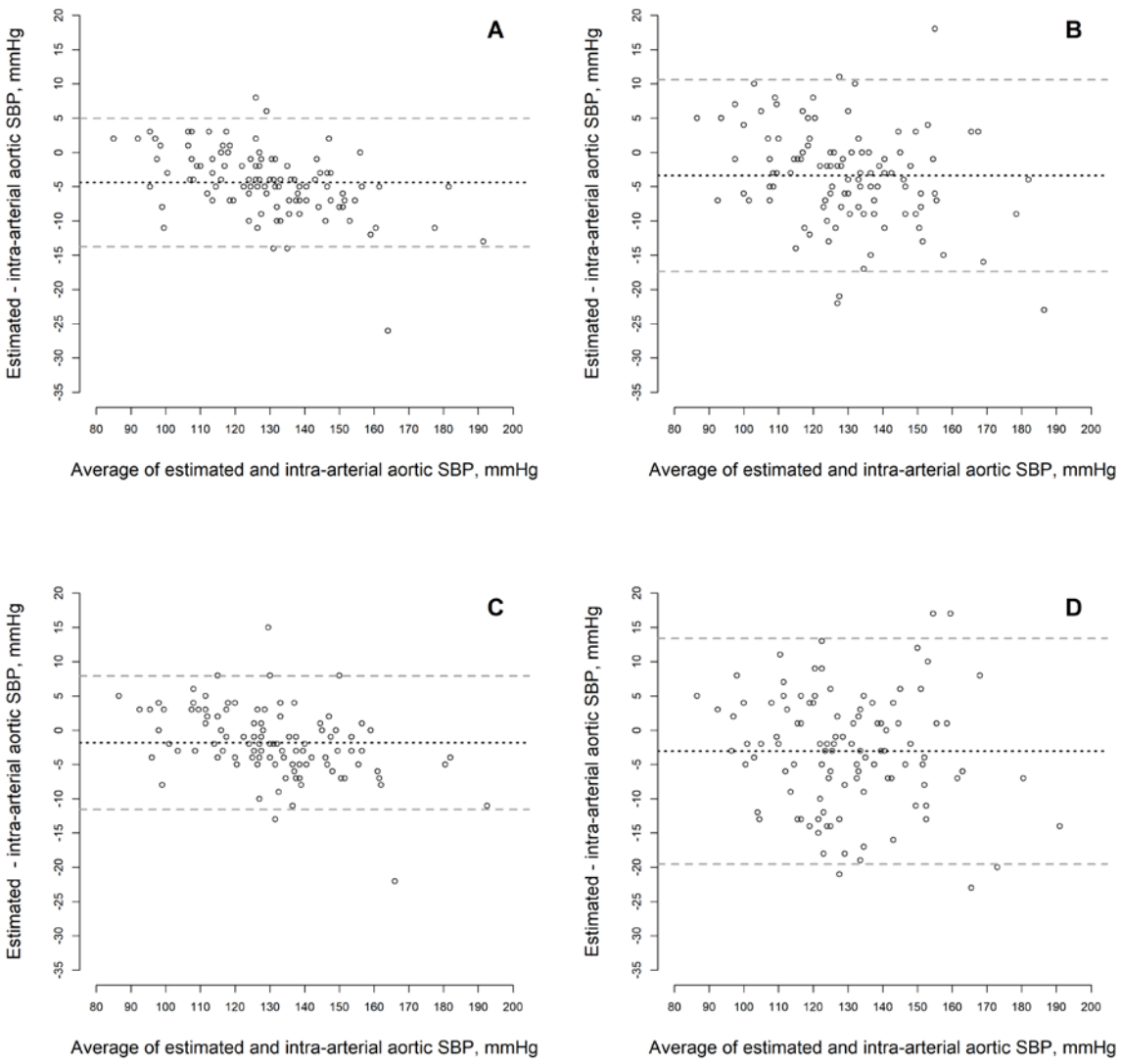


Figure 4.3 Bland-Altman plots of other waveform and calibration combinations for estimated compared with intra-arterial aortic systolic blood pressure.

Estimated aortic SBP was generated in the following ways: brachial waveforms calibrated with aortic mean arterial pressure (MAP)/ diastolic BP (DBP), panel A; brachial waveforms calibrated with brachial SBP/DBP, panel B; radial waveforms calibrated with aortic MAP/DBP, panel C and radial waveforms calibrated with radial SBP/DBP, panel D.

SBP amplification. Aortic-to-brachial SBP amplification was significantly and positively associated with the accuracy of estimated aortic SBP (the difference between estimated and intra-arterial aortic SBP) from all six waveform and calibration methods (Figures 4.4 and 4.5). The strength of the correlations between aortic-to-brachial SBP amplification and accuracy of estimated aortic SBP was highly variable, ranging from r=0.24 (aortic MAP/DBP calibration of radial waveforms) to r=0.68 (brachial MAP/DBP calibration of radial waveforms and brachial SBP/DBP calibration of brachial waveforms; Figures 4.4 and 4.5). Brachial-to-radial SBP amplification was significantly correlated (negatively) with the accuracy of estimated aortic SBP from radial waveforms calibrated with brachial SBP/DBP (r=-0.40, p<0.0001), but not from brachial MAP/DBP calibration (r=0.058, p=0.56; Figure 4.4). From the other calibrations, brachial-to-radial SBP amplification was positively correlated with the accuracy of estimated aortic SBP from three of the four waveform and calibration combinations (Figure 4.5). Aortic-to-brachial SBP amplification remained significantly associated with the accuracy of estimated aortic SBP (estimated – intra-arterial aortic SBP) from all calibration methods after adjustment for age, sex, height, heart rate and estimated glomerular filtration rate (p<0.05 all, Table 4.4). Brachial-to-radial SBP amplification remained significantly associated with the accuracy of estimated aortic SBP (in the four out of six waveform and calibration combinations that had significant univariable associations), following adjustment for the same potential confounders as the models for aortic-to-brachial SBP amplification (p<0.05 all, Table 4.5).

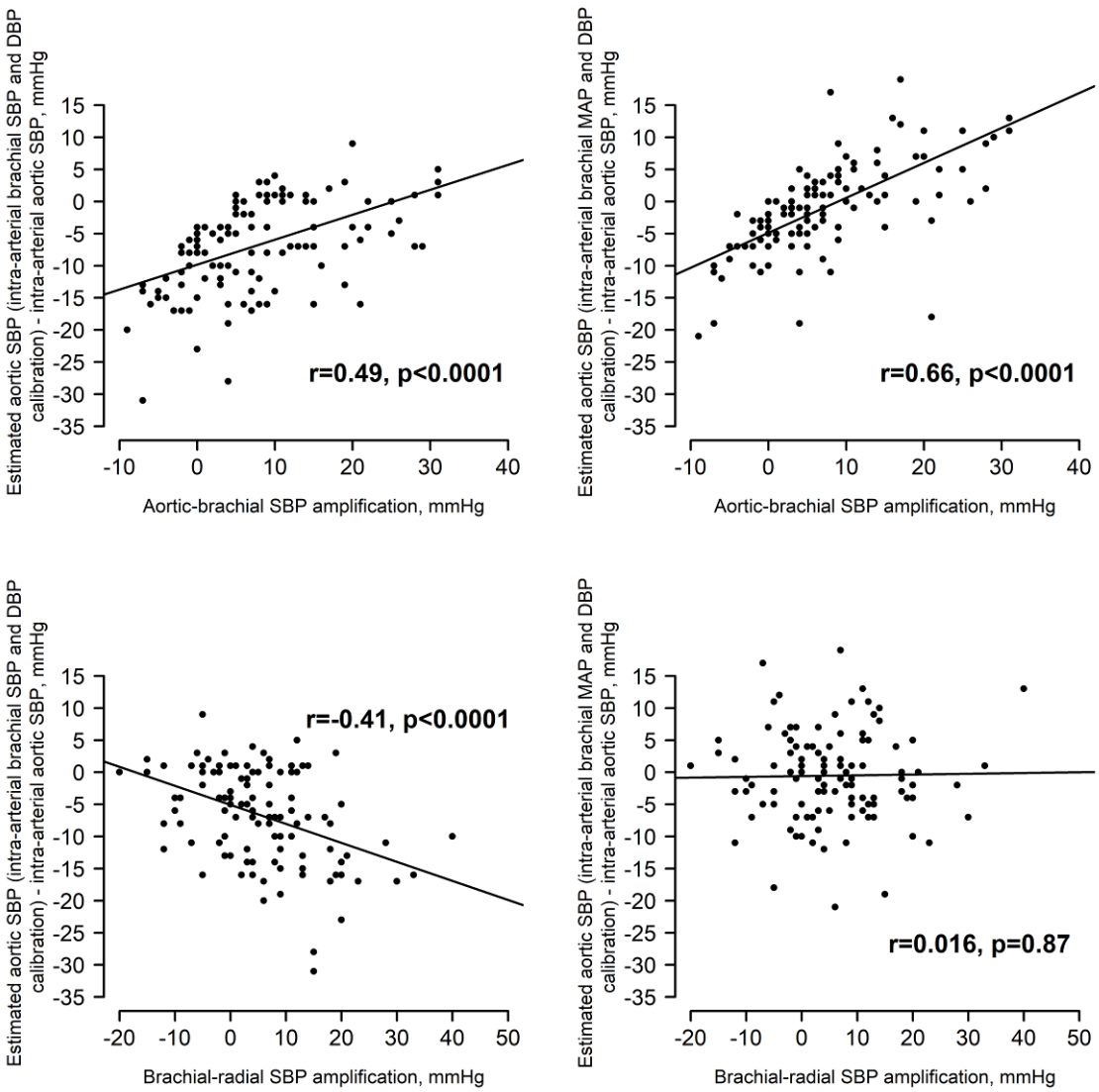


Figure 4.4 SBP amplification and estimated aortic SBP from intra-arterial brachial SBP/DBP or brachial MAP/DBP calibration of radial waveforms.

Scatter plots highlighting the relationship between systolic blood pressure (SBP) amplification (x-axis) and estimated aortic BP accuracy (estimated aortic SBP minus intra-arterial aortic SBP; y-axis). Estimated aortic SBP was generated from radial waveforms using the following calibrations: brachial SBP/diastolic BP (DBP), panels A and B; brachial mean arterial pressure (MAP)/DBP, panels C and D. Pearson correlation coefficients and corresponding p-values are presented with each panel. All calibration values are from intra-arterial BP recordings.

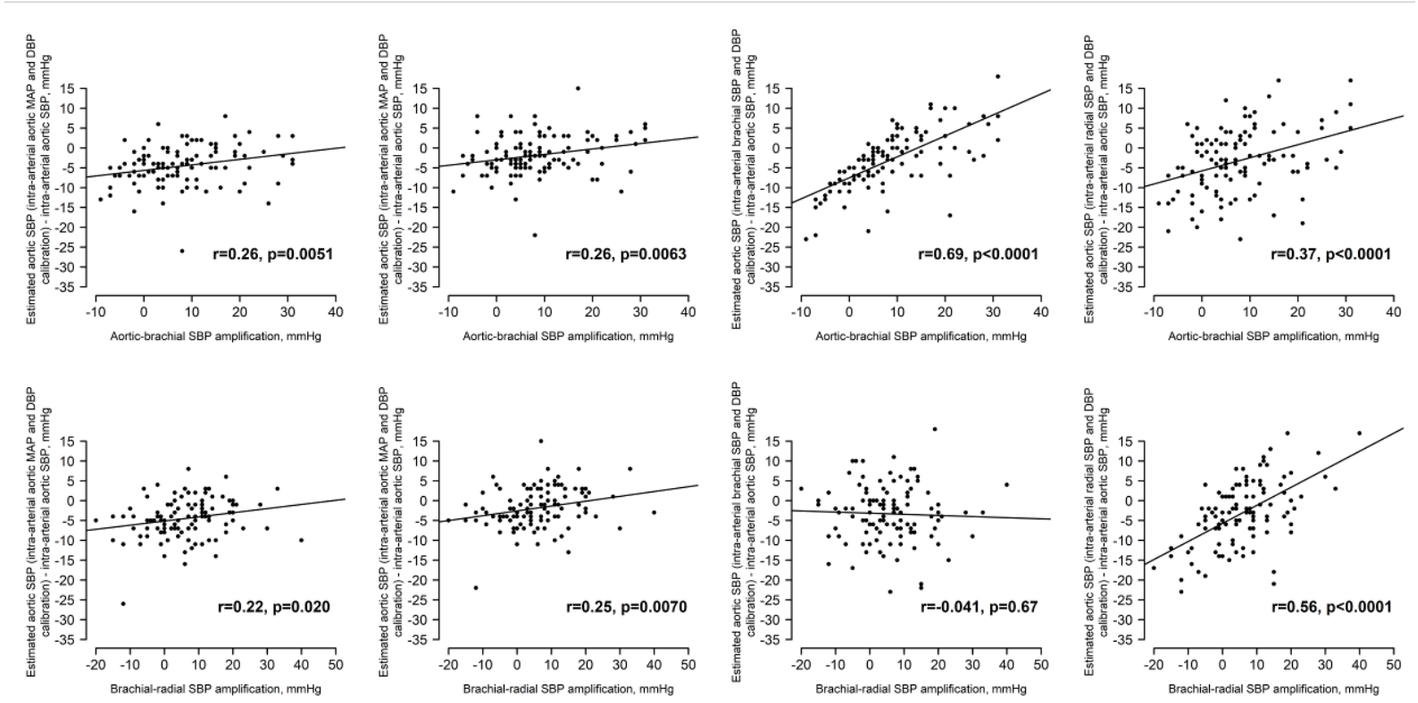


Figure 4.5. SBP amplification and estimated aortic SBP from different calibration methods.

Scatter plots highlighting the relationship between systolic blood pressure (SBP) amplification (x-axis) and estimated aortic BP accuracy (estimated aortic SBP minus intra-arterial aortic SBP; y-axis). Estimated aortic SBP was generated in the following ways: brachial waveforms calibrated with aortic mean arterial pressure (MAP)/ diastolic BP (DBP), panels A and B; brachial waveforms calibrated with brachial SBP/DBP, panels C and D; radial waveforms calibrated with aortic MAP/DBP, panels E and F and; radial waveforms calibrated with radial SBP/DBP, panels G and H. Pearson correlation coefficients and corresponding p-values are presented with each panel. All calibration values are from intra-arterial BP recordings.

Table 4.4. Association between aortic-to-brachial systolic blood pressure amplification and accuracy of estimated aortic systolic blood pressure (difference between estimated aortic and intra-arterial aortic systolic blood pressure) among study participants.

Waveform and calibration combination	Model adjusted R^2	Aor-bra SBP-amp	Age	Sex (1=male)	Height	Heart rate	eGFR
Radial waveforms							
Brachial SBP/DBP	0.29§	0.38 (0.23 to 0.53) §	-0.053 (-0.20 to 0.088)	1.18 (-2.45 to 4.73)	-0.033 (-0.21 to 0.14)	-0.15 (-0.25 to -0.039)†	0.042 (-0.029 to 0.11)
Brachial MAP/DBP	0.50§	0.61 (0.48 to 0.74) §	0.030 (-0.095 to 0.15)	0.84 (-2.31 to 3.93)	-0.052 (-0.20 to 0.098)	-0.16 (-0.25 to -0.067) †	-0.017 (-0.045 to 0.077)
Other waveform and calibration methods							
Brachial waveforms							
Aortic MAP/DBP	0.14†	0.14 (0.027 to 0.24)*	-0.036 (-0.14 to 0.066)	1.00 (-1.62 to 3.56)	-0.004 (-0.12 to 0.13)	-0.14 (-0.21 to -0.059) ‡	-0.00014 (-0.051 to 0.050)
Brachial SBP/DBP	0.50§	0.57 (0.45 to 0.69) §	0.035 (-0.084 to 0.15)	0.94 (-2.06 to 3.87)	-0.041 (-0.19 to 0.10)	-0.16 (-0.25 to -0.069) ‡	0.024 (-0.035 to 0.082)
Radial waveforms							
Aortic MAP/DBP	0.16‡	0.16 (0.050 to 0.27) †	-0.030 (-0.14 to 0.074)	0.86 (-1.83 to 3.50)	0.0022 (-0.13 to 0.13)	-0.16 (-0.24 to -0.077) ‡	-0.0073 (-0.060 to 0.045)
Radial SBP/DBP	0.20‡	0.31 (0.13 to 0.49) †	-0.034 (-0.14 to 0.21)	-0.11 (-4.55 to 4.23)	0.16 (-0.052 to 0.37)	-0.18 (-0.31 to -0.048)*	0.041 (-0.046 to 0.13)

Data are unstandardized beta (95% confidence interval). *p<0.05; †p<0.01, ‡p<0.001, §p<0.0001. BP, blood pressure; SBP, systolic BP; MAP; mean arterial pressure; DBP, diastolic BP; Aor-bra SBP-amp, aortic-to-brachial SBP amplification; Bra-Rad SBP-amp, brachial-to-radial SBP amplification; eGFR, estimated glomerular filtration rate. n=107.

Table 4.5. Association between brachial-to-radial systolic blood pressure amplification and accuracy of estimated aortic systolic blood pressure (difference between estimated aortic and intra-arterial aortic systolic blood pressure) among study participants.

Waveform and calibration combination	Model adjusted R^2	Bra-Rad SBP-amp	Age	Sex (1=male)	Height	Heart rate	eGFR
Radial waveforms							
Brachial SBP/DBP	0.29§	-0.30 (-0.42 to -0.18) §	-0.086 (-0.23 to 0.053)	0.61 (-3.03 to 4.16)	0.16 (-0.0069 to 0.33)	-0.076 (-0.18 to 0.026)	0.066 (-0.0042 to 0.14)
Brachial MAP/DBP	0.065	0.029 (-0.11 to 0.16)	-0.076 (-0.24 to 0.089)	0.38 (-3.92 to 4.59)	0.14 (-0.059 to 0.34)	-0.037 (-0.16 to 0.084)	0.062 (-0.021 to 0.14)
Other waveform/calibration methods							
Brachial waveforms							
Aortic MAP/DBP	0.13†	0.094 (0.009 to 0.18)*	-0.069 (-0.17 to 0.032)	0.97 (-1.66 to 3.55)	0.027 (-0.097 to 0.15)	-0.11 (-0.18 to -0.032) †	0.011 (-0.040 to 0.061)
Brachial SBP/DBP	0.080*	-0.033 (-0.16 to 0.096)	-0.058 (-0.22 to 0.098)	0.45 (-3.60 to 4.42)	0.15 (-0.036 to 0.34)	-0.044 (-0.16 to 0.070)	0.066 (-0.013 to 0.14)
Radial waveforms							
Aortic MAP/DBP	0.16‡	0.13 (0.040 to 0.21) †	-0.071 (-0.18 to 0.032)	0.85 (-1.85 to 3.48)	0.026 (-0.10 to 0.15)	-0.12 (-0.20 to -0.044) †	0.0063 (-0.046 to 0.058)

Radial SBP/DBP	0.42§	0.45 (0.33 to 0.57) §	-0.067 (-0.33 to 0.57)	-0.043 (-3.74 to 3.75)	0.16 (-0.019 to 0.33)	-0.10 (-0.21 to 0.0018)	0.070 (-0.0033 to 0.14)

Data are unstandardized beta (95% confidence interval). *p<0.05, †p<0.01, ‡p<0.001, §p<0.0001. BP, blood pressure; SBP, systolic BP; MAP; mean arterial pressure; DBP, diastolic BP; Aor-bra SBP-amp, aortic-to-brachial SBP amplification; Bra-Rad SBP-amp, brachial-to-radial SBP amplification; eGFR, estimated glomerular filtration rate. n=107.

4.5 Discussion

The best calibration method of peripheral waveforms to accurately estimate aortic BP has been extensively debated, but is yet to be fully understood. There were several novel findings from this study. First, we confirmed the best calibration method to estimate aortic SBP was intra-arterial MAP/DBP on radial waveforms, not SBP/DBP. Second, we found that SBP amplification from the aorta-to-brachial or the brachial-to-radial arteries had a major influence on the accuracy of estimated aortic SBP. Moreover, even when the most accurate calibration was used, there was a significant positive association between the level of aortic-to-brachial SBP amplification and higher estimated aortic SBP. The findings suggest that MAP/DBP is the best calibration method for peripheral (radial) BP waveforms (based on the smallest mean difference) to achieve accurate estimated aortic BP, but this may be improved by better consideration of SBP amplification or perhaps individual waveform characteristics that are related to amplification.

Several previous studies have tested the accuracy of estimated aortic SBP (more specifically, the generalized transfer function) using intra-arterial aortic MAP/DBP calibration of BP waveforms.[106, 118, 178, 188] The present study extends on these by using calibrations from intra-arterial BP at central (aorta) and peripheral (brachial and radial) arterial sites. Calibration of brachial or radial waveforms with the corresponding BP values at each arterial site was expected to produce the most accurate estimate of aortic SBP. However, the reverse was observed. One explanation is that the generalized transfer function used by SphygmoCor assumes that MAP is equivalent between central and peripheral arteries.[106] Thus, if brachial MAP is closer to aortic MAP than radial MAP then brachial MAP/DBP calibration may produce a better estimate of aortic SBP.

The small mean difference and low variability (RMSE and mean absolute difference) of estimated aortic SBP from intra-arterial aortic and brachial MAP/DBP calibration of radial waveforms in this study has not been achieved in studies using non-invasive (cuff) calibration of BP waveforms. The poor accuracy of estimated aortic SBP has generally been attributed to errors in cuff measured BP which would result in inaccurate waveform calibration. However, even though intra-arterial aortic MAP/DBP calibration was one of the best methods and had the lowest variability of measurement error, there was still >10 mmHg error in five participants (Figure 4.3). This shows the method could be modified further to reduce these errors and help individualise estimation of aortic BP to deliver better management of BP.

Some investigators have shown estimated aortic SBP is more accurate, [29] and clinically relevant [36, 98, 101] when MAP/DBP, compared to SBP/DBP is used for calibration of BP

waveforms. SBP/DBP is the most common and recommended calibration method for radial BP waveforms.[124] However, even when we used intra-arterial brachial SBP/DBP for radial waveform calibration, intra-arterial aortic SBP was significantly underestimated (Table 4.3). Intra-arterial brachial MAP/DBP calibration reduced the average error significantly. But, translating MAP/DBP calibration to a non-invasive setting could be difficult because most oscillometric devices do not typically report MAP. Furthermore, calculating MAP using equations based on SBP and DBP is not recommended due to the potential for large individual patient level errors.[124, 182] True MAP is dependent on the waveform shape since, by definition, MAP is the average of pressure points in the waveform. When we calibrated the radial waveforms with intra-arterial brachial MAP/DBP, the estimated aortic SBP was significantly more accurate (smaller mean difference, although similar variability), than from the intra-arterial brachial SBP/DBP calibration (-0.7±7.5 mmHg versus -6.9±7.3 mmHg. $p<0.0001$). A possible reason for this difference in estimated aortic BP is that brachial SBP/DBP calibration does not account for brachial-to-radial SBP amplification,[26, 93] which was on average 5.9±10.3 mmHg. On the other hand, MAP is relatively consistent through the large arteries, [106] thus calibration with MAP/DBP should provide a better calibration because it partially removes the influence of brachial-to-radial SBP amplification on estimated aortic SBP. Indeed, this hypothesis is supported by the significant association between underestimation of aortic SBP from brachial SBP/DBP calibration and brachial-to-radial SBP amplification that was not observed from brachial MAP/DBP calibration (Figure 4.4).

Our novel findings suggest that SBP amplification may influence the accuracy of estimated aortic SBP using current devices that purport to measure aortic BP.[102] In all the calibration methods tested, greater overestimation of aortic SBP was independently related to higher aortic-to-brachial SBP amplification (Table 4.4). In four of the six calibration methods, brachial-to-radial SBP amplification was also related to accuracy (Table 4.5). The correlation between the accuracy of estimated aortic SBP (estimated – intra-arterial aortic SBP) and SBP amplification could be related to an error by the device algorithm that models the relationship between peripheral and aortic waveforms (i.e. the generalized transfer function).[28, 224] Across different levels of SBP amplification there are distinct differences in pressure waveform characteristics.[223] Thus, accounting for these pressure waveform characteristics could help improve the accuracy of estimated aortic BP via modification of device algorithms or to create BP dependent correction factors. Novel methods to achieve more accurate estimated aortic BP may also emerge with advances in technology (e.g. bioinformatics or artificial intelligence) [225] that are separate from conventional waveform methods employed to date.

The main strength of this study is the large dataset of intra-arterial BP measures collected under recommended research conditions.[102] Nonetheless, fluid-filled, as opposed to solid-state, catheters were used and error may be introduced if these are not handled carefully. However, the research protocol was in accordance with expert consensus guidelines,[102] thus this potential limitation is expected to be minimal. Study participants were of a relatively wide age and BP range, but even so, study findings may not be widely generalizable outside patients undergoing cardiac catheterization. Last, in two of the waveform and calibration methods we estimated aortic BP from brachial waveforms using a radial-to-aortic transfer function. This means that some of the error in estimated aortic BP from brachial waveforms may be due to the generalized transfer function and not the calibration method. However, the sub-analysis of SphymoCor CVMS and Xcel data suggests that error due to the transfer function will be negligible, and this is because the brachial-to-aorta generalized transfer function is based on the radial-to-aorta generalized transfer function. Furthermore, the results from this study may be specific to the SphygmoCor generalized transfer function, even though many methods to estimate aortic BP are substantially equivalent to this technique.[175, 226, 227]

Conclusions. This study showed that intra-arterial brachial and aortic MAP/DBP calibration of radial waveforms were the best methods to accurately estimate aortic SBP. However, accuracy was greatly influenced by the level of SBP amplification. Into the future, closer analysis and greater understanding of SBP amplification or individual waveform characteristics that differ according to the level of SBP amplification may help to achieve more accurate BP measurement, perhaps via modification of device algorithms, BP-dependent correction factors or other novel approaches.

4.6 Contributions of Chapter 4 to thesis aims

There is ongoing uncertainty related to the accuracy of devices that estimate aortic BP, centred around the most appropriate way to calibrate peripheral BP waveforms.[29, 89-91, 102, 125, 126] On the issue of waveform calibration, some recent evidence has shown cuff MAP/DBP may lead to more accurate estimates of aortic BP than cuff SBP/DBP calibration.[29] As shown in Chapter 2 cuff BP is inaccurate compared with intra-arterial BP. But, if cuff BP was improved such that it was accurate, it is unclear what the best calibration method to obtain an accurate estimated aortic BP would be. This question was theoretically addressed in Chapter 4 by using precision intra-arterial BP measurements to accurately calibrate the waveform in the study presented in Chapter 4. The influence of SBP amplification on the accuracy of estimated aortic BP was also examined. The study showed that brachial MAP/DBP calibrated radial BP waveforms produced more accurate estimated aortic BP than brachial SBP/DBP calibrations. But, SBP amplification

had a major influence on accuracy for even the most accurate estimates of aortic BP. The associations observed between SBP amplification and accuracy of estimated aortic BP support the modification of methods used to estimate aortic BP, with potential avenues to improve BP measurement including BP-dependent correction factors, refinement of device algorithms or novel approaches that seek to account for individual waveform characteristics that are related to SBP amplification.

Chapter 5 - Conclusions and future directions

This thesis provides novel insights on the accuracy of BP measurement. The study program represents a major advance in understanding the strengths and limitations of BP measurements and possible ways to improve these. Improving methods of BP measurement was a key research goal identified in the 2016 Lancet commission on hypertension.[190] Better BP measurement should improve detection and treatment of high BP. Notionally, this would result in lower rates of cardiovascular disease, improving patient outcomes as well as reducing the immense costs that are associated with high BP.[42] In Chapter 2, the first ever comprehensive analysis on the accuracy of cuff measured BP compared to intra-arterial BP was completed, and this showed there was considerable variability in the accuracy of cuff methods which adversely affected classification of BP. However, the reasons for inaccuracy were unclear. In Chapter 3 a possible reason for cuff inaccuracy was identified with the discovery of four BP phenotypes based on variable central-to-peripheral BP transmission (SBP amplification). These phenotypes were significantly different based on intra-arterial aortic BP, but were not discriminated by cuff BP. Distinct from cuff measured BP, in Chapter 4, the accuracy of a specialist device used to estimate aortic BP was tested. The most accurate estimated aortic SBP was found when radial BP waveforms were calibrated (scaled) using brachial MAP/DBP instead of the more commonly used brachial SBP/DBP calibration. But importantly, SBP amplification had a major influence on accuracy, even for the most accurate estimates. Altogether, the studies in this thesis comprehensively expand understanding of the accuracy of BP measurements.

The key novel finding from Chapter 2 was that inaccuracy of cuff BP adversely influenced BP classification, particularly in prehypertension (120/80 to 139/89 mm Hg) and stage one hypertension (140/90 to 159/99 mm Hg). An important next step is to improve current BP device validation and testing criteria, and there are several key issues to address. Multiple validation criteria exist, that have been defined by different organisations such as the British Hypertension Society, European Society of Hypertension (ESH) and Association for the Advancement of Medical Instrumentation (AAMI).[59] Each criteria have important differences in terms of accuracy criteria, number of patients and characteristics and required BP ranges, recently summarised in detail by Beime et al.[59] The differences create confusion on the best way to validate new BP monitors, and importantly some protocols can theoretically validate a device that is inaccurate in over half of the study population.[138] However, there is progress in this area, with the ESH and AAMI working together on a consensus for validation criteria.[228]

Another important issue that needs to be addressed is the testing and approval of BP devices that are deemed “substantially equivalent” to older, similar devices.[229] The Food and Drug Authority (FDA) in America will approve BP devices for sale if they are deemed as safe and effective as an approved device. The problem with this process is that the accuracy of the new,

'substantially equivalent' device is unclear and in some instances no testing of the new device is performed.[229] This issue could contribute to the poor accuracy of many of the oscillometric devices studied in Chapter 2. Tightening of the FDA processes could help to improve the accuracy of non-invasive BP devices that are available for clinical use. Action on this issue should then lead to improved management of BP.

A study on the health economics of cuff BP inaccuracy would also be beneficial. The economic impact of inaccurate BP classification by the cuff compared with intra-arterial BP could be substantial. One way to perform this analysis could be to use Markov modelling and a detailed cost utility analysis. It would be expected that more accurate BP measurements would more accurately predict quality adjusted life years and therefore be more cost effective than inaccurate BP measurements. This work would add to knowledge around the potential impact of cuff BP inaccuracy, which is critically important given the billions of dollars high BP costs every year across the world.[42]

Another interesting area of future study would be to address how cuff BP inaccuracy could influence absolute cardiovascular risk prediction via calculations such as the Framingham risk score.[230] The algorithm has several input variables, but the impact of cuff BP error on the overall risk score is currently unknown. This study would be of interest with current recommendations of some organisations to treat absolute cardiovascular risk instead of single risk factors.[231-233] It could be hypothesised that a small error in BP measurement would not substantially change the risk score, but a larger error could have a greater effect, and potentially shift the risk category of the patient (e.g. from low risk to medium or high risk) and therefore impact treatment decisions. The size of the effect would likely also depend on the values of the other input variables.

Inaccuracy of cuff measured BP could also provide an explanation for two epidemiological concepts, masked hypertension (normal clinic BP, raised out-of-office BP)[234, 235] and residual cardiovascular risk (patients with treated hypertension that have higher than usual risk).[207] Both concepts might be explained by cuff inaccuracy (underestimation) of BP. In masked hypertension, high BP may be identified later using a different device and a more robust measurement method that takes a series of measures over time (e.g. 24-hour ambulatory BP or home BP). Patients with 'residual risk' have apparently controlled BP, but underestimation by cuff BP could mean they are being undertreated. Therefore, these patients would have uncontrolled BP, and this would lead to the higher risk of cardiovascular disease observed, not residual risk.

The results in Chapter 3 revealed the first in-human discovery of four novel BP phenotypes that were related to cuff accuracy. The findings may have important clinical implications, because patients in phenotypes 3 and 4 had significantly raised aortic SBP that was completely missed by cuff SBP. However, a large scale prospective study (e.g. n>1000) would be required to precisely understand the relation of the phenotypes to clinical outcomes. This kind of study is feasible because of the large number of cardiac catheterisations that are performed around the world every year. The possible primary outcomes could include sub-clinical organ damage markers (e.g. carotid intima-media thickness, left ventricular mass, albumin-creatinine ratio) and/or hard cardiovascular endpoints obtained via data linkage such as cardiovascular mortality and hospitalisations or procedures due to adverse cardiovascular and other clinical events. If the BP phenotypes showed important clinical relevance above and beyond standard cuff BP, this would provide a strong rationale for the development of new, improved methods of non-invasive BP measurement. Such a finding could lead to a paradigm shift in the way BP is measured in the future, whether by a cuff-based device or an entirely novel method.

A second interesting area of future research could aim to characterise the physiology underlying each BP phenotype. This could be achieved by collecting more detailed haemodynamic measurements simultaneous with intra-arterial BP. For example, ultrasound measurements across the upper-limb arteries could provide important insights into the mechanisms underlying the different BP phenotypes. Arterial structure and function measurements could be obtained from ultrasound, providing information on arterial diameters, tapering, blood flow and compliance. Patients in phenotypes 3 and 4 (with significantly higher aortic BP) would be expected to have greater arterial stiffness and abnormal blood flow patterns. These abnormalities could manifest in evidence of sub-clinical organ damage whereby carotid intima media thickness and left ventricular mass would be significantly higher in patients with phenotypes 3 and 4. Fitting the patients with the gold standard of non-invasive cuff BP, a 24-hour ambulatory BP monitor would also provide additional useful information. Analysis of 24-hour BP data would be important to determine if the phenotypes could be discriminated on the basis of the repeated measures taken during monitoring period.

Improved characterisation of the aortic, brachial and radial intra-arterial BP waveforms via waveform separation techniques would also strengthen understanding of the BP phenotypes. One separation technique is the reservoir-excess pressure model,[210, 236] where BP waveforms are separated into reservoir and excess pressure components. The reservoir component is related to arterial compliance and resistance to flow, and the excess pressure is related to flow waves.[236] This model is both physiologically plausible[210, 236] and clinically relevant.[237-241] Phenotypes 3 and 4 would be expected to have a higher reservoir pressure (due to suspected higher aortic

stiffness) and higher excess pressure, due to greater augmentation of the BP waveform. Altogether, greater understanding of the physiological differences between the four phenotypes could lead to development of a non-invasive method to accurately identify each phenotype. This would be a major step forward and would enable testing the prevalence and potential clinical relevance of the phenotypes in populations beyond patients undergoing cardiac catheterisation (e.g. healthy, younger people). This could prove to be a novel tool for early identification of people at high cardiovascular risk.

The results of Chapter 4 showed brachial MAP/DBP calibration of radial waveforms was the most accurate way to estimate aortic BP, but that SBP amplification had a major influence on accuracy. This work adds an important contribution to current literature on the best way to estimate aortic BP. The immediate implications of this work are that radial waveforms processed using the SphygmoCor should be calibrated with MAP/DBP. However, obtaining MAP non-invasively often requires a calculation based on SBP and DBP (e.g. MAP=[(2*DBP) + SBP]/3). These types of equations may be inaccurate in many patients, which would cause error in estimated aortic BP.[124, 182] Using oscillometric MAP could improve the non-invasive calibration methods because this is independent of SBP and DBP,[188] although accuracy of this technique may be specific to certain devices.[102] Furthermore, oscillometric devices seldom display MAP, which creates a problem for implementation of these findings.

Future work could also aim to perform a similar study using a different type of device that purports to estimate aortic BP. Currently >10 different devices that estimate aortic BP are available,[82] and therefore the results from Chapter 4 may not be generalisable beyond the SphygmoCor device. In such studies, MAP/DBP would be expected to be more accurate than SBP/DBP calibration for estimation of aortic BP. SBP amplification would also be associated with the accuracy of estimated aortic BP, although this might only be true in devices that estimate aortic BP via generalised transfer functions.

Other future studies could aim to better understand individual BP waveform features associated with SBP amplification and the error in estimated aortic BP. Better knowledge of these characteristics could help to improve BP measurement and potentially lead to greater accuracy via BP dependent correction factors or modification of device algorithms such as generalised transfer functions. Altogether, this work has the potential to improve and individualise the way BP is measured, so that accurate BP measurement is possible in all people. This should then lead to tangible improvements in diagnosis and management of BP, and ultimately reduce the burden of cardiovascular disease worldwide.

References

1. Global Burden of Metabolic Risk Factors for Chronic Diseases C. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. The lancet Diabetes & endocrinology. 2014;2(8):634-47.

2. Collaboration NCDRF. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet. 2017;389(10064):37-55.

3. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957-67.

4. Task Force for the management of arterial hypertension of the European Society of Hypertension, Task Force for the management of arterial hypertension of the European Society of Cardiology. 2013 ESH/ESC Guidelines for the Management of Arterial Hypertension. Blood Press. 2013;22(4):193-278.

5. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289(19):2560-72.

6. Kallioinen N, Hill A, Horswill MS, et al. Sources of inaccuracy in the measurement of adult patients' resting blood pressure in clinical settings: a systematic review. J Hypertens. 2017;35(3):421-41.

7. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005;45(1):142-61.

8. Bordley J, 3rd, Connor CA, Hamilton WF, et al. Recommendations for human blood pressure determinations by sphygmomanometers. Circulation. 1951;4(4):503-9.

9. Jones DW, Appel LJ, Sheps SG, et al. Measuring blood pressure accurately: new and persistent challenges. JAMA. 2003;289(8):1027-30.

10. Hunyor SN, Flynn JM, Cochineas C. Comparison of Performance of Various Sphygmomanometers with Intra-Arterial Blood-Pressure Readings. Br Med J. 1978;2(6131):159-62.

11. Cheng HM, Wang KL, Chen YH, et al. Estimation of central systolic blood pressure using an oscillometric blood pressure monitor. Hypertens Res. 2010;33(6):592-9.

12. Davies JI, Band MM, Pringle S, et al. Peripheral blood pressure measurement is as good as applanation tonometry at predicting ascending aortic blood pressure. J Hypertens. 2003;21(3):571-6.

13. Narayan O, Casan J, Szarski M, et al. Estimation of central aortic blood pressure: a systematic meta-analysis of available techniques. J Hypertens. 2014;32(9):1727-40.

14. Kobayashi H, Kinou M, Takazawa K. Correlation Between the Brachial Blood Pressure Values Obtained Using the Cuff Method and the Central Blood Pressure Values Obtained Invasively. Intern Med. 2013;52(15):1675-80.

15. Davies JE, Shanmuganathan M, Francis DP, et al. Caution using brachial systolic pressure to calibrate radial tonometric pressure waveforms: lessons from invasive study. Hypertension. 2010;55(1):e4.

16. Ding FH, Li Y, Zhang RY, et al. Comparison of the SphygmoCor and Omron devices in the estimation of pressure amplification against the invasive catheter measurement. J Hypertens. 2013;31(1):86-93.

17. van Popele NM, Bos WJ, de Beer NA, et al. Arterial stiffness as underlying mechanism of disagreement between an oscillometric blood pressure monitor and a sphygmomanometer. Hypertension. 2000;36(4):484-8.

18. Shangguan Q, Wu Y, Xu J, et al. The impact of arm circumference on noninvasive oscillometric blood pressure referenced with intra-aortic blood pressure. Blood Press Monit. 2015.

19. Berliner K, Yildiz M, Garnier B, et al. Blood Pressure Measurements in Obese Persons - Comparison of Intra-Arterial and Auscultatory Measurements. Am J Cardiol. 1961;8(1):10-&.

20. Benmira A, Perez-Martin A, Schuster I, et al. From Korotkoff and Marey to automatic non-invasive oscillometric blood pressure measurement: does easiness come with reliability? Expert Rev Med Devices. 2016;13(2):179-89.

21. Forouzanfar M, Dajani HR, Groza VZ, et al. Oscillometric Blood Pressure Estimation: Past, Present, and Future. IEEE Rev Biomed Eng. 2015;8:44-63.

22. Kelly RP, Gibbs HH, O'Rourke MF, et al. Nitroglycerin Has More Favorable Effects on Left-Ventricular Afterload Than Apparent from Measurement of Pressure in a Peripheral Artery. Eur Heart J. 1990;11(2):138-44.

23. O'Rourke MF. Pulsatile arterial haemodynamics in hypertension. Aust N Z J Med. 1976;6 suppl 2:40-8.

24. Lehmann ED. Citation of "validation" references for sphygmocor-based estimates of central aortic blood pressure. J Clin Endocrinol Metab. 2001;86(4):1844-5.

25. Verbeke F, Segers P, Heireman S, et al. Noninvasive assessment of local pulse pressure: importance of brachial-to-radial pressure amplification. Hypertension. 2005;46(1):244-8.

26. Picone DS, Climie RE, Ahuja KD, et al. Brachial-to-radial SBP amplification: implications of age and estimated central blood pressure from radial tonometry. J Hypertens. 2015;33(9):1876-83; discussion 83.

27. O'Rourke M, Avolio A. Assessment of central arterial pressure? J Hypertens. 2003;21(7):1425-6; author reply 6.

28. Segers P, Mahieu D, Kips J, et al. The use of a generalized transfer function: different processing, different results! J Hypertens. 2007;25(9):1783-7.

29. Papaioannou TG, Karageorgopoulou TD, Sergentanis TN, et al. Accuracy of commercial devices and methods for noninvasive estimation of aortic systolic blood pressure a systematic review and meta-analysis of invasive validation studies. J Hypertens. 2016;34(7):1237-48.

30. World Health Organisation. Global status report on non-communicable diseases 2010. Geneva: World Health Organisation; 2011.

31. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.

32. Schiffrin EL, Tedgui A, Lehoux S. Mechanical Stress and the Arterial Wall. In: Safar ME, O'Rourke MF, Frohlich ED, editors. Blood Pressure and Arterial Wall Mechanics in Cardiovascular Diseases. 1 ed. London: Springer-Verlag London; 2014. p. 98.

33. GBD 2013 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(10010):2287-323.

34. Australian Bureau of Statistics. National Health Survey: First Results, 2014-15. Canberra, Australia: Australian Bureau of Statistics; 2016. Contract No.: 6 September.

35. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.

36. Protogerou AD, Argyris AA, Papaioannou TG, et al. Left-ventricular hypertrophy is associated better with 24-h aortic pressure than 24-h brachial pressure in hypertensive patients: the SAFAR study. J Hypertens. 2014;32(9):1805-14.

37. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322(22):1561-6.

38. Reference Values for Arterial Stiffness Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J. 2010;31(19):2338-50.

39. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2014;63(7):636-46.

40. Breteler MM, van Swieten JC, Bots ML, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology. 1994;44(7):1246-52.

41. Vermeer SE, Hollander M, van Dijk EJ, et al. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke. 2003;34(5):1126-9.

42. Gaziano TA, Bitton A, Anand S, et al. The global cost of nonoptimal blood pressure. J Hypertens. 2009;27(7):1472-7.

43. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA internal medicine. 2014;174(4):588-95.

44. Sprint Research Group, Wright JT, Jr., Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015;373(22):2103-16.

45. Liszka HA, Mainous AG, 3rd, King DE, et al. Prehypertension and cardiovascular morbidity. Ann Fam Med. 2005;3(4):294-9.

46. Huang Y, Su L, Cai X, et al. Association of all-cause and cardiovascular mortality with prehypertension: a meta-analysis. Am Heart J. 2014;167(2):160-8 e1.

47. Chobanian AV. Hypertension in 2017-What Is the Right Target? JAMA. 2017.

48. Sim JJ, Shi J, Kovesdy CP, et al. Impact of achieved blood pressures on mortality risk and end-stage renal disease among a large, diverse hypertension population. J Am Coll Cardiol. 2014;64(6):588-97.

49. Bohm M, Schumacher H, Teo KK, et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. Lancet. 2017;389(10085):2226-37.

50. Boutitie F, Gueyffier F, Pocock S, et al. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. Ann Intern Med. 2002;136(6):438-48.

51. Agarwal R. Implications of Blood Pressure Measurement Technique for Implementation of Systolic Blood Pressure Intervention Trial (SPRINT). J Am Heart Assoc. 2017;6(2).

52. Parati G, Ochoa JE, Bilo G, et al. SPRINT Blood Pressure: Sprinting Back to Smirk's Basal Blood Pressure? Hypertension. 2017;69(1):15-9.

53. Ruiz-Hurtado G, Banegas JR, Sarafidis PA, et al. Has the SPRINT trial introduced a new blood-pressure goal in hypertension? Nat Rev Cardiol. 2017.

54. Gardner RM. Direct blood pressure measurement--dynamic response requirements. Anesthesiology. 1981;54(3):227-36.

55. Zanchetti A, Mancia G. The centenary of blood pressure measurement: A tribute to Scipione Riva-Rocci. J Hypertens. 1996;14(1):1-12.

56. Booth J. A short history of blood pressure measurement. Proc R Soc Med. 1977;70(11):793-9.

57. Geddes LA. The direct and indirect measurement of blood pressure. Chicago: Year Book Medical Publishers, Inc.; 1970.

58. Korotkov NS. Concerning the problem of the methods of blood pressure measurement. J Hypertens. 2005;23(1):5.

59. Beime B, Deutsch C, Gomez T, et al. Validation protocols for blood pressure-measuring devices: status quo and development needs. Blood Press Monit. 2016;21(1):1-8.

60. dabl® Educational Trust. Wrist Devices for Self-measurement of Blood Pressure Dublin, Ireland: dabl® Educational Trust; 2018 [18 June 2018]. Available from: http://www.dableducational.org/sphygmomanometers/devices_2_sbpm.html#WristTable.

61. Erlanger J. Studies in blood pressure estimation by indirect methods. American Journal of Physiology -- Legacy Content. 1916;40(1):82.

62. McCutcheon EP, Rushmer RF. Korotkoff sounds. An experimental critique. Circ Res. 1967;20(2):149-61.

63. Benmira A, Perez-Martin A, Schuster I, et al. From Korotkoff and Marey to automatic non-invasive oscillometric blood pressure measurement: does easiness come with reliability? Expert Rev Med Devices. 2015.

64. Benmira A, Perez-Martin A, Schuster I, et al. An ultrasound look at Korotkoff sounds: the role of pulse wave velocity and flow turbulence. Blood Press Monit. 2017;22(2):86-94.

65. Ramsey M, 3rd. Noninvasive automatic determination of mean arterial pressure. Med Biol Eng Comput. 1979;17(1):11-8.

66. Ramsey M, 3rd. Blood pressure monitoring: automated oscillometric devices. J Clin Monit. 1991;7(1):56-67.

67. Sharman JE, LaGerche A. Exercise blood pressure: clinical relevance and correct measurement. J Hum Hypertens. 2014.

68. Roberts LN, Smiley JR, Manning GW. A comparison of direct and indirect blood-pressure determinations. Circulation. 1953;8(2):232-42.

69. Bos WJW, Van Goudoever J, Wesseling KH, et al. Pseudohypertension and the measurement of blood pressure. Hypertension. 1992;20(1):26-31.

70. Kroeker EJ, Wood EH. Beat-to-beat alterations in relationship of simultaneously recorded central and peripheral arterial pressure pulses during Valsalva maneuver and prolonged expiration in man. J Appl Physiol. 1956;8(5):483-94.

71. Kavanagh-Gray D. Comparison of central aortic and peripheral artery pressure curves. Can Med Assoc J. 1964;90:1468-71.

72. Sharman JE, Laurent S. Central blood pressure in the management of hypertension: soon reaching the goal? J Hum Hypertens. 2013;27(7):405-11.

73. McEniery CM, Cockcroft JR, Roman MJ, et al. Central blood pressure: current evidence and clinical importance. Eur Heart J. 2014;35(26):1719-25.

74. Kuwajima I, Hoh E, Suzuki Y, et al. Pseudohypertension in the elderly. J Hypertens. 1990;8(5):429-32.

75. Umana E, Ahmed W, Fraley MA, et al. Comparison of oscillometric and intraarterial systolic and diastolic blood pressures in lean, overweight, and obese patients. Angiology. 2006;57(1):41-5.

76. Nielsen PE, Larsen B, Holstein P, et al. Accuracy of auscultatory blood pressure measurements in hypertensive and obese subjects. Hypertension. 1983;5(1):122-7.

77. Picone DS, Schultz MG, Otahal P, et al. Accuracy of Cuff-Measured Blood Pressure: Systematic Reviews and Meta-Analyses. J Am Coll Cardiol. 2017;70(5):572-86.

78. Redheuil A, Yu WC, Mousseaux E, et al. Age-related changes in aortic arch geometry: relationship with proximal aortic function and left ventricular mass and remodeling. J Am Coll Cardiol. 2011;58(12):1262-70.

79. Murgo JP, Westerhof N, Giolma JP, et al. Aortic input impedance in normal man: relationship to pressure wave forms. Circulation. 1980;62(1):105-16.

80. Sharman JE. Central pressure should be used in clinical practice. Artery Research. 2015;9:1-7.

81. Kroeker EJ, Wood EH. Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in man. Circ Res. 1955;3(6):623-32.

82. Millasseau S, Agnoletti D. Non-invasive estimation of aortic blood pressures: a close look at current devices and methods. Curr Pharm Des. 2015;21(6):709-18.

83. Hope SA, Meredith IT, Cameron JD. Is there any advantage to using an arterial transfer function? Hypertension. 2003;42(3):e6-7; author reply e6-7.

84. Hope SA, Tay DB, Meredith IT, et al. Use of arterial transfer functions for the derivation of aortic waveform characteristics. J Hypertens. 2003;21(7):1299-305.

85. Hope SA, Meredith IT, Cameron JD. Effect of non-invasive calibration of radial waveforms on error in transfer-function-derived central aortic waveform characteristics. Clin Sci. 2004;107(2):205-11.

86. Hope SA, Tay D, Meredith IT, et al. Reply. J Hypertens. 2004;22(2):433-4.

87. Avolio AP, Cockcroft JR, O'Rourke MF. Use of arterial transfer functions for the derivation of central aortic waveform characteristics in subjects with type 2 diabetes and cardiovascular disease. Diabetes Care. 2004;27(10):2564-5; author reply 5-7, 7.

88. O'Rourke MF, Kim M, Adji A, et al. Use of arterial transfer function for the derivation of aortic waveform characteristics. J Hypertens. 2004;22(2):431-2; author reply 3-4.

89. O'Rourke MF, Adji A, Hoegler S. Calibration of noninvasively recorded upper-limb pressure waves. Hypertension. 2005;46(5):e15; author reply e-6.

90. Adji A, O'Rourke MF. Central aortic pressure calibration: "a bridge too far"? J Hypertens. 2017;35(4):893-4.

91. O'Rourke MF. Calibration of SphygmoCor. J Hypertens. 2017;35(3):645.

92. Cloud GC, Rajkumar C, Kooner J, et al. Estimation of central aortic pressure by SphygmoCor requires intra-arterial peripheral pressures. Clin Sci (Lond). 2003;105(2):219-25.

93. Climie RE, Picone DS, Keske MA, et al. Brachial-to-radial systolic blood pressure amplification in patients with type 2 diabetes mellitus. J Hum Hypertens. 2016;30(6):404-9.

94. Vlachopoulos C, Aznaouridis K, O'Rourke MF, et al. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J. 2010;31(15):1865-71.

95. Vlachopoulos C, Aznaouridis K, O'Rourke M, et al. "Towards the final verdict. Re: ""Central pulse pressure versus peripheral pulse pressure: case still open?""" European Heart Journal; 2017 [Available from: https://academic.oup.com/eurheartj/article/31/15/1865/690304#usercomments.

96. Mitchell GF, Hwang SJ, Larson MG, et al. Transfer function-derived central pressure and cardiovascular disease events: the Framingham Heart Study. J Hypertens. 2016;34(8):1528-34.

97. Kollias A, Lagou S, Zeniodi ME, et al. Association of Central Versus Brachial Blood Pressure With Target-Organ Damage: Systematic Review and Meta-Analysis. Hypertension. 2016;67(1):183-90.

98. Negishi K, Yang H, Wang Y, et al. Importance of Calibration Method in Central Blood Pressure for Cardiac Structural Abnormalities. Am J Hypertens. 2016;29(9):1070-6.

99. de la Sierra A, Pareja J, Fernandez-Llama P, et al. Twenty-four-hour central blood pressure is not better associated with hypertensive target organ damage than 24-h peripheral blood pressure. J Hypertens. 2017;35(10):2000-5.

100. Nakagomi A, Okada S, Shoji T, et al. Crucial Effect of Calibration Methods on the Association Between Central Pulsatile Indices and Coronary Atherosclerosis. Am J Hypertens. 2016.

101. Wassertheurer S, Baumann M. Assessment of systolic aortic pressure and its association to all cause mortality critically depends on waveform calibration. J Hypertens. 2015;33(9):1884-8.

102. Sharman JE, Avolio AP, Baulmann J, et al. Validation of non-invasive central blood pressure devices: Artery Society task force consensus statement on protocol standardization. Eur Heart J. 2017;38(37):2805-12.

103. Cheng HM, Lang D, Tufanaru C, et al. Measurement accuracy of non-invasively obtained central blood pressure by applanation tonometry: a systematic review and meta-analysis. Int J Cardiol. 2013;167(5):1867-76.

104. O'Rourke MF. Use of Generalised Transfer Function in Clinical Studies. Sydney, Australia: AtCor Medical.

105. Sharman JE, Lim R, Qasem AM, et al. Validation of a generalized transfer function to noninvasively derive central blood pressure during exercise. Hypertension. 2006;47(6):1203-8.

106. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension. 2001;38(4):932-7.

107. Chen CH, Nevo E, Fetics B, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. Circulation. 1997;95(7):1827-36.

108. Millasseau SC, Patel SJ, Redwood SR, et al. Pressure wave reflection assessed from the peripheral pulse: is a transfer function necessary? Hypertension. 2003;41(5):1016-20.

109. Hope SA, Tay DB, Meredith IT, et al. Use of arterial transfer functions for the derivation of central aortic waveform characteristics in subjects with type 2 diabetes and cardiovascular disease. Diabetes Care. 2004;27(3):746-51.

110. Wilkinson IB, McEniery C. Use of arterial transfer functions for the derivation of central aortic waveform characteristics in subjects with type 2 diabetes and cardiovascular disease. Diabetes Care. 2004;27(10):2564; author reply 5-7.

111. Carlsen RK, Peters CD, Khatir DS, et al. Estimated aortic blood pressure based on radial artery tonometry underestimates directly measured aortic blood pressure in patients with advancing chronic kidney disease staging and increasing arterial stiffness. Kidney Int. 2016;90(4):869-77.

112. Boutouyrie P, London GM, Sharman JE. Estimating central blood pressure in the extreme vascular phenotype of advanced kidney disease. Kidney Int. 2016;90(4):736-9.

113. Cai TY, Qasem A, Ayer JG, et al. Central blood pressure in children and adolescents: non-invasive development and testing of novel transfer functions. J Hum Hypertens. 2017.

114. Milne L, Keehn L, Guilcher A, et al. Central aortic blood pressure from ultrasound wall-tracking of the carotid artery in children: comparison with invasive measurements and radial tonometry. Hypertension. 2015;65(5):1141-6.

115. Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries: Theoretic, Experimental, and Clinical Principles. Fifth ed. London: Hodder Arnold; 2005.

116. Papaioannou TG, Lekakis JP, Karatzis EN, et al. Transmission of calibration errors (input) by generalized transfer functions to the aortic pressures (output) at different hemodynamic states. Int J Cardiol. 2006;110(1):46-52.

117. Shih YT, Cheng HM, Sung SH, et al. Quantification of the Calibration Error in the Transfer Function-Derived Central Aortic Blood Pressures. Am J Hypertens. 2011;24(12):1312-7.

118. Laugesen E, Rossen NB, Peters CD, et al. Assessment of central blood pressure in patients with type 2 diabetes: a comparison between SphygmoCor and invasively measured values. Am J Hypertens. 2014;27(2):169-76.

119. Soender TK, Van Bortel LM, Moller JE, et al. Impact of calibration on estimates of central blood pressures. J Hum Hypertens. 2012;26(12):706-10.

120. Safar ME, Blacher J, Pannier B, et al. Central pulse pressure and mortality in end-stage renal disease. Hypertension. 2002;39(3):735-8.

121. Wang KL, Cheng HM, Chuang SY, et al. Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality? J Hypertens. 2009;27(3):461-7.

122. Pini R, Cavallini MC, Palmieri V, et al. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARe Dicomano Study. J Am Coll Cardiol. 2008;51(25):2432-9.

123. Roman MJ, Devereux RB, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension. 2007;50(1):197-203.

124. AtCor Medical Brachial Systolic and Diastolic Pressures are preferred when calibrating the Radial Artery Waveform in SphygmoCor Studies. West Ryde, NSW, Australia: AtCor Medical; 2013 2013.

125. O'Rourke MF, Adji A. Pressure Paradox: High Pulse Pressure and Low Mean Pressure Are Favorable Features in Young Adults. Hypertension. 2017.

126. O'Rourke MF, Takazawa K. Flawed measurement of brachial tonometry for calculating aortic pressure? Hypertension. 2009;54(5):e131; author reply e2.

127. Segers P, Mahieu D, Kips J, et al. Flawed Measurement of Brachial Tonometry for Calculating Aortic Pressure? Response. Hypertension. 2009;54(5):e132.

128. Adji A, O'Rourke MF. Brachial artery tonometry and the Popeye phenomenon: explanation of anomalies in generating central from upper limb pressure waveforms. J Hypertens. 2012;30(8):1540-51.

129. Bazaral MG, Welch M, Golding LAR, et al. Comparison of Brachial and Radial Arterial-Pressure Monitoring in Patients Undergoing Coronary-Artery Bypass-Surgery. Anesthesiology. 1990;73(1):38-45.

130. Xu JS, Wu YQ, Su H, et al. The Value of a BP Determination Method Using a Novel Non-Invasive BP Device against the Invasive Catheter Measurement. PLoS One. 2014;9(6):e100287.

131. Segers P, Mahieu D, Kips J, et al. Amplification of the pressure pulse in the upper limb in healthy, middle-aged men and women. Hypertension. 2009;54(2):414-20.

132. Avolio AP, Van Bortel LM, Boutouyrie P, et al. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. Hypertension. 2009;54(2):375-83.

133. Pauca AL, Wallenhaupt SL, Kon ND, et al. Does radial artery pressure accurately reflect aortic pressure? Chest. 1992;102(4):1193-8.

134. Beddhu S, Rocco MV, Toto R, et al. Effects of Intensive Systolic Blood Pressure Control on Kidney and Cardiovascular Outcomes in Persons Without Kidney Disease: A Secondary Analysis of a Randomized Trial. Ann Intern Med. 2017;167(6):375-83.

135. Stergiou GS, Kollias A, Protogerou AD. Evidence on Blood Pressure Measurement Methodology and Clinical Implementation: Research Agenda for the 21st Century. J Am Coll Cardiol. 2017;70(5):587-9.

136. Kannel WB. Role of blood pressure in cardiovascular disease: the Framingham Study. Angiology. 1975;26(1 Pt. 1):1-14.

137. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA. 1997;277(9):739-45.

138. Gerin W, Schwartz AR, Schwartz JE, et al. Limitations of current validation protocols for home blood pressure monitors for individual patients. Blood Press Monit. 2002;7(6):313-8.

139. Cheng HM, Chuang SY, Sung SH, et al. Derivation and Validation of Diagnostic Thresholds for Central Blood Pressure Measurements Based on Long-Term Cardiovascular Risks. J Am Coll Cardiol. 2013;62(19):1780-7.

140. Mitchell GF. Central pressure should not be used in clinical practice. Artery Research. 2015;9:8-13.

141. Cameron JD. Comparison of noninvasive devices for assessing central blood pressure parameters: what to compare, when and why. J Hypertens. 2013;31(1):27-31.

142. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA. 2015;313(16):1657-65.

143. Laugesen E, Knudsen ST, Hansen KW, et al. Invasively Measured Aortic Systolic Blood Pressure and Office Systolic Blood Pressure in Cardiovascular Risk Assessment: A Prospective Cohort Study. Hypertension. 2016.

144. Sprafka JM, Strickland D, Gomez-Marin O, et al. The effect of cuff size on blood pressure measurement in adults. Epidemiology. 1991;2(3):214-7.

145. Temmar M, Jankowski P, Peltier M, et al. Intraaortic pulse pressure amplification in subjects at high coronary risk. Hypertension. 2010;55(2):327-32.

146. Tummers B. DataThief III manual v. 1.1 2005 [Available from: <http://datathief.org/>.

147. O'Brien E, Petrie J, Littler W, et al. The British Hypertension Society protocol for the evaluation of blood pressure measuring devices. J Hypertens. 1993;11(suppl 2):S43-S62.

148. Riley RD, Lambert PC, Staessen JA, et al. Meta-analysis of continuous outcomes combining individual patient data and aggregate data. Stat Med. 2008;27(11):1870-93.

149. Rossen NB, Laugesen E, Peters CD, et al. Invasive validation of arteriograph estimates of central blood pressure in patients with type 2 diabetes. Am J Hypertens. 2014;27(5):674-9.

150. Gould L, Shariff M. Comparison of the left ventricular, aortic and brachial arterial first derivative. Vasc Surg. 1969;3(1):34-9.

151. Liang F, Yin Z, Fan Y, et al. In vivo validation of an oscillometric method for estimating central aortic pressure. Int J Cardiol. 2015;199:439-41.

152. Lin MM, Cheng HM, Sung SH, et al. Estimation of central aortic systolic pressure from the second systolic peak of the peripheral upper limb pulse depends on central aortic pressure waveform morphology. J Hypertens. 2012;30(3):581-6.

153. Westerhof BE, Guelen I, Stok WJ, et al. Individualization of transfer function in estimation of central aortic pressure from the peripheral pulse is not required in patients at rest. J Appl Physiol. 2008;105(6):1858-63.

154. Blank SG, West JE, Muller FB, et al. Wideband external pulse recording during cuff deflation: a new technique for evaluation of the arterial pressure pulse and measurement of blood pressure. Circulation. 1988;77(6):1297-305.

155. Freis ED, Sappington RF, Jr. Dynamic reactions produced by deflating a blood pressure cuff. Circulation. 1968;38(6):1085-96.

156. Gelman ML, Nemati C. A new method of blood pressure recording that may enhance patient compliance. JAMA. 1981;246(4):368-70.

157. Gould BA, Hornung RS, Kieso HA, et al. Evaluation of the Remler M2000 blood pressure recorder. Comparison with intraarterial blood pressure recordings both at hospital and at home. Hypertension. 1984;6(2 Pt 1):209-15.

158. Hayashi S, Yamada H, Bando M, et al. Augmentation index does not reflect risk of coronary artery disease in elderly patients. Circ J. 2014;78(5):1176-82.

159. Melamed R, Johnson K, Pothen B, et al. Invasive blood pressure monitoring systems in the ICU: influence of the blood-conserving device on the dynamic response characteristics and agreement with noninvasive measurements. Blood Press Monit. 2012;17(5):179-83.

160. Muecke S, Bersten A, Plummer J. The mean machine; accurate non-invasive blood pressure measurement in the critically ill patient. J Clin Monit Comput. 2009;23(5):283-97.

161. Omboni S, Parati G, Groppelli A, et al. Performance of the AM-5600 blood pressure monitor: comparison with ambulatory intra-arterial pressure. J Appl Physiol (1985). 1997;82(2):698-703.

162. Raftery EB, Ward AP. The indirect method of recording blood pressure. Cardiovasc Res. 1968;2(2):210-8.

163. Sagiv M, Ben-Sira D, Goldhammer E. Direct vs. indirect blood pressure measurement at peak anaerobic exercise. Int J Sports Med. 1999;20(5):275-8.

164. Vardan S, Mookherjee S, Warner R, et al. Systolic hypertension. Direct and indirect BP measurements. Arch Intern Med. 1983;143(5):935-8.

165. Aakhus S, Torp H, Haugland T, et al. Noninvasive Estimates of Aortic Root Pressures - External Subclavian Arterial Pulse Tracing Calibrated by Oscillometrically Determined Brachial Arterial Pressures. Clin Physiol. 1993;13(6):573-86.

166. Bhatt SD, Hinderliter AL, Stouffer GA. Influence of Sex on the Accuracy of Oscillometric-Derived Blood Pressures. J Clin Hypertens. 2011;13(2):112-9.

167. Borow KM, Newburger JW. Noninvasive estimation of central aortic pressure using the oscillometric method for analyzing systemic artery pulsatile blood flow: comparative study of indirect systolic, diastolic, and mean brachial artery pressure with simultaneous direct ascending aortic pressure measurements. Am Heart J. 1982;103(5):879-86.

168. Costello BT, Schultz MG, Black JA, et al. Evaluation of a brachial cuff and suprasystolic waveform algorithm method to noninvasively derive central blood pressure. Am J Hypertens. 2015;28(4):480-6.

169. Cremer A, Butlin M, Codjo L, et al. Determination of central blood pressure by a noninvasive method (brachial BP and QKD interval). J Hypertens. 2012;30(8):1533-9.

170. Lin AC, Lowe A, Sidhu K, et al. Evaluation of a novel sphygmomanometer, which estimates central aortic blood pressure from analysis of brachial artery suprasystolic pressure waves. J Hypertens. 2012;30(9):1743-50.

171. Lowe A, Harrison W, El-Aklouk E, et al. Non-invasive model-based estimation of aortic pulse pressure using suprasystolic brachial pressure waveforms. J Biomech. 2009;42(13):2111-5.

172. Nagle FJ, Naughton J, Balke B. Comparisons of direct and indirect blood pressure with pressure-flow dynamics during exercise. J Appl Physiol. 1966;21(1):317-20.

173. Nakagomi A, Okada S, Shoji T, et al. Aortic pulsatility assessed by an oscillometric method is associated with coronary atherosclerosis in elderly people. Blood Press. 2016:1-8.

174. Ohte N, Saeki T, Miyabe H, et al. Relationship between blood pressure obtained from the upper arm with a cuff-type sphygmomanometer and central blood pressure measured with a catheter-tipped micromanometer. Heart Vessels. 2007;22(6):410-5.

175. Ott C, Haetinger S, Schneider MP, et al. Comparison of two noninvasive devices for measurement of central systolic blood pressure with invasive measurement during cardiac catheterization. J Clin Hypertens (Greenwich). 2012;14(9):575-9.

176. Park CM, Korolkova O, Davies JE, et al. Arterial pressure: agreement between a brachial cuff-based device and radial tonometry. J Hypertens. 2014;32(4):865-72.

177. Pereira T, Maldonado J, Coutinho R, et al. Invasive validation of the Complior Analyse in the assessment of central artery pressure curves: a methodological study. Blood Press Monit. 2014;19(5):280-7.

178. Pucci G, Cheriyan J, Hubsch A, et al. Evaluation of the Vicorder, a novel cuff-based device for the noninvasive estimation of central blood pressure. J Hypertens. 2013;31(1):77-85.

179. Rajani R, Chowienczyk P, Redwood S, et al. The noninvasive estimation of central aortic blood pressure in patients with aortic stenosis. J Hypertens. 2008;26(12):2381-8.

180. Saul F, Aristidou Y, Klaus D, et al. Comparison of Invasive Blood-Pressure Measurements with Indirect Oscillometric Wrist and Upper Arm Values. Z Kardiol. 1995;84(9):675-85.

181. Smulyan H, Siddiqui DS, Carlson RJ, et al. Clinical utility of aortic pulses and pressures calculated from applanated radial-artery pulses. Hypertension. 2003;42(2):150-5.

182. Smulyan H, Sheehe PR, Safar ME. A preliminary evaluation of the mean arterial pressure as measured by cuff oscillometry. Am J Hypertens. 2008;21(2):166-71.

183. Smulyan H, Mukherjee R, Sheehe PR, et al. Cuff and aortic pressure differences during dobutamine infusion: a study of the effects of systolic blood pressure amplification. Am Heart J. 2010;159(3):399-405.

184. Sueta D, Yamamoto E, Tanaka T, et al. The accuracy of central blood pressure waveform by novel mathematical transformation of non-invasive measurement. Int J Cardiol. 2015;189:244-6.

185. Takazawa K, Kobayashi H, Shindo N, et al. Relationship between radial and central arterial pulse wave and evaluation of central aortic pressure using the radial arterial pulse wave. Hypertens Res. 2007;30(3):219-28.

186. Takazawa K, Kobayashi H, Kojima I, et al. Estimation of central aortic systolic pressure using late systolic inflection of radial artery pulse and its application to vasodilator therapy. J Hypertens. 2012;30(5):908-16.

187. Weber F, Lindemann M, Erbel R, et al. Indirect and direct simultaneous, comparative blood pressure measurements with the Bosstron 2 (R) device. Kidney Blood Press Res. 1999;22(3):166-71.

188. Weber T, Wassertheurer S, Rammer M, et al. Validation of a brachial cuff-based method for estimating central systolic blood pressure. Hypertension. 2011;58(5):825-32.

189. Williams B, Lacy PS, Yan P, et al. Development and validation of a novel method to derive central aortic systolic pressure from the radial pressure waveform using an n-point moving average method. J Am Coll Cardiol. 2011;57(8):951-61.

190. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. Lancet. 2016.

191. American National Standard Non-invasive sphygmomanometers - Part 2: Clinical validation of automated measurement type. ANSI/AAMI/ISO 81060-2:2009. Arlington, Virginia: AAMI; 2009.

192. O'Brien E, Atkins N, Stergiou G, et al. European Society of Hypertension International Protocol revision 2010 for the validation of blood pressure measuring devices in adults. Blood Press Monit. 2010;15(1):23-38.

193. O'Brien E, Pickering T, Asmar R, et al. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. Blood Press Monit. 2002;7(1):3-17.

194. Tholl U, Anlauf M. [Conscientious evaluation of measuring accuracy. Hypertension League provides approval seals for automatic blood pressure units]. MMW Fortschr Med. 1999;141(42):45.

195. White WB, Berson AS, Robbins C, et al. National standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. Hypertension. 1993;21(4):504-9.

196. Stergiou GS, Alpert B, Mieke S, et al. A universal standard for the validation of blood pressure measuring devices: Association for the Advancement of Medical Instrumentation/European Society of Hypertension/International Organization for Standardization (AAMI/ESH/ISO) Collaboration Statement. J Hypertens. 2018;36(3):472-8.

197. Benítez Brito N, Suárez Llanos JP, Fuentes Ferrer M, et al. Relationship between Mid-Upper Arm Circumference and Body Mass Index in Inpatients. PLoS One. 2016;11(8): e0160480.

198. O'Callaghan WG, Fitzgerald DJ, O'Malley K, et al. Accuracy of indirect blood pressure measurement in the elderly. Br Med J (Clin Res Ed). 1983;286(6377):1545-6.

199. Perloff D, Grim C, Flack J, et al. Human blood pressure determination by sphygmomanometry. Circulation. 1993;88(5 Pt 1):2460-70.

200. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, et al. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. Hypertension. 2008;51(4):848-55.

201. Smulyan H, Safar ME. Blood pressure measurement: retrospective and prospective views. Am J Hypertens. 2011;24(6):628-34.

202. Roth GA, Johnson C, Abajobir A, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1-25.

203. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224-60.

204. Amoore JN. Oscillometric sphygmomanometers: a critical appraisal of current technology. Blood Press Monit. 2012;17(2):80-8.

205. Picone DS, Schultz MG, Climie RE, et al. Aortic-to-brachial stiffness gradient and kidney function in type 2 diabetes. J Hypertens. 2016;34(6):1132-9.

206. Peng X, Schultz MG, Picone DS, et al. Arterial reservoir characteristics and central-to-peripheral blood pressure amplification in the human upper limb. J Hypertens. 2017;35(9):1825-31.

207. Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? J Hypertens. 2009;27(8):1509-20.

208. Gaddum N, Alastruey J, Chowienczyk P, et al. Relative contributions from the ventricle and arterial tree to arterial pressure and its amplification: an experimental study. Am J Physiol Heart Circ Physiol. 2017;313(3):H558-H67.

209. Zambanini A, Cunningham SL, Parker KH, et al. Wave-energy patterns in carotid, brachial, and radial arteries: a noninvasive approach using wave-intensity analysis. Am J Physiol Heart Circ Physiol. 2005;289(1):H270-6.

210. Schultz MG, Davies JE, Hardikar A, et al. Aortic reservoir pressure corresponds to cyclic changes in aortic volume: physiological validation in humans. Arterioscler Thromb Vasc Biol. 2014;34(7):1597-603.

211. Kaufmann MA, Pargger H, Drop LJ. Oscillometric blood pressure measurements by different devices are not interchangeable. Anesth Analg. 1996;82(2):377-81.

212. Alpert BS. Validation of the Welch Allyn Spot Vital Signs blood pressure device according to the ANSI/AAMI SP10: 2002. Accuracy and cost-efficiency successfully combined. Blood Press Monit. 2007;12(5):345-7.

213. Rogoza AN, Pavlova TS, Sergeeva MV. Validation of A&D UA-767 device for the self-measurement of blood pressure. Blood Press Monit. 2000;5(4):227-31.

214. Hawkes N. Sixty seconds on . . . measuring blood pressure. BMJ. 2016;353:i2626.

215. Stergiou GS, Lourida P, Tzamouranis D. Replacing the mercury manometer with an oscillometric device in a hypertension clinic: implications for clinical decision making. J Hum Hypertens. 2011;25(11):692-8.

216. Kannel WB, Gordon T, Schwartz MJ. Systolic Versus Diastolic Blood Pressure and Risk of Coronary Heart Disease - Framingham Study. Am J Cardiol. 1971;27(4):335-&.

217. Nakagomi A, Okada S, Shoji T, et al. Comparison of invasive and brachial cuff-based noninvasive measurements for the assessment of blood pressure amplification. Hypertens Res. 2017;40(3):237-42.

218. Shoji T, Nakagomi A, Okada S, et al. Invasive validation of a novel brachial cuff-based oscillometric device (SphygmoCor XCEL) for measuring central blood pressure. J Hypertens. 2017;35(1):69-75.

219. Stergiou GS, Tzamouranis D, Protogerou A, et al. Validation of the Microlife Watch BP Office professional device for office blood pressure measurement according to the International protocol. Blood Press Monit. 2008;13(5):299-303.

220. Omboni S, Riva I, Giglio A, et al. Validation of the Omron M5-I, R5-I and HEM-907 automated blood pressure monitors in elderly individuals according to the International Protocol of the European Society of Hypertension. Blood Press Monit. 2007;12(4):233-42.

221. Franklin SS, Khan SA, Wong ND, et al. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. Circulation. 1999;100(4):354-60.

222. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. Lancet. 2016;388(10060):2665-712.

223. Picone DS, Schultz MG, Peng X, et al. Discovery of new blood pressure phenotypes and relation to accuracy of cuff devices used in daily clinical practice. Hypertension. 2018;epub ahead of print.

224. Karamanoglu M, O'Rourke MF, Avolio AP, et al. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. Eur Heart J. 1993;14(2):160-7.

225. Krittanawong C, Zhang H, Wang Z, et al. Artificial Intelligence in Precision Cardiovascular Medicine. J Am Coll Cardiol. 2017;69(21):2657-64.

226. Climie RE, Schultz MG, Nikolic SB, et al. Validity and reliability of central blood pressure estimated by upper arm oscillometric cuff pressure. Am J Hypertens. 2012;25(4):414-20.

227. Weiss W, Gohlisch C, Harsch-Gladisch C, et al. Oscillometric estimation of central blood pressure: validation of the Mobil-O-Graph in comparison with the SphygmoCor device. Blood Press Monit. 2012;17(3):128-31.

228. Alpert BS. A letter to the Editor on 'Validation protocols for blood pressure-measuring devices: status quo and development needs' by Beime et al., Blood Press Monit 2016; 21:1-8. Blood Press Monit. 2016;21(4):262-3.

229. Alpert BS. Can 'FDA-cleared' blood pressure devices be trusted? A call to action. Blood Press Monit. 2017;22(4):179-81.

230. D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.

231. Jackson R, Lawes CM, Bennett DA, et al. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet. 2005;365(9457):434-41.

232. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. https://www.heartfoundation.org.au/images/uploads/publications/Absolute-CVD-Risk-Full-Guidelines.pdf; 2012.

233. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. 2016.

234. Imai Y, Tsuji I, Nagai K, et al. Ambulatory blood pressure monitoring in evaluating the prevalence of hypertension in adults in Ohasama, a rural Japanese community. Hypertens Res. 1996;19(3):207-12.

235. Pickering TG, Davidson K, Gerin W, et al. Masked hypertension. Hypertension. 2002;40(6):795-6.

236. Wang JJ, O'Brien AB, Shrive NG, et al. Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. Am J Physiol Heart Circ Physiol. 2003;284(4):H1358-68.

237. Climie RE, Srikanth V, Keith LJ, et al. Exercise excess pressure and exercise-induced albuminuria in patients with type 2 diabetes mellitus. Am J Physiol Heart Circ Physiol. 2015;308(9):H1136-42.

238. Narayan O, Davies JE, Hughes AD, et al. Central aortic reservoir-wave analysis improves prediction of cardiovascular events in elderly hypertensives. Hypertension. 2015;65(3):629-35.

239. Davies JE, Lacy P, Tillin T, et al. Excess Pressure Integral Predicts Cardiovascular Events Independent of Other Risk Factors in the Conduit Artery Functional Evaluation Substudy of Anglo-Scandinavian Cardiac Outcomes Trial. Hypertension. 2014.

240. Wang WT, Sung SH, Wang JJ, et al. Excess Pressure Integral Predicts Long-Term All-Cause Mortality in Stable Heart Failure Patients. Am J Hypertens. 2016.

241. Hametner B, Wassertheurer S, Hughes AD, et al. Reservoir and excess pressures predict cardiovascular events in high-risk patients. Int J Cardiol. 2014;171(1):31-6.

242. De Hert SG, Vermeyen KM, Moens MM, et al. Central-to-peripheral arterial pressure gradient during cardiopulmonary bypass: relation to pre- and intra-operative data and effects of vasoactive agents. Acta Anaesthesiol Scand. 1994;38(5):479-85.

243. O'Rourke MF. Influence of ventricular ejection on the relationship between central aortic and brachial pressure pulse in man. Cardiovasc Res. 1970;4(3):291-300.

244. VanBeck JO, White RD, Abenstein JP, et al. Comparison of axillary artery or brachial artery pressure with aortic pressure after cardiopulmonary bypass using a long radial artery catheter. J Cardiothorac Vasc Anesth. 1993;7(3):312-5.

245. Gravlee GP, Brauer SD, Orourke MF, et al. A Comparison of Brachial, Femoral, and Aortic Intra-Arterial Pressures before and after Cardiopulmonary Bypass. Anaesth Intensive Care. 1989;17(3):305-11.

246. Gravlee GP, Wong AB, Adkins TG, et al. A comparison of radial, brachial, and aortic pressures after cardiopulmonary bypass. J Cardiothorac Anesth. 1989;3(1):20-6.

247. Bachmann K, Baeuerlein G. Ambulatory monitoring of arterial blood pressure. Comparison between blood pressure measurements obtained with the Remler M 2000 portable recorder and by radiotelemetry under laboratory conditions and during everyday activities. Biotelem Patient Monit. 1981;8(1-2):47-55.

248. Baeriswyl C, Muller PO, Regamey C. Development and clinical testing of a new electronic device for blood pressure measurement. (Sphygmodigital 4000). Schweizerische Medizinische Wochenschrift. 1982;112(50):1829-30.

249. Breit SN, O'Rourke MF. Comparison of direct and indirect arterial pressure measurements in hospitalised patients. Aust N Z J Med. 1974;4(5):485-91.

250. Fagher B, Magnusson J, Thulin T. Direct and Indirect Blood-Pressure in Normotensive and Hypertensive Subjects. J Intern Med. 1994;236(1):85-90.

251. Forsberg SA, de Guzman M, Berlind S. Validity of blood pressure measurement with cuff in the arm and forearm. Acta Med Scand. 1970;188(5):389-96.

252. Ginsburg J, Duncan S. Direct and indirect blood pressure measurement in pregnancy. The Journal of obstetrics and gynaecology of the British Commonwealth. 1969;76(8):705-10.

253. He B, Miao W. A study on pseudo-hypertension. Chinese Journal of Cardiology. 1994;22(2):93-5+155.

254. Julien J, Pagny JY, Jeunemaitre X, et al. Comparison of 3 methods of blood pressure measurement in obesity. Arch Mal Coeur Vaiss. 1988;81 Spec No:241-5.

255. Karlefors T, Nilsén R, Westling H. On the accuracy of indirect auscultatory blood pressure measurements during exercise. Acta Medica Scandinavica, Supplement. 1966;449:81-7.

256. London SB, London RE. Comparison of indirect pressure measurements (Korotkoff) with simultaneous direct brachial artery pressure distal to the cuff. Adv Intern Med. 1967;13:127-42.

257. Molhoek GP, Wesseling KH, Settels JJ, et al. Evaluation of the Penaz servo-plethysmo-manometer for the continuous, non-invasive measurement of finger blood pressure. Basic Res Cardiol. 1984;79(5):598-609.

258. Moss AJ, Adams FH. Auscultatory and Intra-Arterial Pressure - a Comparison in Children with Special Reference to Cuff Width. J Pediatr. 1965;66(6):1094-+.

259. Murray WB, Gorven AM. Invasive V Noninvasive Blood-Pressure Measurements - the Influence of the Pressure Contour. S Afr Med J. 1991;79(3):134-9.

260. Netea RT, Bijlstra PJ, Lenders JWM, et al. Influence of the arm position on intra-arterial blood pressure measurement. J Hum Hypertens. 1998;12(3):157-60.

261. Ochiai H, Miyazaki N, Miyata T, et al. Assessment of the accuracy of indirect blood pressure measurements. Jpn Heart J. 1997;38(3):393-407.

262. Sánchez G, Gutiérrez E, Monroy JR, et al. Correlation between the direct intra-arterial method and the sphygmomamometric auscultation in the determination of the systemic arterial pressure. Arch Inst Cardiol Mex. 1977;47(6):673-83.

263. Turjanmaa VM, Kalli ST, Uusitalo AJ. Blood pressure level changes caused by posture change and physical exercise: can they be determined accurately using a standard cuff method? J Hypertens Suppl. 1988;6(4):S79-81.

264. Turjanmaa V. Determination of blood pressure level and changes in physiological situations: comparison of the standard cuff method with direct intra-arterial recording. Clin Physiol. 1989;9(4):373-87.

265. Casadei R, Parati G, Pomidossi G, et al. 24-hour blood pressure monitoring: evaluation of Spacelabs 5300 monitor by comparison with intra-arterial blood pressure recording in ambulant subjects. J Hypertens. 1988;6(10):797-803.

266. Elseed AM, Shinebourne EA, Joseph MC. Assessment of techniques for measurement of blood pressure in infants and children. Arch Dis Child. 1973;48(12):932-6.

267. Fukuoka M, Yamori Y, Ueno T. Evaluation of a new non-invasive semiautomatic blood pressure monitoring device. Clinical and Experimental Hypertension - Part A Theory and Practice. 1987;9(1):141-52.

268. Gould BA, Hornung RS, Altman DG. Indirect measurement of blood pressure during exercise testing can be misleading. Br Heart J. 1985;53(6):611-5.

269. Gould BA, Hornung RS, Cashman PM, et al. An evaluation of the Avionics Pressurometer III 1978 at home and in hospital. Clin Cardiol. 1986;9(7):335-43.

270. Graettinger WF, Lipson JL, Cheung DG, et al. Validation of portable noninvasive blood pressure monitoring devices: Comparisons with intra-arterial and sphygmomanometer measurements. Am Heart J. 1988;116(4):1155-60.

271. Gravlee GP, Brockschmidt JK. Accuracy of four indirect methods of blood pressure measurement, with hemodynamic correlations. J Clin Monit. 1990;6(4):284-98.

272. Groppelli A, Omboni S, Parati G, et al. Evaluation of noninvasive blood pressure monitoring devices Spacelabs 90202 and 90207 versus resting and ambulatory 24-hour intra-arterial blood pressure. Hypertension. 1992;20(2):227-32.

273. Holland WW, Humerfelt S. Measurement of Blood-Pressure: Comparison of Intra-Arterial and Cuff Values. Br Med J. 1964;2(5419):1241-3.

274. Hunyor S, Nyberg G. Comparison of intra-arterial and indirect blood pressures at rest and during isometric exercise in hypertensive patients before and after metoprolol. Br J Clin Pharmacol. 1978;6(2):109-14.

275. Lemson J, Hofhuizen CM, Schraa O, et al. The Reliability of Continuous Noninvasive Finger Blood Pressure Measurement in Critically III Children. Anesth Analg. 2009;108(3):814-21.

276. Mejia AD, Egan BM, Schork NJ, et al. Artefacts in measurement of blood pressure and lack of target organ involvement in the assessment of patients with treatment-resistant hypertension. Ann Intern Med. 1990;112(4):270-7.

277. Milsom I, Svahn SO, Forssman L, et al. An evaluation of automated indirect blood pressure measurement during pregnancy. Acta Obstet Gynecol Scand. 1986;65(7):721-5.

278. Nielsen PE, Barras JP, Holstein P. Systolic pressure amplification in the arteries of normal subjects. Scand J Clin Lab Invest. 1974;33(4):371-7.

279. Nielsen PE, Hilden T. Intra-arterial blood pressure measured during 24-hours in evaluation of hypertensive subjects. Acta Med Scand Suppl. 1979;625:92-6.

280. Pereira E, Prys-Roberts C, Dagnino J. Auscultatory measurement of arterial pressure during anaesthesia: a reassessment of Korotkoff sounds. Eur J Anaesthesiol. 1985;2(1):11-20.

281. Pitlik SD, Morduchowicz G, Blai A, et al. Overestimation of blood pressure in the elderly. Isr J Med Sci. 1986;22(6):435-7.

282. Robinson TE, Sue DY, Huszczuk A, et al. Intra-arterial and cuff blood pressure responses during incremental cycle ergometry. Med Sci Sports Exerc. 1988;20(2):142-9.

283. Sagiv M, Hanson PG, Ben-Sira D, et al. Direct vs indirect blood pressure at rest and during isometric exercise in normal subjects. Int J Sports Med. 1995;16(8):514-8.

284. Stolt M, Sjonell G, Astrom H, et al. The reliability of auscultatory measurement of arterial blood pressure. A comparison of the standard and a new methodology. Am J Hypertens. 1990;3(9):697-703.

285. Stolt M, Sjonell G, Astrom H, et al. Factors Affecting the Validity of the Standard Blood-Pressure Cuff. Clin Physiol. 1993;13(6):611-20.

286. Stolt M, Sjonell G, Astrom H, et al. Improved Accuracy of Indirect Blood-Pressure Measurement in Patients with Obese Arms. Am J Hypertens. 1993;6(1):66-71.

287. van Egmond J, Lenders JW, Weernink E, et al. Accuracy and reproducibility of 30 devices for self-measurement of arterial blood pressure. Am J Hypertens. 1993;6(10):873-9.

288. Villani A, Parati G, Groppelli A, et al. Noninvasive Automatic Blood-Pressure Monitoring Does Not Attenuate Nighttime Hypotension - Evidence from 24h Intraarterial Blood-Pressure Monitoring. Am J Hypertens. 1992;5(10):744-7.

289. White WB, Lund-Johansen P, McCabe EJ. Clinical evaluation of the colin abpm 630 at rest and during exercise: An ambulatory blood pressure monitor with gas-powered cuff inflation. J Hypertens. 1989;7(6):477-83.

290. White WB, Lund-Johansen P, McCabe EJ, et al. Clinical evaluation of the Accutracker II ambulatory blood pressure monitor: assessment of performance in two countries and comparison with sphygmomanometry and intra-arterial blood pressure at rest and during exercise. J Hypertens. 1989;7(12):967-75.

291. White WB, Lund-Johansen P, Omvik P. Assessment of four ambulatory blood pressure monitors and measurements by clinicians versus intraarterial blood pressure at rest and during exercise. The American Journal of Cardiology. 1990;65(1):60-6.

292. Wiecek EM, McCartney N, McKelvie RS. Comparison of Direct and Indirect Measures of Systemic Arterial-Pressure during Weightlifting in Coronary-Artery Disease. Am J Cardiol. 1990;66(15):1065-9.

293. Li L, Yang F, Huang J. A study on comparing blood pressure of ankle artery with brachial artery and intra-aortic pressures. Chinese Journal of Cardiology. 1999;27(5):376-8.

294. Alihanoglu YI, Kayrak M, Ulgen MS, et al. The impact of central blood pressure levels on the relationship between oscillometric and central blood pressure measurements: a multicenter invasive study. J Clin Hypertens (Greenwich). 2013;15(9):681-6.

295. Baguet JP, de Poli F, Sosner P, et al. Using a large cuff reduces the difference between peripheral and central blood pressure readings. The BP-CUFF study. Int J Cardiol. 2013;170(2):e43-4.

296. Brett SE, Guilcher A, Clapp B, et al. Estimating central systolic blood pressure during oscillometric determination of blood pressure: proof of concept and validation by comparison with intra-aortic pressure recording and arterial tonometry. Blood Press Monit. 2012;17(3):132-6.

297. Choi CU, Kim EJ, Kim SH, et al. Differing effects of aging on central and peripheral blood pressures and pulse wave velocity: a direct intraarterial study. J Hypertens. 2010;28(6):1252-60.

298. Eckert S, Hammentgen R, Ohlmeier H, et al. 24-Stunden-Langzeitblutdruckmessung: Liefert die auskultatorische oder oszillometrische Meßtechnik genauere Ergebnisse. Nieren- und Hochdruckkrankheiten. 1994;23(5):236-7.

299. Eckert S, Gleichmann S, Gleichmann U. Blood pressure self-measurement in upper arm and in wrist for treatment control of arterial hypertension compared to ABPM. Z Kardiol. 1996;85(Suppl 3):109-11.

300. Fleming SE, Horvath JS, Korda A. Errors in the measurement of blood pressure. Aust N Z J Obstet Gynaecol. 1983;23(3):136-8.

301. Guilcher A, Brett S, Munir S, et al. Estimating central SBP from the peripheral pulse: influence of waveform analysis and calibration error. J Hypertens. 2011;29(7):1357-66.

302. Hoegholm A, Eidemak I, Kristensen KS, et al. Clinical evaluation of the Takeda Medical (A & D) TM 2420 ambulatory blood pressure monitor. Practical experience and comparison with direct and indirect measurements. Scand J Clin Lab Invest. 1992;52(4):261-8.

303. Horvath IG, Nemeth A, Lenkey Z, et al. Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. J Hypertens. 2010;28(10):2068-75.

304. Kayrak M, Ulgen MS, Yazici M, et al. [Comparison between brachial blood pressures obtained by aneroid sphygmomanometer and central aortic pressures: factors affecting the measurements]. Turk Kardiyol Dern Ars. 2008;36(4):239-46.

305. Kayrak M, Ulgen MS, Yazici M, et al. A comparison of blood pressure and pulse pressure values obtained by oscillometric and central measurements in hypertensive patients. Blood Press. 2010;19(2):98-103.

306. Klaus D, Wetzchewald D, Saul F, et al. Vergleich von direkter invasiver Blutdruckmessung mit indirekter Blutdruckmessung mittels Oszillometrie oder Sphygmomanometrie. Nieren- und Hochdruckkrankheiten. 1991;20(4):160-9.

307. Lehmann KG, Gelman JA, Weber MA, et al. Comparative accuracy of three automated techniques in the noninvasive estimation of central blood pressure in men. Am J Cardiol. 1998;81(8):1004-12.

308. Park S-H, Lee S-J, Kim JY, et al. Direct comparison between brachial pressure obtained by oscillometric method and central pressure using invasive method. Soonchunhyang Medical Science. 2011;17(2):65-71.

309. Sharir T, Marmor A, Ting CT, et al. Validation of a method for noninvasive measurement of central arterial pressure. Hypertension. 1993;21(1):74-82.

310. Sugawara R, Horinaka S, Yagi H, et al. Central blood pressure estimation by using N-point moving average method in the brachial pulse wave. Hypertens Res. 2015;38(5):336-41.

311. Zuo JL, Li Y, Yan ZJ, et al. Validation of the central blood pressure estimation by the SphygmoCor system in Chinese. Blood Press Monit. 2010;15(5):268-74.

Appendix 1

Appendix 1 presents information from the Online-only supplemental content from the publication that is presented in Chapter 2 (Accuracy of cuff measured blood pressure: systematic reviews and meta-analyses) of this thesis. The supplemental content was peer-reviewed as part of the overall process for journal publication. Some parts of the original supplemental content have been integrated within Chapter 2 to improve clarity and ease of understanding, with the remainder presented here.

Appendix 1.1 Unpublished study methods

Meta-analysis 1.

Picone et al

52 participants undergoing cardiac catheterization at the Royal Hobart Hospital were studied. Exclusion criteria included arrhythmia or acute myocardial infarction. Upon completion of the diagnostic cardiac catheterization, a fluid-filled catheter was positioned in the ascending aorta and confirmed by fluoroscopy. The catheter was flushed and continuous, stable BP waveform recordings were made for 20 seconds. The catheter was then immediately pulled back to the brachial artery (mid-humerus and confirmed by fluoroscopy) and flushed before recordings were made. A brachial cuff (placed on the contra-lateral upper arm as part of concurrent studies) was then inflated. Stable brachial BP waveform recordings 20 seconds prior to the completion of cuff deflation were used in the analysis. No major hemodynamic shift between the aortic and brachial BP measurements was observed. The intra-arterial pressure signal was converted from Volts to mm Hg via a 2-point calibration method (LabChart version 7.1, AD Instruments, Colorado Springs, CO, USA). The University of Tasmania Health and Medical Human Research Ethics Committee approved the study protocol and participants signed informed consent.

Cheng et al

Study methods were the same as those for Cheng et al, 2010.

Pucci et al

29 participants undergoing diagnostic catheterization were studied. Exclusion criteria were: history of peripheral arterial disease, aortic aneurysm, absent brachial or radial pulses or known obstructive large artery atherosclerotic disease, active malignancy, hypotension (SBP <90mm Hg), valvular heart disease, known left ventricular dysfunction (ejection fraction <50%) or arrhythmias (including frequent ventricular and supraventricular premature beats). A fluid-filled catheter was used for all hemodynamic recordings. Firstly, intra-arterial ascending aortic BP was recorded and then the catheter was pulled back to the brachial artery site (using a pre-defined length) in about 5-10 seconds. Intra-arterial brachial artery BP was then recorded. The fluid-filled catheter-manometer system (ACIST medical systems, Eden Prairie, MN, USA). The study protocol was reviewed and approved by the institutional ethics committee. Written informed consent was obtained from each patient.

Meta-analysis 2

Picone et al

40 participants undergoing cardiac catheterization at the Royal Hobart Hospital were studied. Exclusion criteria included arrhythmia or acute myocardial infarction. Upon completion of the diagnostic cardiac catheterization, a fluid-filled catheter was positioned mid-humerus. A brachial cuff (placed on the contra-lateral upper arm) was then inflated whilst intra-arterial BP waveforms were simultaneously recorded. The intra-arterial pressure 20 seconds prior to the completion of cuff deflation was used in the analysis. The intra-arterial pressure signal was converted from Volts to mm Hg via a 2-point calibration method (LabChart version 7.1, AD Instruments, Colorado Springs, CO, USA). The University of Tasmania Health and Medical Human Research Ethics Committee approved the study protocol and every participant signed informed consent.

Cheng et al

Study methods were the same as those for Cheng et al, 2010.

Pucci et al

29 participants undergoing diagnostic catheterization were studied. Exclusion criteria were: history of peripheral arterial disease, aortic aneurysm, absent brachial or radial pulses or known obstructive large artery atherosclerotic disease, active malignancy, hypotension (SBP <90mm Hg), valvular heart disease, known left ventricular dysfunction (ejection fraction <50%) or arrhythmias (including frequent ventricular and supraventricular premature beats). A fluid-filled catheter was used for brachial artery recordings (ACIST medical systems, Eden Prairie, MN, USA). Brachial cuff BP was measured simultaneously with intra-arterial brachial artery BP from the contralateral arm. The study protocol was reviewed and approved by the institutional ethics committee. Written informed consent was obtained from each patient.

Meta-analysis 3

Broyd et al

Patients undergoing diagnostic angiography were recruited. Prior to angiography the brachial cuff of an oscillometric device was applied to the left upper arm. Intra-arterial access was achieved through either a radial or femoral approach and a 6 French catheter was inserted into the ascending aortic under fluoroscopic guidance and positioned approximately 1cm above the aortic valve. Central pressure was collected intra-arterially from the tip of the fluid-filled catheter using a Combomap console (Volcano Corporation, San Diego, CA). Prior to each measurement, catheters were flushed and the BP trace visually inspected for quality. During all recordings, transducers were maintained at heart level. A simultaneous non-invasive measure was recorded using the suprasystolic blood pressure device (Pulsecor R6.5; Auckland, New

Zealand), ensuring a signal quality was excellent. Meticulous attention was paid to the timing of the non-invasive data acquisition and the identical portion of the intra-arterial data was exported.

Cheng et al

Study methods were the same as those for Cheng et al, 2010.

Korolkova et al

Study methods were the same as those for Park et al, 2014.

Picone et al

We studied 146 participants undergoing cardiac catheterization at the Royal Hobart Hospital. Exclusion criteria included arrhythmia, aortic stenosis or acute myocardial infarction. Prior to the cardiac angiogram, a fluid-filled catheter was positioned in the ascending aorta, confirmed by fluoroscopy. The catheter was flushed and recording commenced. An oscillometric cuff was then inflated to obtain brachial cuff BP. Ten seconds of steady state intra-arterial aortic BP was analyzed, and this was recorded approximately 10 seconds after the brachial cuff BP, to coincide with non-invasive central BP estimation. The intra-arterial pressure signal was converted from Volts to mm Hg via a 2-point calibration method (LabChart version 7.1, AD Instruments, Colorado Springs, CO, USA). The University of Tasmania Health and Medical Human Research Ethics Committee approved the study protocol and every participant signed informed consent.

Pucci et al

29 participants undergoing diagnostic catheterization were studied. Exclusion criteria were: history of peripheral arterial disease, aortic aneurysm, absent brachial or radial pulses or known obstructive large artery atherosclerotic disease, active malignancy, hypotension (SBP <90mm Hg), valvular heart disease, known left ventricular dysfunction (ejection fraction <50%) or arrhythmias (including frequent ventricular and supraventricular premature beats). A fluid-filled catheter was used for intra-arterial aortic BP recordings (ACIST medical systems, Eden Prairie, MN, USA). Intra-arterial ascending aortic BP was recorded and then the catheter was pulled back to the brachial artery site (using a pre-defined length) in about 5-10 seconds. Brachial cuff BP was measured simultaneously with intra-arterial brachial artery BP. Brachial cuff BP and intra-arterial aortic BP data was extracted and used in the present meta-analysis.

Appendix 1.2 Methods for data extraction from published tables.

Meta-analysis 1

Gould and Shariff et al, 1969[150]

Data were extracted from Table 1 on page 35 of the publication. Intra-arterial aortic BP was extracted from the column labelled "Aorta", and intra-arterial brachial BP from the column labelled "B.A".

Kavanagh-Gray, 1964[71]

Data were extracted from Table I page 1469 of the publication. Clinical characteristics were extracted from the "Sex" and "Age" columns. Intra-arterial brachial systolic and diastolic BP was extracted from the column "Brachial artery pressure (mm. Hg) S/D". Intra-arterial aortic systolic and diastolic BP were extracted from the column "Central aortic pressure (mm. Hg) S/D".

Kelly et al, 1990[22]

Data were extracted from Table I on page 141 of the publication. Clinical characteristics were extracted from the "Age" and "Sex" columns. Intra-arterial ascending aortic systolic and diastolic BP were extracted from the columns labelled "AA systolic" and "AA diastolic". Intra-arterial brachial systolic and diastolic BP were extracted from the columns labelled "BA systolic" and "BA diastolic". Heart rate data was extracted from the column labelled "Heart rate". In all cases only the data labelled "C" were extracted because this was collected under control (baseline conditions).

Meta-analysis 2

Berliner et al, 1961[19]

Table 1 (pages 11-12) of the publication reported the brachial cuff BP and the highest and lowest intra-arterial brachial BP taken during a simultaneous recording period. The highest and lowest intra-arterial brachial BP values were averaged and used in the meta-analysis.

Freis et al, 1968[155]

Data was extracted from Table 5 of the publication (page 1093) and used for analysis.

Gelman et al, 1981[156]

Table 2 of the publication (page 370) reported a "representative raw data sample" of Group 3 (Cardiac catheterizations). Data from five subjects was reported and the IBP column (brachial

cuff BP) and the BAP column (intra-arterial brachial BP) were extracted and used in the meta-analysis.

Hunyor et al, 1978[10]

This study compared seven different brachial cuff BP device against intra-arterial brachial BP in nine participants. The individual data was presented in Table 2 (page 161). Data from the comparison between brachial cuff BP device "Accoson" (a standard mercury sphygmomanometer) and intra-arterial brachial BP was used in the meta-analysis.

Raftery and Ward, 1968[162]

Data were extracted from Table 1 (page 212) of the publication. Age, height, weight were extracted as clinical characteristics. Brachial cuff systolic and diastolic BP data were extracted from the "indirect" column in the "systolic" section and the "Phase V diastolic" section. Intra-arterial brachial BP were extracted from the "direct" columns of the same sections of the table.

Roberts et al, 1953[68]

Table 1 of the publication (pages 234-235) reported the individual brachial cuff and intra-arterial brachial BP data. Column 4 reported the brachial cuff data and was labelled "Cuff". This column corresponded to the intra-arterial brachial column labelled "Sanb." Both these columns were extracted and used in analysis. The diastolic BP extracted was from the 5th Korotkoff sound, unless this value was 0, in which case, the 4th Korotkoff sound was extracted.

Meta-analysis 3

Borow et al, 1982[167]

Clinical data (age, sex and heart rate) were extracted from Table I on page 881 of the publication. Systolic and diastolic blood pressure data from the "Mean Ao" and "Mean Din" columns were extracted from Table II on page 882 of the publication. "Din" refers to the brachial cuff device that was used in the study, the Dinamap 845.

Nagle et al, 1966[172]

This study comprised two subjects. The supine resting "direct recording" and "auscultation" systolic and diastolic blood pressures were extracted from Table 1. Heart rate during supine rest was extracted from Table 2, as well as subject age and weight. Under the heading "Procedures" in the text of the publication, the authors state that both subjects are male.

Appendix 1.3 Description of study quality score attributes

Meta-analysis 1

A study quality score was developed to assess the methods used in each study included in the meta-analysis. The scoring system considered five study attributes and one point was awarded per attribute when the highest standard was achieved. If the highest standard was not achieved for an attribute, then a zero was assigned for that attribute. Thus a study could achieve a score from 0 to 5 points. A description is presented below.

1. Type of catheter

- **a)** micromanometer tip: 1 point OR
- **b)** fluid filled catheter manometer system – description of frequency and damping characteristics: 1 point OR
- **c)** Fluid filled catheter manometer system – insufficient detail for b): 0 points

2. Sequence of aortic and brachial BP measurements

- **a)** Simultaneous: 1 point OR
- **b)** sequential, describing the time between measurements and that no major hemodynamic changes occurred: 1 point OR
- **c)** sequential, insufficient detail for b): 0 points

3. Position of catheter in aorta/brachial artery

- a) described with sufficient detail to ascertain position (aortic BP was required to be measured in the proximal aorta or aortic arch): 1 point OR
- b) general description: 0 points

4. Pressure wave capture length

- **a)** > 1 beat of continuously captured data, with a description that the recording was of good quality (i.e. period of capture was stable): 1 point OR
- **b)** 1 beat: 0 points OR
- **c)** or no description: 0 points

5. Participant characteristics

- **a)** description of patient inclusion/exclusion criteria (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 1 point OR
- **b)** detailed description of the patient clinical characteristics (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 1 point OR

c) no, or poor, description of the patient inclusion/exclusion criteria (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 0 points OR

d) no or poor description of patient clinical characteristics (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 0 points

Meta-analysis 2

A study quality score was developed to assess each study included in the meta-analysis. The scoring system considered six study attributes and one point was awarded per attribute when the highest standard was achieved. If the highest standard was not achieved for an attribute, then a zero was assigned for that attribute. Thus, a study could achieve a score from 0 to 6 points. A description is presented below.

1. Type of catheter used

a) micromanometer tip: 1 point OR

b) fluid filled catheter manometer system – description of frequency and damping characteristics: 1 point OR

c) Fluid filled catheter manometer system – insufficient detail for b): 0 points

2. Sequence of brachial cuff and intra-arterial brachial BP measurement protocol

a) Simultaneous: 1 point OR □

b) sequential, describing the time between measurements and that no major hemodynamic changes occurred: 1 point OR □

c) sequential, insufficient detail for b): 0 points

3. Position of catheter in brachial artery

a) described with sufficient detail to ascertain position: 1 point OR

b) general description: 0 points

4. Pressure wave capture length

a) > 1 beat of continuously captured data, with a description that the recording was of good quality (i.e. period of capture was stable): 1 point OR

b) 1 beat: 0 points OR

c) or no description: 0 points

5. Patient characteristics description

a) description of patient inclusion/exclusion criteria (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 1 point OR

b) detailed description of the patient clinical characteristics (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 1 point OR

c) no, or poor, description of the patient inclusion/exclusion criteria (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 0 points OR

d) no or poor description of patient clinical characteristics (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 0 points

Meta-analysis 3

A study quality score was developed to assess the risk of bias for each study included in the meta-analysis. The scoring system considered five study attributes and one point was awarded per attribute when the highest standard was achieved. If the highest standard was not achieved for an attribute, then a zero was assigned for that attribute. Thus, a study could achieve a score from 0 to 5 points. A description is presented below.

1. Type of catheter

a) micromanometer tip: 1 point OR

b) fluid filled catheter manometer system – description of frequency and damping characteristics: 1 point OR

c) Fluid filled catheter manometer system – insufficient detail for b): 0 points

2. Sequence of aortic and brachial BP measurements

a) Simultaneous: 1 point OR

b) sequential, describing the time between measurements and that no major hemodynamic changes occurred: 1 point OR

c) sequential, insufficient detail for b): 0 points

3. Position of catheter in aorta/brachial artery

a) described with sufficient detail to ascertain position (aortic BP was required to be measured in the proximal aorta or aortic arch): 1 point OR

b) general description: 0 points

4. Pressure wave capture length

a) > 1 beat of continuously captured data, with a description that the recording was of good quality (i.e. period of capture was stable): 1 point OR

b) 1 beat: 0 points OR

c) or no description: 0 points

5. Participant characteristics

a) description of patient inclusion/exclusion criteria (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 1 point OR

b) detailed description of the patient clinical characteristics (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 1 point OR

c) no, or poor, description of the patient inclusion/exclusion criteria (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 0 points OR

d) no or poor description of patient clinical characteristics (with reference to conditions that may cause hemodynamic instability / difficulty to obtain accurate measurements): 0 points

Appendix 1.4 Additional statistical methods

Mean absolute difference was calculated as the absolute value of the BP difference at the individual participant level. This approach provides a measure of agreement between a "predicted" value (cuff BP) and "observed" value (intra-arterial BP). Linear mixed modelling was used for one-stage meta-analysis to account for the clustering of individuals within studies.

Each individual data set was normally distributed except for mean absolute difference data which were square root transformed to obtain normal distributions and back transformed for presentation.

In several studies, multiple brachial cuff devices were tested on the same subjects. In each of these cases, the preference was to use mercury sphygmomanometry data, because this is the current brachial cuff reference standard. This protocol was used to ensure that each subject was included once in the analysis so that there was not greater weighting toward certain data where variance may be reduced due to data being from the same subject.

Subject characteristic analysis (Online Tables 13-15) was derived from individual data, and in the cases that this was unavailable, aggregate data extracted from published studies was used. Therefore, two-stage meta-analysis was used to calculate the subject characteristics.

Using linear mixed modelling, clinical and demographic factors (Online Tables 19-20) were assessed to determine correlations and potential predictors of the difference between cuff BP and intra-arterial brachial or aortic BP. This analysis was performed in a subset of studies where the variables (e.g. age, sex, body mass index) were available.

Sensitivity analyses were among studies that received the maximum study quality score to assess whether results were influenced by study design factors (Online Tables 20-22) and separately to assess published, compared with unpublished data sources (Online Tables 23-25). These analyses were completed using linear mixed modelling, with the study score or publication status included as a variable (0=non-maximum rated study, 1=maximum rated study and 0=published, 1=published). Linear mixed models were also used for sensitivity analysis of the number of cuff BP measures (0=single cuff BP or uncertain, 1=average of multiple cuff BP) and type of catheter (0=fluid-filled, 1=micromanometer-tipped). BP classification analysis was performed separately for single cuff BP (or uncertain number of measurements) compared with average of multiple cuff BP measurements.

Appendix 1.5 Reasons for discrepancies between number of subjects analyzed with number of subjects reported in publication.

Meta-analysis 1

Kavanagh-Gray, 1964[71]

50 subjects in publication, 49 used in analysis.

One extreme data point judged to be non-physiological was identified whereby aortic SBP was 120 mm Hg and brachial SBP 250 mm Hg. [71] The subject was a 24-year-old male with aortic valvular incompetence. This data was extracted from a published table and we were unable to contact the relevant author to verify this result and, therefore, removed this subject from all analyses.

Meta-analysis 2

Bos et al, 1992[69]

76 subjects in publication, 57 used in analysis.

Group A (n=19) was excluded because the intra-arterial BP was measured in the aorta.

Gelman et al, 1981[156]

20 subjects in publication, 5 used in analysis.

Data was extracted from a table in the publication (see Appendix 1.2), however, individual data was only reported for five subjects.

Gould et al, 1984[157]

26 subjects in publication, 28 used in analysis.

Extra data available from the raw thesis data provided.

Melamed et al, 2012[159]

53 subjects in publication, 3 used in analysis.

47 patients excluded because the radial artery was used for intra-arterial BP measurement. A further three subjects were excluded due to data being recorded in the presence of a blood conserving device that was determined to influence the natural frequency of the intra-arterial pressure system and therefore may affect the accuracy of these measurements.

Muecke et al, 2009[38]

18 subjects in publication, 2 used in analysis.

16 patients excluded because the radial artery was used for intra-arterial BP measurement.

Sagiv et al, 1999[163]

14 subjects in publication, 12 used in analysis.

Data was extracted from a scatter plot (see Appendix Table 1.3), however, could not be extracted for two subjects.

Vardan et al, 1983[164]

26 subjects in publication, 24 used in analysis.

Data was extracted from a scatter plot (see Appendix Table 1.3), however, could not be extracted for two subjects.

Meta-analysis 3

Aakhus et al, 1993[165]

26 subjects in publication, 28 used in analysis.

Extra data was available from the author that was not used in the original publication.

Bos et al, 1992[69]

76 subjects in publication, 19 used in analysis.

Groups B, C and D (n=13, 15, 29) were excluded because the intra-arterial BP was measured in the brachial artery.

Cremer et al, 2012

145 subjects in publication, 144 used in SBP analysis, 142 in DBP and PP analysis.

One data point unavailable for all analysis. 2 subjects did not have intra-arterial DBP available.

Laugesen et al 2014[118]**/Rossen et al, 2014**[149]

34 subjects in Laugesen et al, 22 in Rossen et al. 37 total used in analysis.

Data were pooled for analysis due to use of identical study protocols except for the type of cuff BP device. Many subjects were included in both studies, therefore, all data from Laugesen et al was used, and additional subjects from the Rossen et al study were subsequently pooled for the analysis.

Lin AC et al, 2012 [170]

37 subjects in publication, 35 used in analysis.

2 subjects excluded due to intra-arterial aortic BP recording in subclavian root.

Lowe et al, 2009[171]

16 subjects in publication, 37 used in analysis.

Extra data was available from the author that was not used in the original publication.

Pucci et al, 2013[178]

50 subjects in publication, 58 used in analysis.

8 subjects excluded from publication due to poor quality radial tonometry waveforms. These are included in the current analysis because the brachial cuff and intra-arterial aortic BP data was good quality.

Saul et al, 1995[180]

100 subjects in publication, 97 used in analysis.

Data was extracted from a scatter plot (see Appendix Table 1.3), however, could not be extracted for three subjects.

Smulyan et al, 2003[181]

50 subjects in publication, 25 used in analysis.

25 subjects excluded due to recording of intra-aortic BP from the descending aorta.

Takazawa et al, 2012[186]

66 subjects in publication, 52 used in analysis.

14 subjects excluded due to identical data in Takazawa et al, 2007[185].

Weber et al, 1999[187]

33 subjects in publication, 36 used in analysis.

Extra data was available from the author that was not used in the original publication.

Appendix Table 1.1 Preferred Reporting Items for Systematic Reviews and Meta-analyses- individual participant data checklist.

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	26
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	27
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	28
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons,	28

		outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	Protocol available on request
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	29
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	29
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Table 1.2
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	29-30
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	30

		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardizing or translating variables within the IPD datasets to ensure common scales or measurements across studies.	30
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	30, Appendix Table 1.3
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	30-31
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	29-31
Synthesis methods	14	Describe the meta-analysis methods used to synthesize IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable).	31 Appendix 1.4

		• Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analyzed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analyzed as potential effect modifiers, and whether these were pre-specified.	30-31
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	29-31
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	31
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	32, Appendix Figures 1.1-1.6

Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	Tables 2.1.-2.3
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	32
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	Appendix Tables 1.16-1.21
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Figures 2.1-2.3
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	36, Figures 2.1-2.3
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	

Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	Appendix Tables 1.16-1.21
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarize the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	58, Online Tables 13-21
Discussion			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome.	58-62
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	61-62
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	62
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	58-62
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	No funding

Appendix Table 1.2 Systematic review search terms.

A search of four online databases (PubMed [Medline], Scopus, Web of Knowledge and Embase) was conducted from the earliest available records to 9 May 2016. There were slight modifications of the search terms for each meta-analysis, as outlined in this table. The search terms were similar across the databases, with the exception of differences in the controlled language between each. Manual searches of reference lists within identified articles were also undertaken.

Meta-analysis 1. Intra-arterial aortic and intra-arterial brachial BP	
PubMed	(((invasive OR invasively OR intra arterial OR direct OR true OR catheter* OR simultaneous* OR pull back OR needle OR wire)) AND (aorta OR aortic OR central)) AND (brachi* OR ((upper) AND (limb OR arm)) OR peripher*)) AND (pulse OR arterial pressure [MeSH Major Topic] OR pressure* OR blood pressure determination [MeSH Major Topic]))))) NOT (animals [mh] not (humans [mh] and animals [mh])))
Scopus	TITLE-ABS-KEY (invasive*) OR TITLE-ABS-KEY (intra arterial) OR TITLE-ABS-KEY (direct) OR TITLE-ABS-KEY (true) OR TITLE-ABS-KEY (catheter*) OR TITLE-ABS-KEY (simultaneous*) OR TITLE-ABS-KEY (pull back) OR TITLE-ABS-KEY (needle) OR TITLE-ABS-KEY (wire) AND TITLE-ABS-KEY (aorta) OR TITLE-ABS-KEY (aortic) OR TITLE-ABS-KEY (central) AND TITLE-ABS-KEY (brachi*) OR TITLE-ABS-KEY ((upper) AND (limb OR arm)) OR TITLE-ABS-KEY (peripher*) AND TITLE-ABS-KEY (pressure*) OR TITLE-ABS-KEY (pulse) OR INDEXTERMS (blood pressure determination) OR INDEXTERMS (arterial pressure) AND SRCTYPE (j) AND KEY (human*) AND (EXCLUDE (DOCTYPE , "re"))
Web of Knowledge	((invasive OR invasively OR intra arterial OR direct OR true OR catheter* OR simultaneous* OR pull back OR needle OR wire) AND (aorta OR aortic OR central) AND ((brachi* OR ((upper) AND (limb OR arm)) OR peripher*)) AND (pulse OR pressure*)) Refined by: RESEARCH AREAS: (CARDIOVASCULAR SYSTEM CARDIOLOGY) AND [excluding]DOCUMENT TYPES: (REVIEW) Timespan: All years. Search language=Auto

Appendix Table 1.2 (continued)

Embase	invasive OR invasively OR intra AND arterial OR direct OR true OR catheter* OR simultaneous* OR (pull AND back) OR needle OR wire AND (aorta OR aortic OR central) AND (brachi* OR (upper AND (limb OR arm)) OR peripher*) AND (pulse OR pressure* OR blood AND pressure AND measurement OR 'arterial pressure') NOT (animal NOT (human AND animal)) AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim)
Meta-analysis 2. Cuff BP and intra-arterial brachial BP	
PubMed	(((invasive OR invasively OR intra arterial OR direct OR true OR catheter* OR simultaneous* OR needle OR wire OR blood pressure determination [MeSH Major Topic]) AND (noninvasive OR indirect OR oscillometr* OR cuff OR auscultat* OR accura* OR casual OR office OR clinic) AND (brachi* OR ((upper) AND (limb OR arm)) OR peripher* OR oscillometr* OR cuff OR auscultat* OR sphygmomano* OR korotko*) AND (pulse OR arterial pressure [MeSH Major Topic] OR pressure*))) NOT (animal* NOT (human AND animal))
Scopus	TITLE-ABS-KEY (invasive) OR TITLE-ABS-KEY (invasively) OR TITLE-ABS-KEY (intra arterial) OR TITLE-ABS-KEY (direct) OR TITLE-ABS-KEY (true) OR TITLE-ABS-KEY (catheter*) OR TITLE-ABS-KEY (simultaneous*) OR TITLE-ABS-KEY (needle) OR TITLE-ABS-KEY (wire) OR INDEXTERMS (blood pressure determination) AND TITLE-ABS-KEY (noninvasive) OR TITLE-ABS-KEY (indirect) OR TITLE-ABS-KEY (oscillometr*) OR TITLE-ABS-KEY (cuff) OR TITLE-ABS-KEY (auscultat*) OR TITLE-ABS-KEY (accura*) OR TITLE-ABS-KEY (casual) OR TITLE-ABS-KEY (office) OR TITLE-ABS-KEY (clinic) AND TITLE-ABS-KEY (brachi*) OR TITLE-ABS-KEY ((upper) AND (limb OR arm)) OR TITLE-ABS-KEY (peripher*) OR TITLE-ABS-KEY (oscillomet*) OR TITLE-ABS-KEY (cuff) OR TITLE-ABS-KEY (auscultat*) OR TITLE-ABS-KEY (korotko*) OR TITLE-ABS-KEY (sphygmomanomet*) AND TITLE-ABS-KEY (pressure*) OR TITLE-ABS-KEY (pulse) OR INDEXTERMS (arterial pressure) AND SRCTYPE (j) AND KEY (human*)

Appendix Table 1.2 (continued)

Web of Knowledge	invasive OR invasively OR intra arterial OR direct OR true OR catheter* OR simultaneous* OR needle OR wire OR 'blood pressure determination') AND (noninvasive OR indirect OR oscillometr* OR cuff OR auscultat* OR accura* OR casual OR office OR clinic) AND (brachi* OR ((upper) AND (limb OR arm)) OR peripher* OR oscillometr* OR cuff OR auscultat* OR sphygmomano* OR korotko*) AND (pulse OR 'arterial pressure' OR pressure*))) NOT (animal* NOT (human AND animal))) Refined by: RESEARCH AREAS: (CARDIOVASCULAR SYSTEM CARDIOLOGY) Timespan: All years. Search language=Auto
Embase	invasive OR invasively OR intra AND arterial OR direct OR true OR catheter* OR simultaneous* OR needle OR wire OR 'blood pressure measurement' AND (noninvasive OR indirect OR oscillometr* OR cuff OR auscultat* OR accura* OR casual OR office OR clinic) AND (brachi* OR (upper AND (limb OR arm)) OR peripher* OR oscillometr* OR cuff OR auscultat* OR sphygmomano* OR korotko*) AND (pulse OR 'arterial pressure' OR pressure*) NOT (animal* NOT ('human' AND 'animal'))
Meta-analysis 3.	Cuff BP and intra-arterial aortic BP
PubMed	((invasive OR invasively OR intra arterial OR direct OR true OR catheter* OR simultaneous* OR pull back OR needle OR wire)) AND (aorta OR aortic OR central)) AND (brachi* OR ((upper) AND (limb OR arm)) OR peripher* OR oscillometr* OR cuff OR auscultat* OR korotko* OR sphygmoman* OR noninvasive OR indirect)) AND (pulse OR arterial pressure[MeSH Major Topic] OR pressure* OR blood pressure determination[MeSH Major Topic]))))) NOT (animals [mh] not (humans [mh] and animals [mh]))
Scopus	TITLE-ABS-KEY (invasive*) OR TITLE-ABS-KEY (intra arterial) OR TITLE-ABS-KEY (direct) OR TITLE-ABS-KEY (true) OR TITLE-ABS-KEY (catheter*) OR TITLE-ABS-KEY (simultaneous*) OR TITLE-ABS-KEY (pull back) OR TITLE-ABS-KEY (needle) OR TITLE-ABS-KEY (wire) AND TITLE-ABS-KEY (aorta) OR TITLE-ABS-KEY (aortic) OR TITLE-ABS-KEY (central) AND TITLE-ABS-KEY (brachi*) OR TITLE-ABS-KEY ((upper) AND (limb OR arm)) OR TITLE-ABS-

Appendix Table 1.2 (continued)

	KEY (peripher*) OR TITLE-ABS-KEY (oscillomet*) OR TITLE-ABS-KEY (cuff) OR TITLE-ABS-KEY (auscultat*) OR TITLE-ABS-KEY (korotko*) OR TITLE-ABS-KEY (sphygmomanomet*) OR TITLE-ABS-KEY (noninvasive) OR TITLE-ABS-KEY (indirect) AND TITLE-ABS-KEY (pressure*) OR TITLE-ABS-KEY (pulse) OR INDEXTERMS (blood pressure determination) OR INDEXTERMS (arterial pressure) AND SRCTYPE (j) AND KEY (human*) AND (EXCLUDE (DOCTYPE , "re"))
Web of Knowledge	invasive OR invasively OR intra arterial OR direct OR true OR catheter* OR simultaneous* OR pull back OR needle OR wire) AND (aorta OR aortic OR central) AND ((brachi* OR ((upper) AND (limb OR arm)) OR peripher* OR oscillometr* OR cuff OR auscultat* OR korotko* OR sphygmoman* OR noninvasive OR indirect)) AND (pulse OR pressure*)))) Refined by: RESEARCH AREAS: (CARDIOVASCULAR SYSTEM CARDIOLOGY) AND [excluding]DOCUMENT TYPES: (REVIEW) Timespan: All years. Search language=Auto
Embase	invasive OR invasively OR intra AND arterial OR direct OR true OR catheter* OR simultaneous* OR (pull AND back) OR needle OR wire AND (aorta OR aortic OR central) AND (brachi* OR (upper AND (limb OR arm)) OR peripher* OR oscillometr* OR cuff OR auscultat* OR korotko* OR sphygmoman* OR noninvasive OR indirect) AND (pulse OR pressure* OR blood AND pressure AND measurement OR 'arterial pressure') NOT (animal NOT (human AND animal)) AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim)

Appendix Table 1.3 Validation of individual data extracted from scatter plots.

Meta-analysis 1.					
Study name	Intra-arterial brachial SBP (mm Hg)	Intra-arterial aortic SBP (mm Hg)	Brachial - aortic SBP (mm Hg)	Correlation coefficient	Published figure used for data extraction
Kobayashi et al, 2013[14] (published data)	141.8 ± 19.8	140.1 ± 18.5	1.7 ± 5.2	0.97	Figure 4 on page 1678 of the publication. Intra-arterial brachial SBP was on the x-axis and intra-arterial aortic SBP on the y-axis.
Kobayashi et al, 2013 (extracted data)	141.6 ± 18.9	140.0 ± 20.8	1.6 ± 5.4	0.97	
Meta-analysis 2.					
Study name	Cuff SBP (mm Hg)	Intra-arterial brachial SBP (mm Hg)	Cuff – intra-arterial brachial SBP (mm Hg)	Correlation coefficient	Published figure used for data extraction
Blank et al, 1988[154] (published data)			-15	0.94	Figure 4 (left), on page 1301 of the publication. Intra-arterial brachial SBP was on the x-axis and brachial cuff (auscultatory) SBP on the y-axis.
Blank et al, 1988 (extracted data)	138.4 (38.1)	152.7 (35)	-14.3	0.95	

Appendix Table 1.3 (continued)

Kobayashi et al, 2013[14] (published data)	133.5 (18.6)	141.8 (19.8)	-8.3 (8.7)	0.89	Figure 3 (left), on page 1677 of the publication. Brachial cuff SBP was on the x-axis and intra-arterial brachial SBP on the y-axis.
Kobayashi et al, 2013 (extracted data)	133.5 (18.6)	141.6 (19.3)	-8.2 (8.8)	0.89	
Sagiv et al, 1999[163] (published data)	107 (7)	101 (6)	-	0.68	Figure 1 (top left), on page 277 of the publication. Intra-arterial brachial SBP was on the x-axis and brachial cuff (auscultatory) SBP on the y-axis.
Sagiv et al, 1999 (extracted data)	106 (8)	100 (5)	-	0.67	
Vardan et al, 1983[164] (published data)	183.1 (17.6)	182.2 (21.0)	-	-	Figure (top left) on page 937 of the publication. Brachial cuff SBP was on the x-axis and intra-arterial brachial SBP on the y-axis. The 'x' plot markers, which corresponded to the first SBP measurement were extracted.
Vardan et al, 1983 (extracted data)	183.6 (17.9)	181.6 (22.1)	-	-	

Appendix Table 1.3 (continued)

Meta-analysis 3.					
Study name	Cuff SBP (mm Hg)	Intra-arterial aortic SBP (mm Hg)	Cuff – intra-arterial aortic SBP (mm Hg)	Correlation coefficient	Published figure used for data extraction
Davies et al, 2003[12] (published data)	137.0 (26)	134.0 (28)	3.4 (10.5)	0.92	Figure 2 (top), on page 574 of the publication. Intra-arterial aortic SBP was on the x-axis and brachial cuff SBP on the y-axis.
Davies et al, 2003 (extracted data)	137.2 (27)	133.8 (26)	3.4 (10.4)	0.92	
Kobayashi et al, 2013[14] (published data)	133.5 (18.6)	138.1 (18.5)	-4.7 (9.0)	0.88	Figure 2 (left), on page 1677 of the publication. Brachial cuff SBP was on the x-axis and intra-arterial aortic SBP on the y-axis.
Kobayashi et al, 2013 (extracted data)	133.5 (18.6)	138.3 (18.5)	-4.8 (9.1)	0.88	
Saul et al, 1995[180] (published data)	150.0	149.0	0.9 (11.1)	0.91	Figure 2 (top, labelled Abb. 2 in publication). Brachial cuff SBP (labelled RR syst. Oberarm links) was on the x-axis and intra-arterial aortic SBP (labelled RR syst. Aorta) on the y-axis.
Saul et al, 1995 (extracted data)	150.3	149.2	1.0 (11.4)	0.91	

Appendix Table 1.4 Individual quality scores of each study included in meta-analysis 1.

Study	Type of catheter	Sequence of aortic and brachial blood pressure measurements	Position of catheter in aorta/brachial artery	Pressure wave capture length	Participant characteristics	Total
Cheng et al, 2010[11]	1	1	1	1	1	5
Cheng et al, unpublished	1	1	1	1	1	5
Davies et al, 2010[15]	1	0	1	1	1	4
Ding et al, 2013[16]	1	1	1	1	1	5
Gould and Shariff, 1969[157]	0	0	1	0	1	2
Kavanagh-Gray, 1964[71]	0	0	1	0	1	2
Kelly et al, 1990[22]	1	1	1	0	1	4
Kobayashi et al, 2013[14]	1	0	1	0	1	3
Liang et al, 2015[151]	1	1	1	1	1	5
Lin et al, 2012[152]	1	1	1	1	1	5
Picone et al, unpublished	1	1	1	1	1	5
Pucci et al, unpublished	0	1	1	1	1	4
Westerhof et al, 2008[153]	1	1	1	0	0	3

The study quality score was developed in consideration of 5 study attributes. One point was awarded per attribute when the highest standard was achieved, whilst if the highest standard was not achieved then a zero was assigned for that attribute. The maximum score of 5/5 indicated the highest study quality. Studies with a rating of 5/5 were used in sensitivity analysis to assess any impact of study protocols on the analysis.

Appendix Table 1.5 Individual quality scores of each study included in meta-analysis 2.

Study	Type of catheter	Sequence of measurement protocol	Position of catheter in brachial artery	Pressure wave capture length	Participant characteristics description	Arm used or description of differences	Total
Berliner et al, 1961[19]	0	1	1	1	1	1	5
Blank et al, 1988[154]	0	1	1	0	0	1	3
Bos et al, 1992*[69]	1	1	1	1	1	0/1	5/6
Cheng et al, 2010[11]	1	1	1	1	1	1	6
Cheng et al, unpublished	1	1	1	1	1	1	6
Ding et al, 2013[16]	1	1	1	1	1	1	6
Freis et al, 1968[155]	0	1	1	0	1	1	4
Gelman et al, 1981[156]	0	0	1	0	0	1	2
Gould et al, 1984[157]	0	1	1	1	0	1	4
Hayashi et al, 2014[158]	1	1	1	1	1	0	5
Hunyor et al, 1978[10]	0	1	1	1	1	1	5
Kobayashi et al,	1	1	1	1	1	0	5
Lin et al, 2012[152]	1	1	1	1	1	1	6
Melamed et al,	0	1	1	1	1	1	5
Muecke et al, 2009[160]	1	1	1	1	1	1	6
Omboni et al, 1997[161]	0	1	1	1	1	0	4

Appendix Table 1.5 (continued)

Picone et al, unpublished	1	1	1	1	1	1	6
Pucci et al, unpublished	0	1	1	1	1	1	5
Raftery and Ward, 1968[162]	1	1	1	0	0	1	4
Roberts et al, 1953[68]	0	1	1	0	0	1	3
Sagiv et al, 1999[163]	1	1	1	1	1	0	5
Vardan et al, 1983[164]	1	1	1	0	0	0	3

The study quality score was developed in consideration of 6 study attributes. One point was awarded per attribute when the highest standard was achieved, whilst if the highest standard was not achieved then a zero was assigned for that attribute. The maximum score of 6/6 indicated the highest study quality. Studies with a rating of 6/6 were used in sensitivity analysis to assess any impact of study protocols on the analysis. *In the study of Bos et al, 1992, 13/57 patients had an inter-arm BP difference > 5mm Hg and thus received a study quality score of 5/6. From the same study, 46/57 patients had an inter-arm BP difference < 5mm Hg and received a study quality score of 6/6.

Appendix Table 1.6 Individual quality scores of each study included in meta-analysis 3.

Study	Type of catheter	Sequence of measurement protocol	Position of catheter in aorta	Pressure wave capture length	Participant characteristics description	Total
Aakhus et al, 1993[165]	0	0	1	1	1	3
Bhatt et al, 2011[166]	0	1	1	1	1	4
Borow et al, 1982[167]	0	1	1	1	1	4
Bos et al, 1992[69]	1	1	1	1	1	5
Broyd et al, unpublished	0	1	1	1	1	4
Cheng et al, 2010[11]	1	1	1	1	1	5
Cheng et al, unpublished	1	1	1	1	1	5
Costello et al, 2015[168]	0	1	1	1	1	4
Cremer et al, 2012[169]	1	1	1	1	1	5
Davies et al, 2003[12]	0	1	1	1	1	4
Ding et al, 2013[16]	1	1	1	1	1	5
Kobayashi et al, 2013[14]	1	1	1	0	1	4
Korolkova et al, unpublished	0	1	1	1	1	4

Appendix Table 1.6 (continued)

Laugesen[118]/Rossen et al[149], 2014	0	1	1	1	1	4
Lin AC et al, 2012[170]	0	1	1	1	1	4
Lin MM et al, 2012[152]	1	1	1	1	1	5
Lowe et al, 2009[171]	0	1	1	1	1	4
Milne et al, 2015[114]	1	1	1	1	1	5
Nagle et al, 1966[172]	0	1	1	0	1	3
Nakagomi et al, 2016[173]	0	1	1	1	1	4
Ohte et al, 2007[174]	1	1	1	1	1	5
Ott et al, 2012[175]	0	0	1	1	1	3
Park et al, 2014[176]	1	1	1	1	1	5
Pereira et al, 2014[177]	0	1	1	1	1	4
Picone et al, unpublished	1	1	1	1	1	5
Pucci et al, 2013[178]	0	1	1	1	1	4
Pucci et al, unpublished	0	1	1	1	1	4
Rajani et al, 2008[179]	1	1	1	1	1	5
Saul et al, 1995[180]	0	1	1	1	0	3
Smulyan et al, 2003[181]	1	1	1	1	1	5
Smulyan et al, 2008[182]	0	1	1	1	1	4

Appendix Table 1.6 (continued)

Smulyan et al, 2010[183]	1	1	1	1	1	5
Sueta et al, 2015[184]	0	1	1	0	0	2
Takazawa et al, 2007[185]	1	1	1	1	1	5
Takazawa et al, 2012[186]	1	1	1	1	1	5
Weber et al, 1999[187]	1	1	1	1	0	4
Weber et al, 2011[188]	1	1	1	1	1	5
Williams et al, 2011[189]	1	1	1	1	1	5

The study quality score was developed in consideration of 5 study attributes. One point was awarded per attribute when the highest standard was achieved, whilst if the highest standard was not achieved then a zero was assigned for that attribute. The maximum score of 5/5 indicated the highest study quality. Studies with a rating of 5/5 were used in sensitivity analysis to assess any impact of study protocols on the analysis.

Appendix Table 1.7 Details of each study included in meta-analysis 1.

No	Study	n	Age (years)	Male (%)	Measurement protocol	Catheter type	Pressure wave capture time	Study exclusion criteria
1	Cheng et al, 2010 [11]	100	62.1 ± 12.6	78	Sequential (brachial to aorta)	Micromanometer tip	Aorta: 30 beats Brachial: 20-30 beats	Acute coronary syndrome, peripheral arterial disease, abnormal sinus rhythm and > 3mm Hg pressure difference between left and right arms
2	Cheng et al, unpublished	15	61.6 ± 13.9	70	Sequential (brachial to aorta)	Micromanometer tip	Aorta: 30 beats Brachial: 20-30 beats	Same as No 1 (Cheng et al, 2010)
3	Davies et al, 2010 [15]	12	54 ± 10	67	Simultaneous	Micromanometer tip	1 minute	Previous coronary intervention, valvular pathology, regional wall motion abnormality, arrhythmia, use of nitrates < 24hrs before procedure
4	Ding et al, 2013 [16]	33	60.1 ± 8.7	64	Simultaneous	Fluid-filled	At least 10 stable beats	Failure to measure central SBP, arrhythmia, severe valvular disease, heart failure defined as left ventricular ejection fraction <50%, >5 mm Hg difference in SBP between left and right arms

5	Gould and Shariff, 1969 [150]	23	N/A	N/A	Unclear	Fluid-filled	Not reported	None reported
6	Kavanagh-Gray, 1964 [71]	49	31.4 ± 16.5	48	"Either simultaneously or in quick succession"	Fluid-filled	Not reported	None reported
7	Kelly et al, 1990 [22]	14	53.7 ± 9.8	93	Sequential (brachial to aorta)	Micromanometer tip	Not reported	None reported. Note: no patients had evidence of valvular disease or left ventricular dysfunction
8	Kobayashi et al, 2013 [14]	20	68.9 ± 8.1	65	Sequential (aorta to brachial)	Micromanometer tip	Not reported	>10 mm Hg difference in BP between left and right arms
9	Liang et al, 2015 [151]	40	63.0 ± 10.9	60	Sequential (brachial to aorta)	Micromanometer tip	10 stable beats	>10% variation of heart rate or mean arterial pressure during measurements
10	Lin et al, 2012 [152]	78	65.9 ± 12.9	80	Simultaneous	Micromanometer tip	At least two respiratory cycles / at least 20 beats	Acute coronary syndrome, peripheral arterial disease, abnormal sinus rhythm

11	Picone et al, unpublished	52	60.5 ± 10.3	68	Sequential (aorta to brachial)	Fluid-filled	Aorta and brachial 20 seconds of stable data	>5 mm Hg difference in BP between left and right arms
12	Pucci et al, unpublished	29	68.3 ± 10.9	86	Sequential (brachial to aorta)	Fluid-filled	At least 10 seconds	History of peripheral arterial disease, aortic aneurysm, absent brachial or radial pulses or known obstructive large artery atherosclerotic disease, active malignancy, hypotension (<90 mm Hg), valvular heart disease, known left ventricular dysfunction (ejection fraction <50%) or arrhythmias (including frequent ventricular and supraventricular premature beats)
13	Westerhof et al, 2008 [153]	50	51.3 ± 8.5	86	Sequential (brachial to aorta)	Fluid-filled	One beat	None reported

Data are mean ± standard deviation, n or percentage. SBP, systolic blood pressure

Appendix Table 1.8 Details of the studies included in meta-analysis 2.

No	Study	n	Age (years)	Male (%)	Brachial cuff method	Intra-arterial measurement method	Pressure wave capture time
1	Berliner et al, 1961[19]	100	55.8 ± 13.2	56	Mercury sphygmomanometry	20 Gauge needle and electromanometer	50-80 seconds pre non-intra-arterial BP and 20-30 seconds during non-invasive BP
2	Blank et al, 1988[154]	11	-	-	Mercury sphygmomanometry	Fluid-filled or micromanometer tip	Unclear
3	Bos et al, 1992 (groups B, C, D)[69]	57	61 (52-83)	61	Mercury sphygmomanometry	Fluid-filled	One beat corresponding to the non-invasive Korotkoff sounds
4	Cheng et al, 2010[11]	100	60 ± 11	74	Oscillometric device	Micromanometer tip	20-30 beats (at least two respiratory cycles)
5	Cheng et al, unpublished	14	61.6 ± 13.9	70	Oscillometric device	Micromanometer tip	20-30 beats (at least two respiratory cycles)
6	Ding et al, 2013[16]	33	60.1 ± 8.7	64	Oscillometric device	Fluid-filled	At least 10 stable beats

7	Freis et al, 1968[155]	6	Range: 26-38	100	Mercury sphygmomanometry	16 Gauge needle and strain gauge pressure transducer	One beat corresponding to the non-invasive Korotkoff sounds
8	Gelman et al, 1981[156]	5	63.1 ± 10.3	66	Auscultatory sphygmomanometry	Fluid-filled	Unclear
9	Gould et al, 1984[157]	28	50 (23-67)	75	Mercury sphygmomanometry	Fluid-filled	Unclear
10	Hayashi et al, 2014[158]	55	Unclear	Unclear	Oscillometric device	Fluid-filled	Unclear
11	Hunyor et al, 1978[10]	9	25-80	Unclear	Mercury sphygmomanometry	Fluid-filled	Average of 15 complexes immediately preceding cuff inflation
12	Kobayashi et al, 2013[14]	20	68.9 ± 8.1	65	Oscillometric device	Micromanometer tip	Unclear
13	Lin et al, 2012[152]	78	61 ± 10	83	Oscillometric device	Micromanometer tip	Mean of 10 stable consecutive pulses immediately prior to brachial BP measurement
14	Melamed et al, 2012[159]	3	68.7 ± 9.6	50	Oscillometric device	Fluid-filled	10 seconds
15	Muecke et al, 2009[160]	2	38.5 ± 19.1	100	Oscillometric device	Fluid-filled	60 seconds

16	Omboni et al, 1997[161]	12	45.9 ± 10.8	75	Mercury sphygmomanometry	Fluid-filled	Unclear – non-invasive brachial BP taken every 2 minutes over a 20 min period
17	Picone et al, unpublished	40	61.4 ± 10.9	70	Oscillometric device	Fluid-filled	Average of 20 seconds of stable data
18	Pucci et al, unpublished	29	68.3 ± 10.9	86	Oscillometric device	Fluid-filled	
19	Raftery and Ward, 1968[162]	50	26.7 (18-44)	0	Mercury sphygmomanometry	Thin walled needle and inductance manometer	Unclear
20	Roberts et al, 1953[68]	47	Unclear	Unclear	Mercury sphygmomanometry	Cournand needle and electromanometer	Unclear
21	Sagiv et al, 1999[163]	12	60.4	82	Mercury sphygmomanometry	Fluid-filled	Several respiratory cycles
22	Vardan et al, 1983[164]	24	59.4 ± 10.9	53	Mercury sphygmomanometry	Fluid-filled	Unclear

Details of the studies included in meta-analysis 2 (Appendix Table 1.8 continued)

No	Measurement protocol	Study exclusion criteria	Same or different arms for measurement	DBP 4th or 5th Korotkoff sound
1	Simultaneous	Atrial fibrillation	Same	Unclear
2	Simultaneous	Unclear	Same	Unclear
3	Simultaneous	Left/right arm BP difference > 10 mm Hg, valvular disease or arrhythmia	Different	5th
4	Sequential (intra-arterial then brachial cuff BP)	Acute coronary syndrome, PAD, abnormal sinus rhythm and left/right arm BP difference >3mm Hg	Different	N/A
5	Sequential (intra-arterial then brachial cuff BP)	Acute coronary syndrome, peripheral arterial disease, abnormal sinus rhythm and >3mm Hg pressure difference between left and right arms	Different	N/A
6	Simultaneous	Failure to measure central systolic BP, arrhythmia, severe valvular disease, heart failure defined as left ventricular EF <50%, left/right arm BP difference >5mm Hg	Different	N/A
7	Simultaneous	Obesity or cardiovascular abnormalities	Same	4th
8	Sequential (intra-arterial then brachial cuff BP)	Unclear	Different	5th
9		Bundle branch block, pacemaker, severe aortic failure	Different	5th

10	Simultaneous	Moderate or severe mitral/aortic valve disease, LV outflow tract obstruction	Unclear	N/A
11	Simultaneous	None listed	Same	5th
12	Sequential (brachial cuff then intra-arterial)	Left/right arm BP difference > 10 mm Hg	Different	N/A
13	Sequential intra-arterial brachial then brachial cuff	Acute coronary syndrome, PAD, abnormal sinus rhythm and >3mm Hg pressure difference between L/R arms	Different	N/A
14	Simultaneous	Lower extremity catheter, inability to measure non-invasive BP in the same arm as the arterial line, lack of oscillations suitable for measurement despite optimal fast flush test technique	Same	N/A
15	Sequential (intra-arterial then brachial cuff)	Past history of hypertension or > 60 years of age. Participants were also excluded if arm circumference exceeded brachial cuff manufacturer recommendations (n=1) and if hypothermic (n=1)	Same	N/A
16	Simultaneous	"None of the patients had TOD or other major diseases in addition to HTN"	Different	5th
17	Simultaneous	>5 mm Hg difference between left and right arms.	Different	N/A
18	Simultaneous	History of peripheral arterial disease, aortic aneurysm, absent brachial or radial pulses or known obstructive large artery atherosclerotic disease, active malignancy, hypotension (<90 mm Hg), valvular heart disease,	Different	N/A

		known left ventricular dysfunction (ejection fraction <50%) or arrhythmias (including frequent ventricular and supraventricular premature beats)		
19	Simultaneous	Unclear	Same	5th
20	Simultaneous	Unclear	Same	5th
21	Simultaneous	None stated, however no participants were judged to have coronary artery disease or any major risk factors.	Different	5th
22	Simultaneous	Unclear	Different	5th

Data are presented as mean ± standard deviation, range (minimum-maximum) or percentage. BP, blood pressure; DBP, diastolic BP

Appendix Table 1.9 Details of the studies included in meta-analysis 3.

No	Study	n	Age (years)	Male (%)	Brachial cuff method	Intra-arterial measurement method	Pressure wave capture time
1	Aakhus et al, 1993[165]	28	62.9 ± 9.9	89	Oscillometric	Fluid-filled	At least five cardiac cycles (aortic)
2	Bhatt et al, 2011[166]	98	58 ± 12	55	Oscillometric	Fluid-filled	Not reported
3	Borow et al, 1982[167]	30	60 ± 11	73	Oscillometric	Fluid-filled	Not reported
4	Bos et al, 1992 (group A)[69]	19	63 ± 11.4	84	Mercury sphygmomanometer	Fluid-filled	Not reported
5	Broyd et al, unpublished	25	58.3 ± 10.2	72	Oscillometric	Fluid-filled	7-10 cardiac cycles
6	Cheng et al, 2010[11]	100	61.9 ± 13.2	74	Oscillometric	Micromanometer tip	30 seconds (aortic)
7	Cheng et al, unpublished	17	61.9 ± 13.2	74	Oscillometric	Micromanometer tip	30 seconds (aortic)
8	Costello et al, 2015[168]	40	63.1 ± 10.3	66	Oscillometric	Fluid-filled	10-15 seconds (aortic)
9	Cremer et al, 2012[169]	144	60.8 ± 12.7	66	Oscillometric	Fluid-filled	Mean of 5 consecutive beats (aortic)
10	Davies et al, 2003[12]	28	60 ± 10	71	Oscillometric	Fluid-filled	Unclear
11	Ding et al, 2013[16]	33	60.1 ± 8.7	64	Oscillometric	Fluid-filled	At least 10 stable beats
12	Kobayashi et al, 2013[14]	20	68.9 ± 8.1	65	Oscillometric	Micromanometer tip	Unclear

13	Korolkova et al, unpublished	14	68.8 ± 9.1	64	Oscillometric	Fluid-filled	7-10 cardiac cycles
14	Laugesen[118]/Rossen et al, 2014[149]	37	64.8 ± 10.4	84	Oscillometric	Fluid-filled	10 seconds
15	Lin AC et al, 2012[170]	35	64 ± 12	68	Oscillometric	Fluid-filled	Unclear
16	Lin MM et al, 2012[152]	78	64.1 ± 14	74	Oscillometric	Micromanometer tip	20-30 beats
17	Lowe et al, 2009[171]	37	N/A	N/A	Oscillometric	Fluid-filled	10 seconds
18	Milne et al, 2015[114]	9	10.5 ± 5	44	Aneroid sphygmomanometer	Micromanometer tip	5-10 seconds
19	Nagle et al, 1966[172]	2	48.5 ± 12	100	Auscultation	Fluid-filled	30-40 pressure pulses
20	Nakagomi et al, 2016[173]	139	66.7 ± 12.2	76	Oscillometric	Fluid-filled	At least 10 seconds
21	Ohte et al, 2007[174]	82	64.3 ± 9.4	79	Oscillometric	Micromanometer tip	Mean of 5 cardiac cycles
22	Ott et al, 2012[175]	52	63.7 ± 11	58	Oscillometric	Fluid-filled	Unclear
23	Park et al, 2014[176]	6	65 ± 20	67	Oscillometric	Micromanometer tip	7-10 cardiac cycles
24	Pereira et al, 2014[177]	15	62.1 ± 10.6	53	Oscillometric	Fluid-filled	15 seconds
25	Picone et al, unpublished	146	62.3 ± 10.6	70	Oscillometric	Fluid-filled	10 seconds
26	Pucci et al, 2013[178]	58	61 ± 11	62	Oscillometric	Fluid-filled	Unclear
27	Pucci et al, unpublished	29	68.3 ± 10.9	86	Oscillometric	Fluid-filled	Unclear

28	Rajani et al, 2008[179]	14	74 ± N/A	71	Oscillometric	Micromanometer tip	At least 20 consecutive waveforms
29	Saul et al, 1995[180]	97	59.3 ± N/A	69	Oscillometric	Fluid-filled	Unclear
30	Smulyan et al, 2003[181]	25	54.4 ± 12.4	52	Oscillometric	Micromanometer tip	Several respiratory cycles
31	Smulyan et al, 2008[182]	100	60.4 ± 11.9	82	Oscillometric	Fluid-filled	Several respiratory cycles
32	Smulyan et al, 2010[183]	25	57.2 ± 10.9	82	Oscillometric	Micromanometer tip	Several respiratory cycles
33	Sueta et al, 2015[184]	85	69.8 ± 10.0	74	Oscillometric	Unclear	Unclear
34	Takazawa et al, 2007[185]	18	61 ± 10	83	Oscillometric	Micromanometer tip	Mean of 10 stable consecutive pulses immediately prior to brachial BP measurement
35	Takazawa et al, 2012[186]	52	63.4 ± 9.7	74	Oscillometric	Micromanometer tip	10 stable consecutive pulses
36	Weber et al, 2011[188]	30	59 ± 11	87	Oscillometric	Micromanometer tip	3-4 minutes
37	Weber et al, 1999[187]	36	53.3 ± 10.4	85	Automatic Korotkoff sounds	Fluid-filled	10 beats (5 before oscillometric mark on trace and 5 after)
38	Williams et al, 2011[189]	20	61 ± 8.6	75	Oscillometric	Micromanometer tip	10, ten second blocks

Details of the studies included in meta-analysis 3 (Appendix Table 1.9 continued)

No	Measurement protocol	Study exclusion criteria
1	Sequential (brachial cuff then aorta then brachial cuff. Average of brachial cuff BP used in analysis)	Aortic valvular disease, arrhythmias, clinical signs of subclavian arterial disease (neck vessel murmurs or left or right arm pressure differences ≥ 10 mm Hg)
2	Simultaneous	Acute coronary syndrome, contraindication to BP cuff placement on either arm, arrhythmia, upper extremity arterial disease.
3	Simultaneous	"No patients had peripheral vascular disease"
4	Simultaneous	Valvular disease, arrhythmia
5	Simultaneous	Failure to obtain satisfactory intra-arterial and/or non-invasive waveforms
6	Sequential (intra-arterial aortic then brachial cuff)	Acute coronary syndrome, PAD, abnormal sinus rhythm and >3mm Hg pressure difference between L/R arms
7	Sequential (intra-arterial aortic then brachial cuff)	Acute coronary syndrome, PAD, abnormal sinus rhythm and >3mm Hg pressure difference between L/R arms
8	Sequential (oscillometric brachial then ascending aortic)	Unclear
9	Simultaneous	Bundle branch block, pacemaker, severe aortic failure
10	Sequential (oscillometric brachial then ascending aortic)	Left radial artery easily palpated and history of subclavian or brachial stenosis

11	Simultaneous	Failure to measure cSP, arrhythmia, severe valvular disease, heart failure defined as LV ejection fraction <50%, >5mm Hg difference in SBP between left and right arms
12	Simultaneous	>10 mm Hg difference in brachial BP
13	Simultaneous	Failure to obtain satisfactory intra-arterial and/or non-invasive waveforms
14	Sequential oscillometric brachial then ascending aortic	Atrial fibrillation or other cardiac arrhythmias, diagnosis of subclavian or brachial artery stenosis
15	Sequential	Age <30 or >80 years, atrial fibrillation or atrial flutter, aortic stenosis or aortic regurgitation of any severity, mitral stenosis or mitral regurgitation graded more than mild in severity, severe pulmonary hypertension, ventricular septal defect or other significant intracardiac shunt, aortic coarctation, ventricular pacemaker, hemodynamic instability, active ischemic symptoms, use of intravenous vasoactive or inotropic medications, history of coronary artery bypass surgery, history of aortic valve replacement, history of thoracic or abdominal aortic surgery and history of left mastectomy with axillary node dissection.
16	Simultaneous	Acute coronary syndrome, PAD, abnormal sinus rhythm and >3mm Hg pressure difference between L/R arms
17	Sequential oscillometric brachial then ascending aortic	Cardiovascular instability causing aortic and brachial mean pressure differences of > 9mm Hg
18	Sequential	Arrhythmia, clinical evidence of heart failure

19	Simultaneous	Unclear
20	Simultaneous	Prior coronary surgical revascularization, hemodynamically significant valvular heart disease, left ventricular outflow tract obstruction and renal insufficiency, patients with arrhythmias
21	Simultaneous	Acute coronary syndrome, primary valvular heart disease or atrial fibrillation
22	Sequential aortic then oscillometric brachial then aortic	Arrhythmia
23	Simultaneous	Failure to obtain satisfactory intra-arterial and/or non-invasive waveforms
24	Sequential oscillometric brachial then ascending aortic	PAD, large artery atherosclerotic disease, aortic aneurysm, active malignancy, hypotension - SBP<90mm Hg, valvular heart disease, LV dysfunction (EF<50%), frequent arrhythmias
25	Sequential oscillometric brachial then ascending aortic	Arrhythmia, acute myocardial infarction, aortic stenosis
26	Sequential	History of peripheral arterial disease, aortic aneurysm, absent brachial or radial pulses or known obstructive large artery atherosclerotic disease, active malignancy, hypotension (SBP <90mm Hg), valvular heart disease, known left ventricular dysfunction (EF<50%) or arrhythmias (including frequent ventricular and supraventricular premature beats)
27	Sequential	History of peripheral arterial disease, aortic aneurysm, absent brachial or radial pulses or known obstructive large artery atherosclerotic disease, active malignancy, hypotension (SBP <90mm Hg), valvular heart disease, known left ventricular

		dysfunction (EF <50%) or arrhythmias (including frequent ventricular and supraventricular premature beats)
28	Sequential oscillometric brachial then ascending aortic	Atrial fibrillation, significant ventricular ectopy
29	Sequential aortic then oscillometric brachial	Unclear
30	Sequential (aortic then brachial cuff)	Arrhythmia, significant valvular disease or any constitutional illnesses
31	Simultaneous	"More than mild valvular heart disease", atrial fibrillation, frequent premature beats
32	Simultaneous	Frequent atrial or ventricular premature beats, atrial fibrillation, significant valve disease
33	Simultaneous	Unclear
34	Sequential aortic then oscillometric brachial	Arrhythmia
35	Sequential aortic then oscillometric brachial	Arrhythmia, inadequate quality data
36	Simultaneous	Unstable clinical conditions, arrhythmias, valvular heart disease
37	Simultaneous	Upper arm >35cm, arrhythmia
38	Sequential oscillometric brachial then ascending aortic	Atrial fibrillation or significant valvular disease

BP, blood pressure; L/R, left/right; PAD, peripheral arterial disease; cSP, central systolic pressure; LV, left ventricle; SBP, systolic BP; EF, ejection fraction

Appendix Table 1.10 Reasons individual participant data was not obtained from studies eligible for meta-analysis 1.

Studies where IPD was not sought	Reason
1. Bazaral et al, 1990[129]	Corresponding author passed away, unable to contact others

Studies where IPD not provided	Reason
1. De Hert et al, 1994[242]	Author unable to access data
2. O'Rourke, 1970[243]	Author unable to access data
3. VanBeck et al, 1993[244]	No response
4. Gravlee et al, 1989[245]	Author unable to access data
5. Gravlee et al, 1989[246]	Author unable to access data
6. Karamanoglu et al, 1993[224]	Author unable to access data

IPD, individual participant data

Appendix Table 1.11 Reasons individual participant data was not obtained from studies eligible for meta-analysis 2.

Studies where IPD was not sought	Reason
1. Bachmann et al, 1981[247]	Could not find contact information
2. Baeriswyl et al, 1982[248]	Incorrect details available and could not find new information
3. Breit et al, 1974[249]	Could not find contact information
4. Fagher et al, 1994[250]	Could not find contact information
5. Forsberg et al, 1970[251]	Could not find contact information
6. Ginsburg and Duncan 1969[252]	Could not find contact information
7. He et al, 1994[253]	Could not find contact information
8. Julien et al, 1988[254]	Could not find contact information
9. Karlefors et al, 1966[255]	Could not find contact information
10. Kuwajima et al, 1990[74]	Incorrect details available and could not find new information
11. London et al, 1967[256]	Could not find contact information
12. Molhoek et al, 1984[257]	Could not find contact information
13. Moss et al, 1965[258]	Author passed away
14. Murray 1991[259]	Could not find contact information
15. Netea et al, 1998[260]	Incorrect details available and could not find new information
16. Ochiai et al, 1997[261]	Incorrect details available and could not find new information
17. Sanchez et al, 1977[262]	Could not find contact information
18. Turjanmaa et al, 1988[263]	Could not find contact information
19. Turjanmaa, 1989[264]	Could not find contact information
Studies where IPD not provided	**Reason**
1. Casadei et al, 1988[265]	Data unavailable to author
2. Elseed et al, 1973[266]	No response
3. Fukuoka et al, 1987[267]	No response
4. Gould et al, 1985[268]	Data unavailable to author

Appendix Table 1.11 (continued)

5. Gould et al, 1986[269]	Data unavailable to author
6. Graettinger et al, 1988[270]	No response
7. Gravlee et al, 1990[271]	Data unavailable to author
8. Groppelli et al, 1992[272]	Data unavailable to author
9. Holland and Humerfelt, 1964[273]	Data unavailable to author
10. Hunyor et al, 1978[274]	No response
11. Lemson et al, 2009[275]	Data not provided after initial contact
12. Mejia et al, 1990[276]	No response
13. Milsom et al, 1986[277]	Unable to assist
14. Nielsen et al, 1974[278]	No response
15. Nielsen et al, 1979[279]	No response
16. Nielsen et al, 1983[76]	No response
17. Pereira et al, 1985[280]	No response
18. Pitlik et al, 1986[281]	No response
19. Robinson et al, 1988[282]	No response
20. Sagiv et al, 1995[283]	No response
21. Stolt et al, 1990[284]	No response
22. Stolt et al, 1993[285]	No response
23. Stolt et al, 1993[286]	No response
24. Van Egmond et al, 1993[287]	No response
25. Villani et al, 1992[288]	Data unavailable to author
26. White et al, 1989[289]	Data unavailable to author
27. White et al, 1989[290]	Data unavailable to author
28. White et al, 1990[291]	Data unavailable to author
29. Wiecek et al, 1990[292]	No response

IPD, individual participant data

Appendix Table 1.12 Reasons individual participant data was not obtained from studies eligible for meta-analysis 3.

Studies where IPD was not sought	Reason
1. Li et al, 1999[293]	Unable to find contact information
Studies where IPD not provided	**Reason**
1. Alihanoglu et al, 2013[294]	No response
2. Baguet et al, 2013[295]	No response
3. Brett et al, 2012[296]	No response
4. Choi et al, 2010 [297]	No response
5. Cloud et al, 2013 [92]	No response
6. Eckert et al, 1994 [298]	No response
7. Eckert et al, 1996 [299]	No response
8. Fleming et al, 1983 [300]	No response
9. Guilcher et al, 2011[301]	No response
10. Høegholm et al, 1992[302]	No response
11. Hope et al, 2004[85]	No response
12. Horvath et al, 2010[303]	No response
13. Kayrak et al, 2008[304]	No response
14. Kayrak et al, 2010[305]	No response
15. Klaus et al, 1991[306]	No response
16. Lehmann et al, 1998[307]	No response
17. Park et al, 2011[308]	No response
18. Shangguan et al, 2015[18]	No response
19. Sharir et al, 1993[309]	Data unavailable to the author
20. Sugawara et al, 2015[310]	No response
21. Umana et al, 2006[75]	No response
22. Zuo et al, 2010[311]	No response

IPD, individual participant data

Appendix Table 1.13 Concordance of systolic blood pressure only classification using guideline based thresholds.

Number of subjects and percentage concordance between brachial cuff and intra-arterial brachial (panel A) and aortic (panel B) systolic blood pressure (SBP) for classification of BP control.

A		**Intra-arterial brachial systolic blood pressure**			
N=735		**Normal**	**Prehypertension**	**Stage 1 hypertension**	**Stage 2 hypertension**
Brachial cuff systolic blood pressure	**Normal**	103(63)	54 (32)	6 (4)	1 (1)
	Prehypertension	15 (6)	131 (52)	77 (37)	7 (5)
	Stage 1 hypertension	0 (0)	15 (10)	86 (54)	51 (36)
	Stage 2 hypertension	0 (0)	1 (1)	26 (14)	162 (85)
B		**Intra-arterial aortic systolic blood pressure**			
N=1823		**Normal**	**Prehypertension**	**Stage 1 hypertension**	**Stage 2 hypertension**
Brachial cuff systolic blood pressure	**Normal**	360 (78)	91 (20)	6 (2)	2 (0)
	Prehypertension	125 (19)	363 (55)	150 (22)	14 (4)
	Stage 1 hypertension	14 (3)	96 (22)	238 (54)	104 (21)
	Stage 2 hypertension	1(0)	7 (3)	44 (19)	208 (78)

Data are presented as n (%), each row adds to 100%. Linear mixed modelling was used to account for clustering of subjects within studies. Brachial cuff SBP measurements were classified based on Joint National Committee 7 (JNC7) guidelines, and compared for concordance with classification of the corresponding intra-arterial brachial (panel A) and aortic (panel B) SBP. The proportion of intra-arterial brachial or aortic measures concordant with brachial cuff SBP is reported as a percentage. A value of 100% within the shaded boxes is equal to complete concordance of SBP classification. According to JNC 7, based on SBP only, normal <120 mm Hg; prehypertension 120-139 mm Hg; stage 1 hypertension 140-159 mm Hg and stage 2 hypertension ≥160 mm Hg.

Appendix Table 1.14 Univariable and multivariable analysis of clinical and demographic associations with the difference between brachial cuff and intra-arterial brachial systolic, diastolic blood pressure and pulse pressure.

Systolic BP difference	Univariable			Multivariable		
n=474, 9 studies	Estimate	95% CI	P value	Estimate	95% CI	P value
Age (years)	-0.1	-0.2 to -0.0	0.033	-0.067	-0.2 to 0.0	0.13
Body mass index (kg/m^2)	0.4	0.2 to 0.5	<0.0001	0.33	0.2 to 0.5	0.0003
Type of brachial cuff device (0=oscillometric, 1=mercury)	8.2	0.6 to 15.7	0.034	6.38	-1.2 to 13.8	0.098
Diastolic BP difference	**Univariable**			**Multivariable**		
n=518, 12 studies	Estimate	95% CI	P value	Estimate	95% CI	P value
Age (years)	0.08	0.02 to 0.1	0.014	-	-	-
Pulse pressure difference	**Univariable**			**Multivariable**		
n=474, 9 studies	Estimate	95% CI	P value	Estimate	95% CI	P value
Age (years)	-0.2	-0.3 to -0.1	<0.0001	-0.16	-0.2 to -0.1	0.0002
Body mass index (kg/m^2)	0.3	0.1 to 0.4	0.001	0.24	0.1 to 0.4	0.006
Type of brachial cuff device (0=oscillometric, 1=mercury)	8.4	3.0 to 13.7	0.002	5.70	-1.1 to 12.4	0.10

Linear mixed modelling used to account for participant clustering within studies. BP, blood pressure; 95% CI, 95% confidence interval. Clinical and demographic data was not available from all studies, therefore this analysis is on a subset of subjects and studies as reported in the table.

Appendix Table 1.15 Univariable and multivariable analysis of clinical and demographic associations with the difference between brachial cuff and intra-arterial aortic systolic, diastolic blood pressure and pulse pressure.

Systolic BP difference	Univariable			Multivariable		
n=1225, 21 studies	Estimate	95% CI	P value	Estimate	95% CI	P value
Age (years)	-0.2	-0.3 to -0.1	<0.0001	-0.2	-0.2 to 0.1	<0.0001
Sex (0=female, 1=male)	5.0	3.5 to 6.4	<0.0001	4.1	2.3 to 5.9	<0.0001
Heart rate (beats/min)	0.1	0.1 to 0.2	<0.0001	0.1	0.1 to 0.2	<0.0001
Body mass index (kg/m^2)	0.2	0.0 to 0.3	0.015	0.1	-0.0 to 0.2	0.13
Measurement protocol (0=simultaneous, 1=sequential)	6.6	1.0 to 12.2	0.02	7.3	1.5 to 13.0	0.014
Diastolic BP difference	Univariable			Multivariable		
n=1373, 25 studies	Estimate	95% CI	P value	Estimate	95% CI	P value
Age (years)	0.2	0.1 to 0.2	<0.0001	0.2	0.1 to 0.2	<0.0001
Sex (0=female, 1=male)	1.2	0.2 to 2.1	0.021	1.3	0.3 to 2.2	0.008
Body mass index (kg/m^2)	-0.2	-0.3 to -0.1	<0.0001	-0.1	-0.2 to -0.1	0.001
Pulse pressure difference	Univariable			Multivariable		
n=1225, 21 studies	Estimate	95% CI	P value	Estimate	95% CI	P value
Age (years)	-0.4	-0.4 to -0.3	<0.0001	-0.3	-0.4 to -0.3	<0.0001
Sex (0=female, 1=male)	3.9	2.4 to 5.4	<0.0001	4.1	2.7 to 5.5	<0.0001
Heart rate (beats/min)	0.2	0.1 to 0.2	<0.0001	0.2	0.1 to 0.2	<0.0001
Body mass index (kg/m^2)	0.2	0.2 to 0.2	<0.0001	0.3	0.1 to 0.4	0.0001

Linear mixed modelling used to account for participant clustering within studies. BP, blood pressure; 95% CI, 95% confidence interval. Clinical and demographic data was not available from all studies, therefore this analysis is on a subset of subjects and studies as reported in the table.

Appendix Table 1.16 Sensitivity analysis for meta-analysis 1 based on study quality scores.

Comparison of participant characteristics and blood pressure between maximum rated studies (5/5) based on our study quality rating versus those studies that did not receive the maximum rating.

	Mean difference (95% CI) between non-maximum rated studies (<5) and maximum rated (=5) or %	P value of difference
Age (years)	12.4 (1.2 to 23.3)	0.031
Male sex	72% (max rated) vs 73% (non-max rated)	0.95
Height (cm)	-7.8 (-15.7 to -0.02)	0.055
Weight (kg)	-1.1 (-13.3 to 10.8)	0.86
Body mass index (kg/m^2)	2.0 (-0.5 to 4.4)	0.12
Heart rate (beats/min)	-3.0 (-7.3 to 1.3)	0.18
Intra-arterial brachial – intra-arterial aortic SBP, mm Hg	-0.2 (-6.6 to 6.1)	0.96
Intra-arterial brachial – intra-arterial aortic DBP, mm Hg	1.5 (-0.2 to 3.2)	0.078
Intra-arterial brachial – intra-arterial aortic PP, mm Hg	-3.0 (-9.6 to 3.5)	0.37
Intra-arterial brachial SBP (mm Hg)	8.7 (0.7 to 16.5)	0.033
Intra-arterial aortic SBP (mm Hg)	9.1 (-0.7 to 18.6)	0.069
Intra-arterial brachial DBP (mm Hg)	2.4 (-3.0 to 7.7)	0.38
Intra-arterial aortic DBP (mm Hg)	1.0 (-3.8 to 5.8)	0.68
Intra-arterial brachial PP (mm Hg)	7.4 (-1.1 to 15.6)	0.084
Intra-arterial aortic PP (mm Hg)	10.6 (2.2 to 18.8)	0.014

Data are mean (95% confidence interval (95% CI)) or percentage. A positive mean difference indicates a higher value for the maximum rated studies versus the non-maximum rated studies, whereas a negative mean difference indicates a higher value for the non-maximum rated studies compared with the maximum rated studies. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

Appendix Table 1.17 Sensitivity analysis for meta-analysis 2 based on study quality scores. Comparison of participant characteristics and blood pressure between maximum rated studies (6/6) based on our study quality rating versus those studies that did not receive the maximum rating.

	Mean difference (95% CI) between non-maximum rated studies (=0) and maximum rated (=1) or %	P value of difference
Age (years)	-1.6 (-8.1 to 4.9)	0.64
Male sex	71% (max rated) vs 59% (non-max rated)	0.002
Height (cm)	2.0 (-1.7 to 5.7)	0.29
Weight (kg)	2.1 (-6.0 to 10.0)	0.61
Body mass index (kg/m^2)	-0.2 (-3.0 to 2.5)	0.90
Heart rate (beats/min)	No data in non-maximum rated studies	-
Brachial cuff – intra-arterial brachial SBP, mm Hg	-2.0 (-6.6 to 2.4)	0.38
Brachial cuff – intra-arterial brachial DBP, mm Hg	-2.0 (-5.4 to 1.4)	0.27
Brachial cuff – intra-arterial brachial PP, mm Hg	-0.2 (-4.5 to 4.0)	0.91
Brachial cuff SBP (mm Hg)	5.0 (-7.3 to 16.9)	0.43
Intra-arterial brachial SBP (mm Hg)	6.2 (-6.1 to 18.2)	0.32
Brachial cuff DBP (mm Hg)	-1.2 (-8.0 to 5.5)	0.74
Intra-arterial brachial DBP (mm Hg)	0.9 (-5.3 to 6.9)	0.78
Brachial cuff PP (mm Hg)	4.7 (-4.1 to 13.4)	0.30
Intra-arterial brachial PP (mm Hg)	3.0 (-5.1 to 11.0)	0.47

Data are mean (95% confidence interval (95% CI)) or percentage. A positive mean difference indicates a higher value for the maximum rated studies versus the non-maximum rated studies, whereas a negative mean difference indicates a higher value for the non-maximum rated studies compared with the maximum rated studies. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

Appendix Table 1.18 Sensitivity analysis for meta-analysis 3 based on study quality scores. Comparison of meta-analysis 3 participant characteristics and blood pressure between maximum rated studies (5/5) based on our study quality rating versus those studies that did not receive the maximum rating.

	Mean difference (95% CI) between non-maximum rated studies (=0) and maximum rated (=1) or %	P value of difference
Age (years)	-4.1 (-10.6 to 2.2)	0.21
Male sex	72% (max rated) vs 67% (non-max rated)	0.032
Height (cm)	-4.0 (-9.9 to 1.7)	0.18
Weight (kg)	-11.2 (-22.5 to -0.1)	0.053
Body mass index (kg/m^2)	-2.8 (-5.8 to 0.2)	0.072
Heart rate (beats/min)	-0.7 (-3.1 to 1.7)	0.57
Brachial cuff – intra-arterial aortic SBP (mm Hg)	2.0 (-2.0 to 5.8)	0.33
Brachial cuff – intra-arterial aortic DBP (mm Hg)	0.3 (-3.3 to 3.7)	0.89
Brachial cuff – intra-arterial aortic PP (mm Hg)	1.7 (-3.1 to 6.5)	0.48
Brachial cuff SBP (mm Hg)	-3.2 (-9.5 to 2.9)	0.31
Intra-arterial aortic SBP (mm Hg)	-5.1 (-11.2 to 0.9)	0.10
Brachial cuff DBP (mm Hg)	-1.4 (-5.8 to 2.9)	0.52
Intra-arterial aortic DBP (mm Hg)	-1.6 (-4.7 to 1.4)	0.31
Brachial cuff PP (mm Hg)	-1.2 (-6.6 to 4.0)	0.65
Intra-arterial aortic PP (mm Hg)	-2.8 (-7.9 to 2.1)	0.27

Data are mean (95% confidence interval (95% CI)) or percentage. A positive mean difference indicates a higher value for the maximum rated studies versus the non-maximum rated studies, whereas a negative mean difference indicates a higher value for the non-maximum rated studies compared with the maximum rated studies. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

Appendix Table 1.19 Comparison of meta-analysis 1 participant characteristics and blood pressure between published and unpublished data

	Mean difference (95% CI) or n (%) between published studies (=0) and unpublished studies (=1)	P value of difference
N	416 (81%) published, 99 (19%) unpublished	
Age (years)	7.3 (-6.9 to 21.1)	0.31
Male sex	71% (published) vs 78% (unpublished)	0.20
Height (cm)	-0.6 (-8.8 to 7.5)	0.90
Weight (kg)	5.5 (-2.6 to 13.4)	0.19
Body mass index (kg/m^2)	1.9 (0.1 to 3.7)	0.043
Heart rate (beats/min)	-1.3 (-6.4 to 3.7)	0.62
Intra-arterial brachial – intra-arterial aortic SBP (mm Hg)	-0.4 (-7.9 to 7.0)	0.92
Intra-arterial brachial – intra-arterial aortic DBP (mm Hg)	-1.6 (-3.5 to 0.3)	0.10
Intra-arterial brachial – intra-arterial aortic PP (mm Hg)	0.4 (-7.4 to 8.0)	0.93
Intra-arterial brachial SBP (mm Hg)	4.4 (-6.6 to 15.2)	0.43
Intra-arterial aortic SBP (mm Hg)	5.0 (-7.9 to 17.6)	0.45
Intra-arterial brachial DBP (mm Hg)	-2.8 (-9.0 to 3.3)	0.38
Intra-arterial aortic DBP (mm Hg)	-1.2 (-6.8 to 4.2)	0.66
Intra-arterial brachial PP (mm Hg)	7.4 (-2.3 to 17.0)	0.13
Intra-arterial aortic PP (mm Hg)	7.1 (-4.2 to 18.3)	0.22

Data are mean (95% confidence interval (95% CI)) or percentage. A positive mean difference indicates a higher value for the unpublished studies versus the published studies, whereas a negative mean difference indicates a higher value for the published studies compared with the unpublished studies. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

Appendix Table 1.20 Comparison of meta-analysis 2 participant characteristics and blood pressure between published and unpublished data

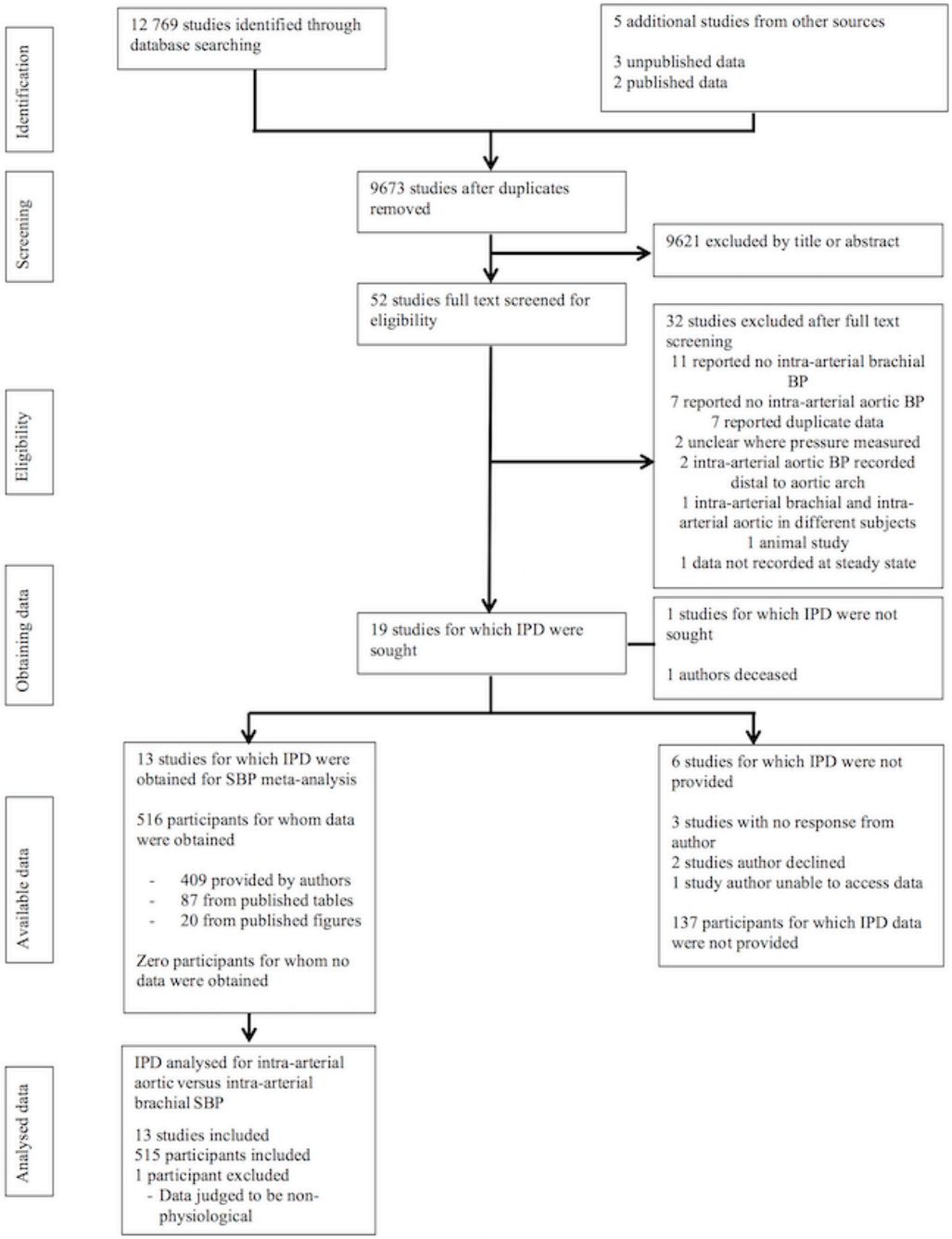
	Mean difference (95% CI) or n (%) between published studies (=0) and unpublished studies (=1)	P value of difference
N	648 (88%) published, 87 (12%) unpublished	
Age (years)	10.3 (-5.2 to 24.9)	0.20
Male sex	58% (published) vs 77% (unpublished)	0.002
Height (cm)	1.3 (-4.7 to 7.2)	0.66
Weight (kg)	0.2 (-13.1 to 13.2)	0.98
Body mass index (kg/m^2)	-0.7 (-5.3 to 3.9)	0.77
Heart rate (beats/min)	-2.5 (-10.8 to 5.7)	0.56
Brachial cuff – intra-arterial brachial SBP (mm Hg)	-5.2 (-12.7 to 2.1)	0.17
Brachial cuff – intra-arterial brachial DBP (mm Hg)	-0.8 (-6.4 to 4.6)	0.77
Brachial cuff – intra-arterial brachial PP (mm Hg)	-4.1 (-10.2 to 2.0)	0.20
Brachial cuff SBP (mm Hg)	-8.8 (-31.8 to 13.7)	0.45
Intra-arterial brachial SBP (mm Hg)	-3.6 (-27.1 to 19.4)	0.76
Brachial cuff DBP (mm Hg)	-7.9 (-20.6 to 4.4)	0.22
Intra-arterial brachial DBP (mm Hg)	-7.2 (-17.3 to 2.7)	0.16
Brachial cuff PP (mm Hg)	-1.4 (-16.0 to 12.9)	0.85
Intra-arterial brachial PP (mm Hg)	2.4 (-10.0 to 14.6)	0.70

Data are mean (95% confidence interval (95% CI)) or percentage. A positive mean difference indicates a higher value for the unpublished studies versus the published studies, whereas a negative mean difference indicates a higher value for the published studies compared with the unpublished studies. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

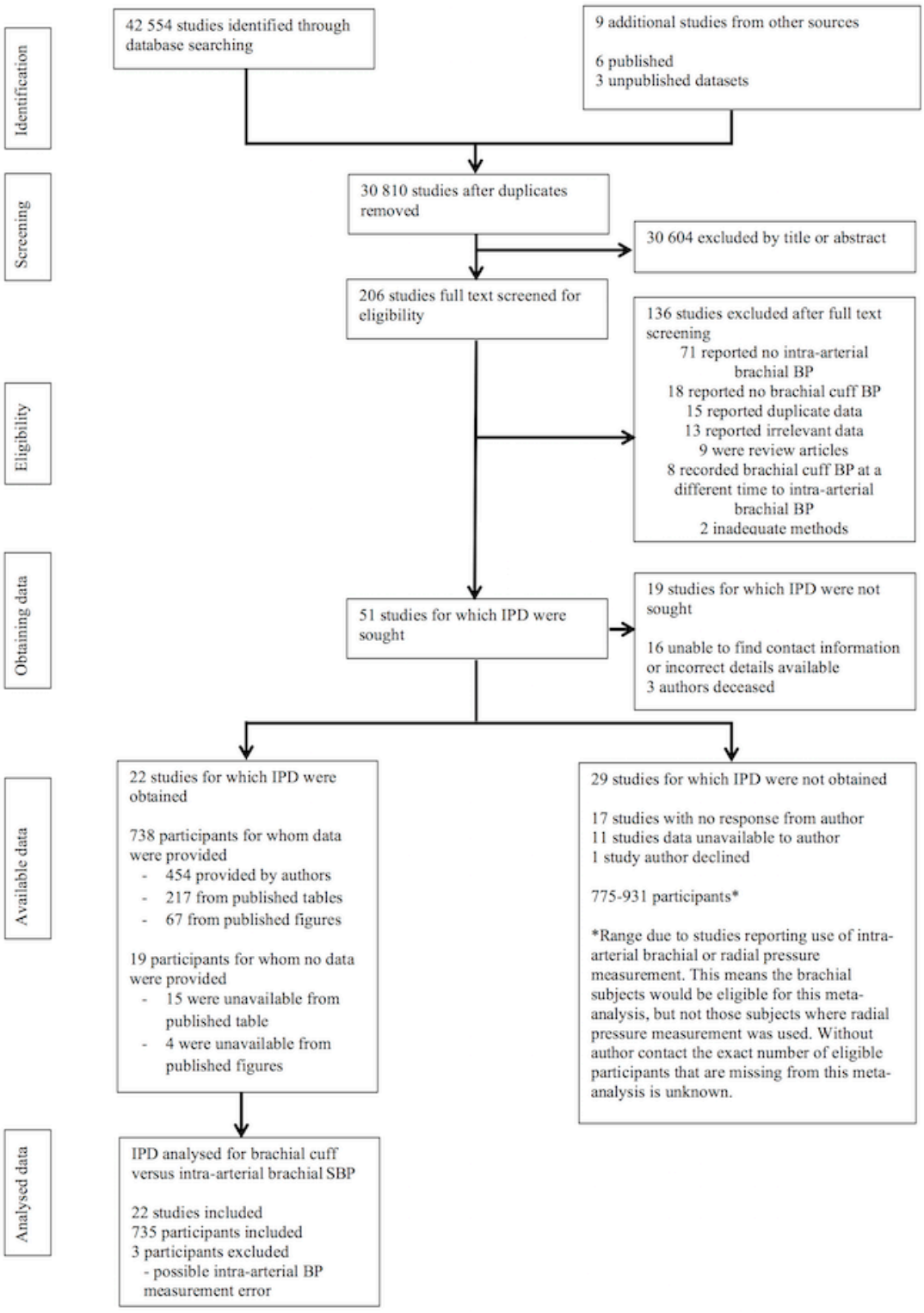
Appendix Table 1.21 Comparison of meta-analysis 3 participant characteristics and blood pressure between published and unpublished data

	Mean difference (95% CI) or n (%) between published studies (=0) and unpublished studies (=1)	P value of difference
N	1493 (81%) published, 351 (19%) unpublished	
Age (years)	4.1 (-3.8 to 11.7)	0.31
Male sex	68% (published) vs 73% (unpublished)	0.057
Height (cm)	2.5 (-5.0 to 9.9)	0.51
Weight (kg)	0.4 (-14.3 to 14.7)	0.96
Body mass index (kg/m^2)	-0.3 (-4.0 to 3.3)	0.87
Heart rate (beats/min)	-1.7 (-4.9 to 1.4)	0.29
Brachial cuff – intra-arterial brachial SBP (mm Hg)	-0.9 (-6.0 to 4.1)	0.73
Brachial cuff – intra-arterial brachial DBP (mm Hg)	-1.3 (-3.1 to 5.6)	0.56
Brachial cuff – intra-arterial brachial PP (mm Hg)	-2.3 (-8.3 to 3.7)	0.47
Brachial cuff SBP (mm Hg)	1.9 (-6.3 to 9.8)	0.66
Intra-arterial aortic SBP (mm Hg)	2.4 (-5.8 to 10.4)	0.56
Brachial cuff DBP (mm Hg)	-1.0 (-6.5 to 4.4)	0.72
Intra-arterial aortic DBP (mm Hg)	-2.2 (-6.0 to 1.6)	0.27
Brachial cuff PP (mm Hg)	3.5 (-3.0 to 10.0)	0.30
Intra-arterial aortic PP (mm Hg)	5.0 (-1.4 to 11.2)	0.12

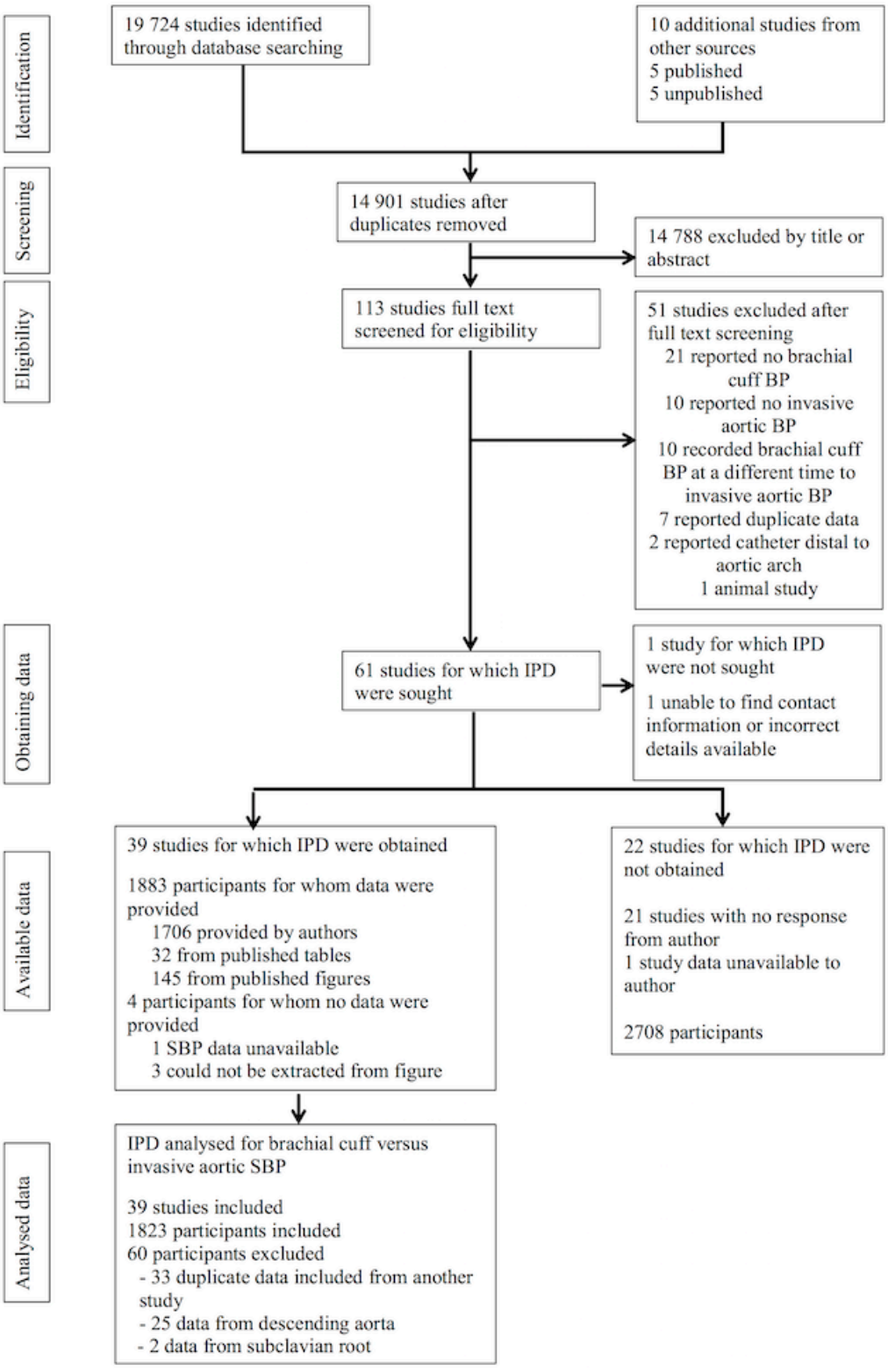
Data are mean (95% confidence interval (95% CI)) or percentage. A positive mean difference indicates a higher value for the unpublished studies versus the published studies, whereas a negative mean difference indicates a higher value for the published studies compared with the unpublished studies. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.



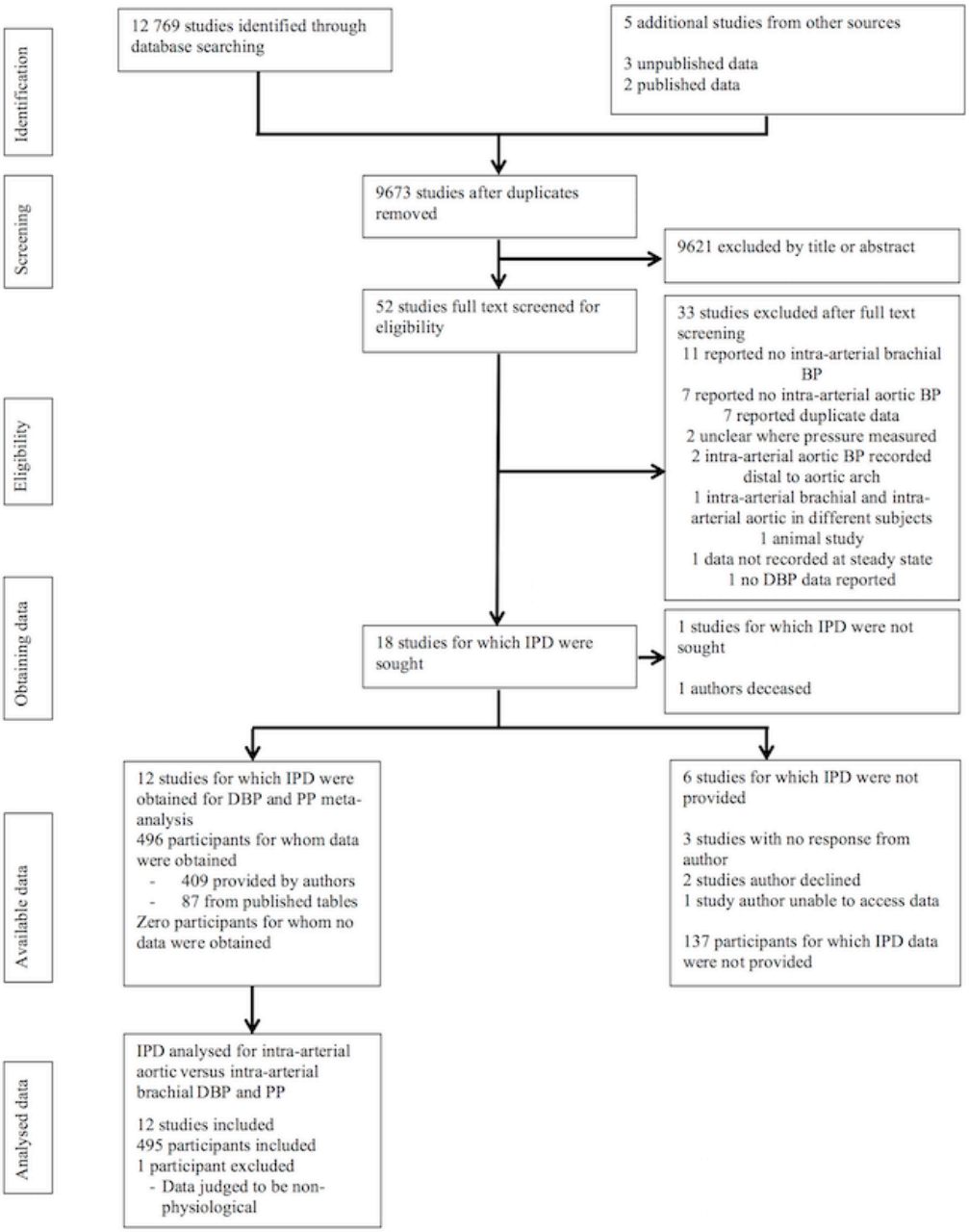
Appendix Figure 1.1 Study flow diagram for systolic blood pressure in meta-analysis 1. Formatted as recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analysis of individual participant data (PRISMA-IPD).



Appendix Figure 1.2 Study flow diagram for systolic blood pressure in meta-analysis 2. Formatted as recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analysis of individual participant data (PRISMA-IPD).

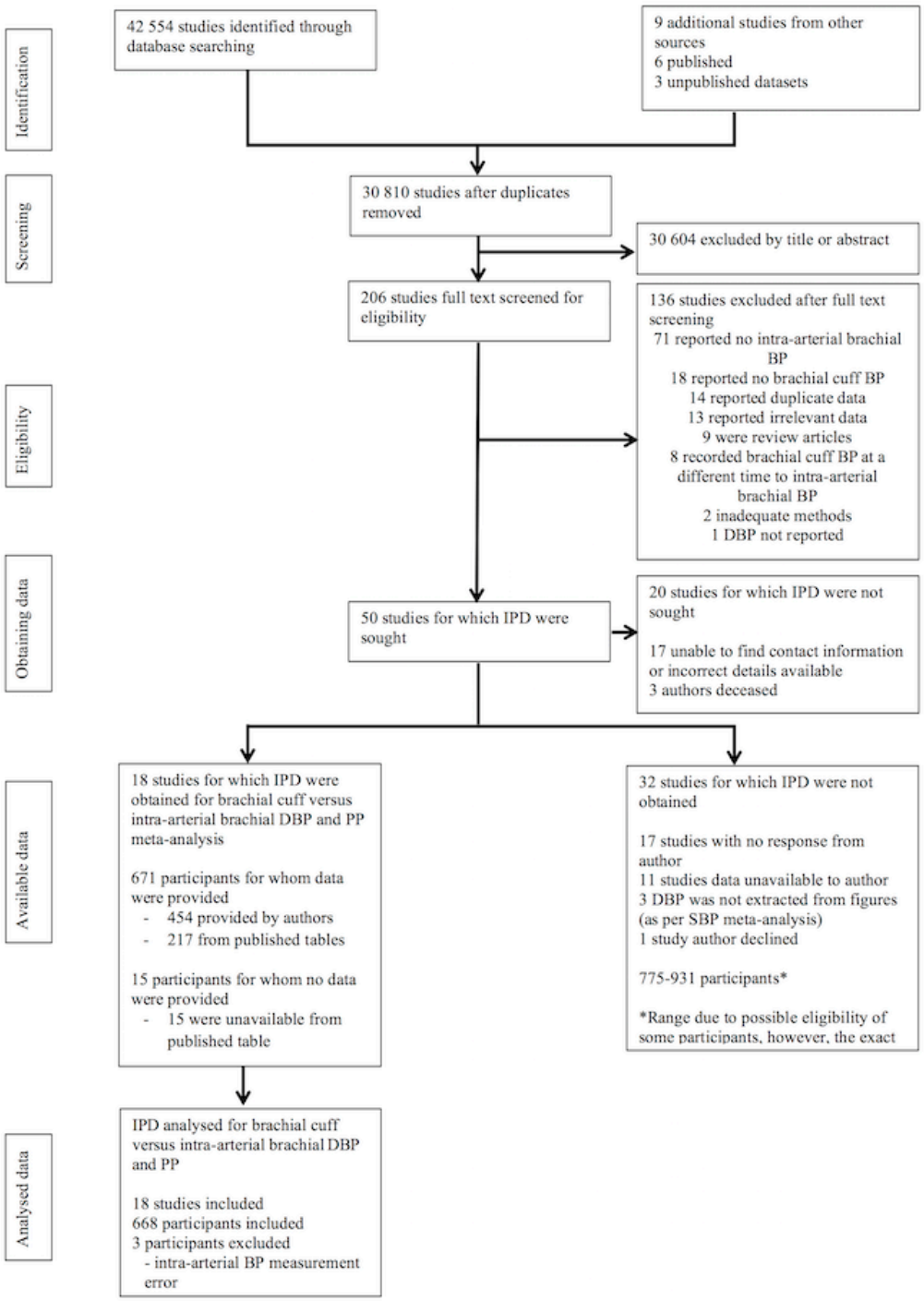


Appendix Figure 1.3 Study flow diagram for systolic blood pressure in meta-analysis 3. Formatted as recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analysis of individual participant data (PRISMA-IPD).



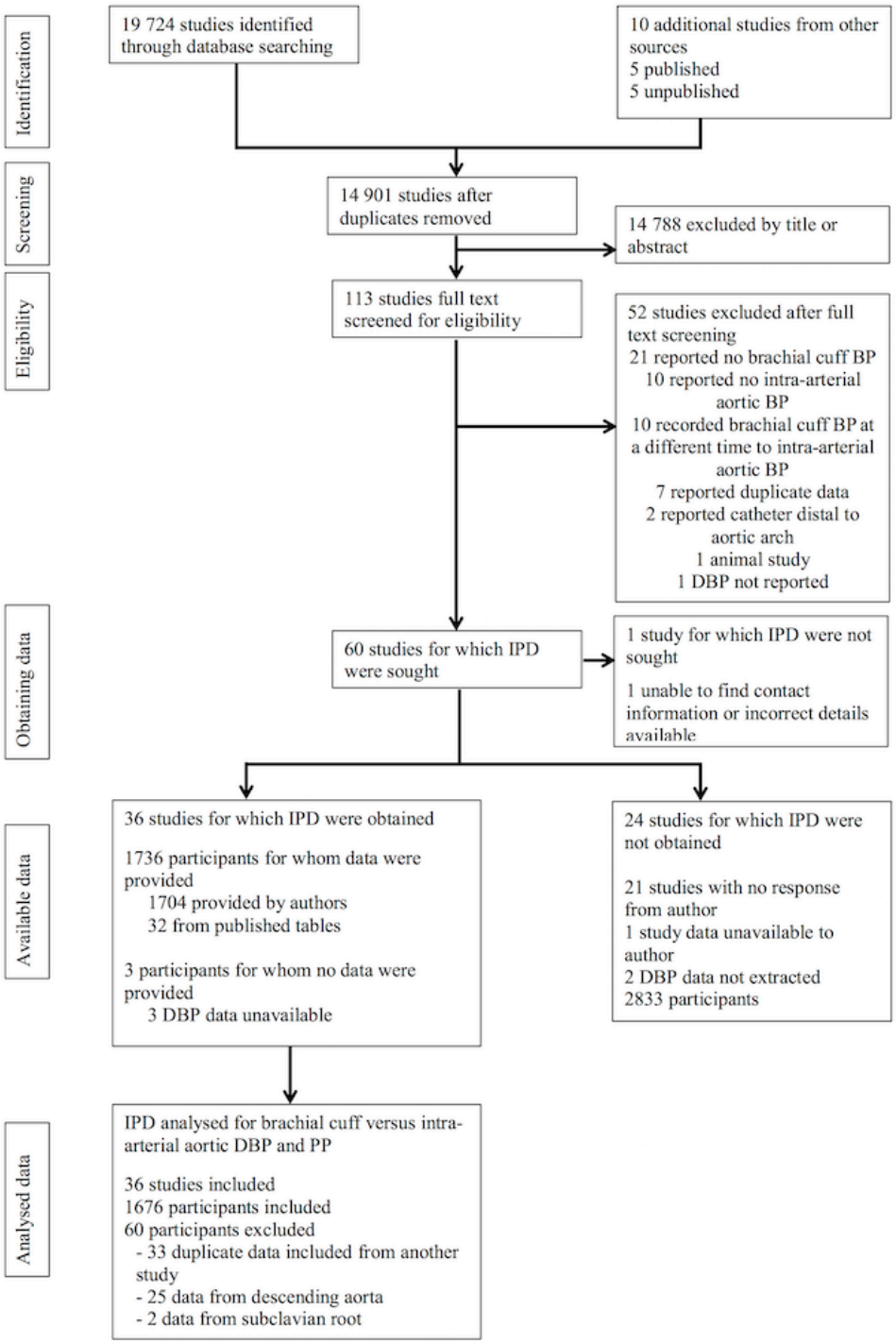
Appendix Figure 1.4 Study flow diagram for diastolic blood pressure and pulse pressure in meta-analysis 1.

Formatted as recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analysis of individual participant data (PRISMA-IPD) statement.



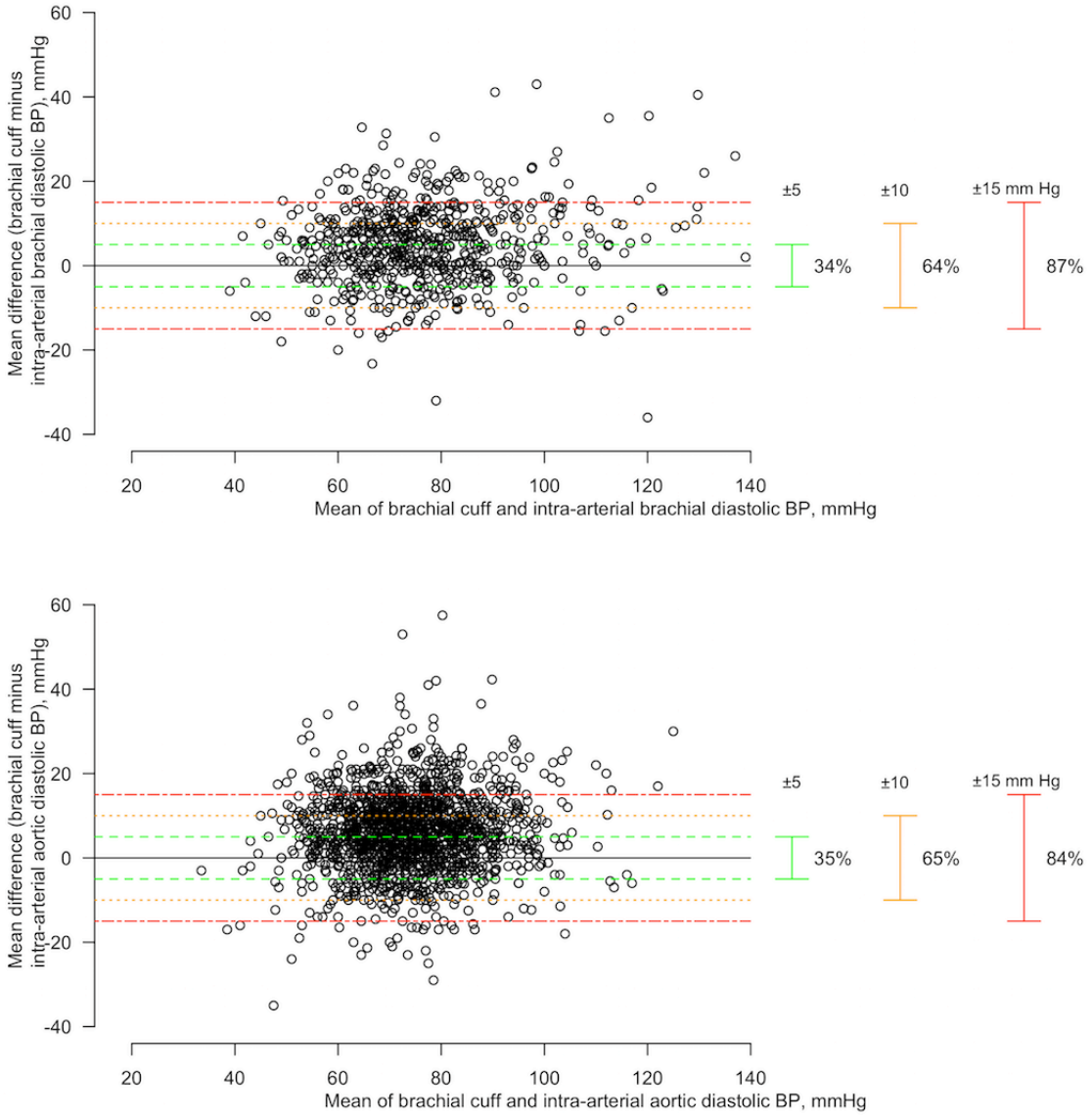
Appendix Figure 1.5 Study flow diagram for diastolic blood pressure and pulse pressure in meta-analysis 2.

Formatted as recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analysis of individual participant data (PRISMA-IPD) statement.



Appendix Figure 1.6 Study flow diagram for diastolic blood pressure and pulse pressure in meta-analysis 3.

Formatted as recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analysis of individual participant data (PRISMA-IPD) statement.



Appendix Figure 1.7 Agreement plot of brachial cuff DBP and intra-arterial brachial and aortic DBP.

Plots of brachial cuff and intra-arterial brachial (top panel), and brachial cuff and intra-arterial aortic (bottom panel) diastolic blood pressure (BP). The mean of the brachial cuff diastolic BP and intra-arterial diastolic BP is on the x-axis and the mean difference between brachial cuff diastolic BP and the intra-arterial diastolic BP is on the y-axis. The proportion of brachial cuff systolic BP values within ±5 mm Hg of the intra-arterial systolic BP measures is represented by the dashed line (green), and reported under the ±5 error bar. The same presentation is provided for cuff systolic BP values within ±10 mm Hg (dotted line (orange)) and ±15 mm Hg (dot-dashed line (red)). The solid black horizontal line represents the mean difference calculated as brachial cuff – intra-arterial BP.

Appendix 2

Appendix 2 presents information from the Online-only supplemental content from the publication that is presented in Chapter 3 (Discovery of new blood pressure phenotypes and relation to accuracy of cuff devices used in daily clinical practice) of this thesis. The supplemental content was peer-reviewed as part of the overall process for journal publication. Some parts of the original supplemental content have been integrated within Chapter 3 to improve clarity and ease of understanding, with the remainder presented here.

Appendix 2.1 Pucci et al methods.

29 participants undergoing diagnostic catheterization were recruited. Exclusion criteria were: history of peripheral arterial disease, aortic aneurysm, absent brachial or radial pulses or known obstructive large artery atherosclerotic disease, active malignancy, hypotension (SBP <90mmHg), valvular heart disease, known left ventricular dysfunction (ejection fraction <50%) or arrhythmias (including frequent ventricular and supraventricular premature beats). Intra-arterial BP was recorded with a fluid-filled catheter (ACIST medical systems, Eden Prairie, MN, USA). First, intra-arterial ascending aortic BP was recorded and then the catheter was pulled back to the brachial artery (using a pre-defined length) in approximately 5-10 seconds. Brachial cuff BP was measured simultaneously with intra-arterial brachial artery BP using an Omron HEM-9000AI. This device uses the same brachial BP algorithm as the Omron HEM-907 device, which has been validated according to international guidelines.[220]

Appendix 2.2 Expanded results.

Aortic and radial augmentation index increased stepwise across the four BP phenotypes (Table 2 of the manuscript). The following additional analysis was performed to examine whether radial augmentation index provided information distinct from the BP phenotypes, or whether it could be used as a non-invasive method to discriminate BP phenotypes:

1. The relationship between aortic and radial augmentation index was strong (albeit not perfect) when assessed across all subjects ($r=0.71$, $p<0.0001$). However, the relationships varied substantially between the 4 phenotypes (phenotype 1, $r=0.61$, $p=0.0002$; phenotype 2, $r=0.81$, $p<0.0001$; phenotype 3, $r=0.41$, $p=0.038$; phenotype 4, $r=0.62$, $p=0.0013$). Thus, considerable variation in aortic augmentation index cannot be explained by radial augmentation index.
2. Cuff BP was significantly increasing, or trending towards increasing, across quartiles of radial augmentation index (Table S2 below), which was in contrast to the 4 phenotypes where there were no differences in cuff BP (nor any trends), no matter how or when it was measured ($p>0.2$ all, Table 3 of the manuscript).
3. There was a trend for intra-arterial brachial SBP to increase across quartiles of radial augmentation index (Table S2 below), whereas intra-arterial brachial SBP was near to unchanged across phenotypes 1 to 4 ($p=0.90$, Table 2 of the manuscript).
4. There was a significant correlation between cuff SBP and radial augmentation index ($r=0.24$, $p=0.0080$), whereas neither aortic-to-brachial SBP amplification nor brachial-to-radial SBP amplification were significantly correlated with cuff SBP ($r=-0.076$, $p=0.41$ and $r=-0.0019$, $p=0.98$, respectively).
5. When we tested the univariable correlations of cuff error (cuff SBP – invasive aortic SBP) with aortic-to-brachial SBP amplification and radial AIx, there were significant relationships ($r=0.44$ and $r=-0.34$, respectively, $p<0.001$ for both). However, when both variables were entered into a multiple regression analysis, only aortic-to-brachial SBP amplification was significantly related to the cuff error (Table S3 below).
6. Addition of radial AIx to the multivariable analyses in Table S4 did not significantly alter the relationship between aortic SBP and BP phenotype.

Taken altogether, although radial augmentation index may be a useful waveform feature to help delineate phenotypic differences irrespective of cuff BP, the level of SBP amplification provides information that is separate and additive to that of radial augmentation index.

Appendix Table 2.1 Intra-arterial and cuff blood pressure across quartiles of radial augmentation index.

Variable	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value
Aortic SBP	124±15	125±21	133±16	144±24	0.00022
Brachial SBP	139±16	133±21	138±15	147±24	0.065
Aortic-brachial SBP amplification	15.6±10.1	8.2±8.5	5.2±6.4	2.9±5.1	<0.0001
Brachial-radial SBP amplification	11.8±9.3	9.2±10.9	3.4±8.3	-2.3±7.4	<0.0001
Aortic PP	55±17	59±1	63±16	75±19	0.00016
Brachial PP	73±16	69±18	69±15	79±19	0.081
Cuff SBP (simultaneous with intra-arterial brachial) *	127±15	128±16	130±13	138±22	0.062
Cuff PP (simultaneous with intra-arterial brachial) *	53±10	55±13	55±10	62±16	0.020

SBP, systolic BP; PP, pulse pressure. Data are mean±standard deviation. *n=122. Units for SBP, SBP amplification and PP are mmHg. P-value calculated by analysis of variance.

Appendix Table 2.2 Multiple linear regression on the associations with cuff systolic blood pressure error (cuff – intra-arterial aortic systolic blood pressure).

Variable	β (95%CI)	P-value
Aortic-brachial SBP amplification	0.43 (0.20 to 0.65)	0.00044
Radial augmentation index	-0.12 (-0.30 to 0.057)	0.20

SBP, systolic blood pressure. Adjusted R^2=0.19, p<0.0001.