Accuracy of cuff measured blood pressure: compendium of three separate systematic reviews and individual participant data meta-analyses

Dean S. Picone (BMedRes(Hons))[a], Martin G. Schultz (PhD)[a], Petr Otahal(GDipSci)[a], Svend Aakhus(MD, PhD)[b], Ahmed M. Al-Jumaily (PhD)[c], J. Andrew Black(MBBS(Hons))[a,d], Willem J. Bos(MD, PhD)[e], John B. Chambers(MD)[f], Chen-Huan Chen(MD)[g], Hao-Min Cheng(MD, PhD)[g], Antoine Cremer(MD)[h], Justin E. Davies(PhD)[i], Nathan Dwyer(MBBS, PhD)[a,d], Brian A. Gould(MD, PhD)[j], Alun D. Hughes(MBBS, PhD)[k], Peter S. Lacy(PhD)[l], Esben Laugesen(MD, PhD)[m], Fuyou Liang(PhD)[n], Roman Melamed(MD)[o], Sandy Muecke(PhD)[p], Nobuyuki Ohte(MD, PhD)[q], Sho Okada(MD, PhD)[r], Stefano Omboni(MD)[s], Christian Ott(MD)[t], Xiaoqing Peng(MPharm)[a], Telmo Pereira(PhD),[u] Giacomo Pucci(MD)[v], Ronak Rajani(MD)[f], Philip Roberts-Thomson(MBBS)[a,d], Niklas B. Rossen(MD, PhD)[m], Daisuke Sueta(MD, PhD)[w], Manish D. Sinha(PhD)[x], Roland E. Schmieder(MD)[t], Harold Smulyan(MD)[y] Velandai K. Srikanth(PhD)[a,z,aa], Ralph Stewart(MD)[bb], George A. Stouffer(MD)[cc], Kenji Takazawa(MD, PhD)[dd], Jiguang Wang(MD, PhD)[ee], Berend E. Westerhof(PhD)[ff], Franz Weber(MD)[gg], Thomas Weber(MD)[hh], Bryan Williams(MD)[l], Hirotsugu Yamada(MD, PhD)[ii], Eiichiro Yamamoto(MD, PhD)[w], James E. Sharman(PhD)[a]

[a]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
[b]Department of Circulation and Medical Imaging, Faculty of Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway
[c]Institute of Biomedical Technologies, Auckland University of Technology, Auckland, New Zealand
[d]Royal Hobart Hospital, Hobart, Tasmania
[e]St Antonius Hospital, Department of Internal Medicine, Nieuwegein, The Netherlands
[f]Cardiology Department, Guy's and St Thomas' Hospitals, London, United Kingdom
[g]Department of Medicine, National Yang-Ming University, Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan
[h]Department of Cardiology/Hypertension, University Hospital of Bordeaux, Bordeaux, France
[i]International Centre for Circulatory Health, Imperial College London, London, United Kingdom
[j]BMI Hospital Blackheath, London, United Kingdom
[k]Institute of Cardiovascular Sciences, University College London, London, United Kingdom
[l]Institute of Cardiovascular Sciences University College London (UCL) and National Institute for Health Research (NIHR) UCL/UCL Hospitals Biomedical Research Centre, London, United Kingdom
[m]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark
[n]School of Naval Architecture, Ocean and Civil Engineering, Shanghai Jiao Tong University, Shanghai, China
[o]Abbott Northwestern Hospital, Allina Health, Minneapolis, United States
[p]Department of Critical Care Medicine, Flinders University, Adelaide, Australia
[q]Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
[r]Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba, Japan
[s]*Cli*nical Research Unit, Italian Institute of Telemedicine, Varese, Italy

[t]Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany
[u]Polytechnic Institute of Coimbra, ESTES, Department of Cardiopneumology, General Humberto Delgado Street 102, Lousã, Portugal
[v]Unit of Internal Medicine at Terni University Hospital, Department of Medicine, University of Perugia, Perugia, Italy
[w]Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
[x]Department of Clinical Pharmacology and Department of Paediatric Nephrology, Kings College London, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[y]Department of Medicine, State University of New York, Upstate Medical University, Cardiology Division, Syracuse, United States
[z]Central Clinical School, Faculty of Medicine, Monash University, Melbourne, Australia
[aa]Department of Medicine, Peninsula Health, Melbourne, Australia
[bb]Green Lane Cardiovascular Service, Auckland City Hospital, University of Auckland, Auckland, New Zealand
[cc]Division of Cardiology, University of North Carolina at Chapel Hill, Chapel Hill, United States
[dd]Center for Health Surveillance and Preventive Medicine, Tokyo Medical University Hospital, Tokyo, Japan
[ee]Centre for Epidemiological Studies and Clinical Trials, Shanghai Key Laboratory of Hypertension, The Shanghai Institute of Hypertension, Department of Hypertension, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[ff]Department of Pulmonary Diseases, VU University Medical Center, Amsterdam, The Netherlands
[gg]Department of Nephrology, Center for Internal Medicine, University Clinic Essen, University Duisburg-Essen, Germany
[hh]Cardiology Department, Klinikum Wels-Grieskirchen, Wels, Austria
[ii]Department of Cardiovascular Medicine, Tokushima University Hospital, Tokushima, Japan

Funding: None.
Disclosures: None.

Address for correspondence:
Professor James E. Sharman
Menzies Institute for Medical Research
University of Tasmania
Private Bag 23, Hobart, 7000
Australia
Telephone: +61 3 6226 4709
Fax: +61 3 6226 7704
Email: James.Sharman@utas.edu.au

Abstract

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

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

Methods: Three separate, but closely related, 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: Total studies and participants were n=74 and n=3,073. Intra-arterial brachial systolic BP (SBP) was higher, and intra-arterial brachial diastolic BP was lower than aortic values (8.0 mmHg, 95%CI 5.9 to 10.1; p<0.0001; -1.0 mmHg, 95%CI -2.0 to -0.1; p=0.038 respectively). Cuff BP underestimated intra-arterial brachial SBP but overestimated intra-arterial diastolic BP (-5.7 mmHg, 95%CI -8.0 to -3.5, p<0.0001; 5.5 mmHg, 95%CI 3.5 to 7.5, p<0.0001). Cuff and intra-arterial aortic SBP showed a small mean difference (0.3 mmHg, 95%CI -1.5 to 2.1, p=0.77) but poor agreement (mean absolute difference 8.0 mmHg, 95%CI 7.1 to 8.9). Concordance between BP classification using JNC7 cuff BP (normal, prehypertension, hypertension stages 1 and 2) compared with intra-arterial brachial BP was 60%, 50%, 53% and 80%, and for 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 for 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 do not undermine the well-established clinical importance of cuff BP, but indicate that stronger accuracy standards for BP devices may improve cardiovascular risk management.

Keywords: blood pressure determination, sphygmomanometers, hemodynamics

Abbreviations

BP = blood pressure
SBP = systolic blood pressure
DBP = diastolic blood pressure
PP = pulse pressure
JNC 7 = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7

Condensed Abstract: Cuff BP is the principal method for hypertension management, however, questions have been raised regarding accuracy. We performed the first comprehensive analysis of cuff BP compared with intra-arterial BP, via three individual participant data meta-analyses. The key finding was cuff BP has variable accuracy for measuring either brachial or aortic intra-arterial BP. This adversely affects cuff BP classification, particularly for prehypertension and stage one hypertension. The clinical importance of cuff BP is unquestionable, but our findings suggest that improved accuracy standards for BP devices is desirable and this may improve cardiovascular risk management.

Introduction

Cardiovascular disease is the number one cause of mortality worldwide, with elevated blood pressure (BP) as the single largest risk factor (1-3). 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 (4). Importantly, even relatively small error in cuff BP measurement can have major public health ramifications, with an inaccuracy of 5 mmHg 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) (5). On the one hand, BP underestimation leads to missed therapeutic potential and unnecessary elevation of cardiovascular risk (6), whereas BP overestimation creates unnecessary additional cost and exposure to possible adverse effects of treatment (5). The recognition of prehypertension as a non-benign clinical presentation (7), and the benefit to some patient populations of achieving low BP targets (8) 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. Firstly, 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) (9-11). Secondly, cuff BP devices being tested for accuracy against other non-invasive measurements according to international validation protocols may perform to a “pass” standard even when clinically significant measurement errors occur among many patients (12). Thirdly, there can be large individual variability in intra-arterial BP between the aorta and brachial artery (9,13,14), but whether oscillometric or auscultatory cuff BP accurately measures either aortic or brachial BP has never been systematically determined.

This is important to resolve given the possibility that aortic BP is more clinically relevant than brachial BP (13,15-17), and the burgeoning of commercial devices purporting to measure aortic BP (18) to enable (theoretical) better assessment of risk related to BP.(19) However, this is a controversial concept (20,21) in which some investigators advocate there is a lack of evidence to justify the need to depart from standard cuff BP (20,22). Adding to this debate is the suggestion that brachial cuff BP may already appropriately measure aortic BP, eliminating the need for specialist devices (23-25).

The issues detailed above 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 highly relevant to validation protocol standards for cuff BP devices and could ultimately lead to improved clinical management of cardiovascular risk through more accurate BP measurement and classification. To address key knowledge deficits, we completed a series of three separate but interrelated systematic reviews and individual participant data meta-analyses to determine the accuracy of cuff BP methods. We firstly aimed to determine the true level of intra-arterial BP 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). The potential clinical consequences of cuff BP measurement error were determined by the concordance between cuff BP and intra-arterial BP for BP classification according to criteria of The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (26).

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. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) (Online Table 1) (27). 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 others results. Discrepancies were resolved via consensus. In the interests of focusing on the results of cuff BP compared with intra-arterial BP, the results from meta-analysis 1 are provided in the online supplement.

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 (Online Table 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 (Online Appendix 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 (28), due to possible haemodynamic changes between measurement periods (29). 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 haemodynamic 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), 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 (30). For meta-analyses 1 and 3, studies that measured aortic BP distal to the aortic arch were excluded due to potential amplification of SBP along the aorta (31) contributing 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-SI format were standardised to SI units, except for pressure units. Individual data supplied by authors were checked for consistency with published aggregate data where available, and 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 (Online Appendix 2), or from figure scatterplots using extraction software, when possible (32). 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 (Online Table 3). A quality score was applied to each study in order to account for important study design attributes that may have impacted on data quality (Online Appendix 3 and Tables 4-6). 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 mmHg different from intra-arterial BP were determined as a measure of accuracy (33).

BP classification

To determine accuracy of cuff BP for BP classification, each individuals cuff BP was classified according to JNC 7 criteria (normal BP <120/80 mmHg, prehypertension SBP 120-139 or DBP 80-89 mmHg, stage 1 hypertension SBP 140-159 or DBP 90-99 mmHg and stage 2 hypertension SBP ≥160 or DBP ≥100 mmHg),(26) 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 mmHg), the corresponding intra-arterial BP for that individual was classified into the appropriate category (e.g. normal, prehypertension, stage 1 or 2 hypertension), and found to be concordant if also falling into the same normal BP classification (<120/80 mmHg). This approach enabled an assessment of the potential impact of cuff BP inaccuracy on clinical practice, but also recognizes 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 hypertension at a cut point of ≥140/90 mmHg 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 one-stage and two-stage meta-analysis were used. The results generated from each method are considered equivalent in individual participant data meta-analysis (34). 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 synthesised using random effects meta-analysis due to the observational nature of the data. ~~Pooled~~ Correlation coefficients from individual studies were used to calculate summary correlation coefficients ~~regarding~~ on the relationship between BP measurements in each meta-analysis. This same method was used for sensitivity and specificity analyses for cuff BP delineating hypertension based on the 140/90 mmHg cut point. Linear mixed modelling (one-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 (35) and Rossen et al (36) 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 separately to assess published, compared with unpublished data sources. Furthermore, to determine the influence on results of meta-analyses 2 and 3, sensitivity analyses were conducted for single compared with the average of multiple cuff BP measures, as well as the type of catheter used for intra-arterial BP measurement. 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 detailed in Online Appendix 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, leaving 13 studies (9,11,13,14,37-42), 22 studies (43), and 39 studies (9,11,24,35,36,38,41,44-70) for SBP analysis, whereas 12 studies (11,13,14,37-42), 18 studies (10,11,38,41,47,71-80), and 36 studies (11,35,36,38,41,44-60,62-70) were available for analysis relating to DBP and PP (see Online Tables 7-10 and Online References). Systematic review flow diagrams and study characteristics for all meta-analyses are detailed in Online Figures 1-6 and Tables 7-12. Data were extracted from published tables in 10~~1~~ studies (Online Appendix 2), (10,13,14,39,46,53,71-73,79,80) and from published figures in 6~~5~~ studies (Online Table 3) (9,24,81-83). 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 (Online Tables 13-15). When individual participant data were checked as per guidelines (27), 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 (reasons for this are explained in Online Appendix 5).

Meta-analyses on BP differences

See online supplementary material for all results from ~~In~~ meta-analysis 1 (Online Appendix 6 and Online Figures 7-9). ~~brachial artery SBP was significantly higher than aortic SBP and PP (p<0.0001; **Figure 1A, C**). On the other hand, brachial DBP was marginally, but significantly lower than aortic DBP (p=0.038; **Figure 1B**). The range of differences for SBP, DBP and PP was large (-9 to 62 mmHg, -22 to 25 mmHg and -17 to 62 mmHg respectively, Online Figure 7). The pooled correlation coefficients showed strong associations between intra-arterial brachial and aortic SBP (r=0.92, 95%CI 0.88 to 0.95), DBP (r=0.93, 95%CI 0.91 to 0.95) and PP (r=0.89, 95%CI 0.86 to 0.93, p<0.0001 all, Online Figure 8).~~

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 1~~2~~A-C**). The mean absolute difference for SBP was 7.9 mmHg, 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 (Online Table 16). 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=0.89, 95%CI 0.86 to 0.93), DBP (r=0.78, 95%CI 0.72 to 0.85) and PP (r=0.82, 95%CI 0.76 to 0.88, p<0.0001 all, Online Figure 10~~9~~).

In meta-analysis 3, there was no significant difference between brachial cuff and intra-arterial aortic SBP (**Figure 23A**, 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 mmHg (95%CI) 7.1 to 8.9. Brachial cuff methods significantly overestimated intra-arterial aortic DBP and, thus, significantly underestimated intra-arterial aortic PP (**Figure 23B and C,** 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=0.88, 95%CI 0.86 to 0.90), DBP (r=0.75, 95%CI 0.70 to 0.80) and PP (r=0.81, 95%CI 0.76 to 0.85, p<0.0001 all, Online only Figure 101). 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 prehypertension or stage 1 hypertension, only 50-60% 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 hypertension (≥160/100 mmHg) 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 mmHg, **Table 1**). There were similar findings and

when BP classification was only based on SBP thresholds (Online Table 17). 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 prehypertension categories changed from 60% to 71% and from 50% to 66%). However, concordance remained similar or was reduced among other categories (**Table 2)**. The revised thresholds shifted the systematic underestimation of risk using cuff BP compared with intra-arterial brachial BP among the categories of prehypertension and stage 1 hypertension to a more even distribution of over- and under-estimation of the correct BP classification category. For example, in the category of cuff BP prehypertension, the percentage of intra-arterial brachial BP cases that were in the stage 1 hypertension category reduced from 36% to 17% (cuff underestimation). However, in the category of cuff BP prehypertension, 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 hypertension, the percentage of intra-arterial brachial BP cases that were either in stage 2 hypertension or prehypertension categories changed from 32% to 20% (cuff underestimation) and from 13% to 26% (cuff overestimation), respectively. With respect to delineating hypertension at the traditional cut point of 140/90 mmHg, in meta-analysis 2 sensitivity was 78.5% (95%CI 66.8 to 87.0), whilst 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 mmHg different from intra-arterial brachial SBP in 465 (67%), 275 (41%) and 173 (26%) of subjects respectively (**Figure 34A**). Similarly, when compared with intra-arterial aortic BP, brachial cuff SBP was ≥5, ≥10 or ≥15

mmHg different in 1236 (67%), 748 (40%) and 411 (22%) of subjects respectively (**Figure 34B**). Results were similar for DBP differences, although there was better agreement for DBP differences ≥15 mmHg (Online Figure 121).

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 (Online Tables 18-19). 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.

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, Online Tables 20-22). There were no significant differences in BP values for published versus unpublished data ($p>0.05$, Online Tables 23-25). In meta-analysis 2 and 3, there were no significant differences when data was analyzed based on single cuff BP measures versus the average of multiple cuff BP measures. Correlations between cuff and intra-arterial BP were similar irrespective of the number of cuff BP measures as was ~~Furthermore,~~ BP classification analysis. ~~was consistent irrespective of the number of cuff~~

measures. Differences between cuff and intra-arterial BP were not significantly influenced by the type of catheter used for intra-arterial BP measurement (data not shown).

Discussion

With hypertension as the single major risk factor for global disease burden,(1) the accuracy of clinic BP methods is critical. On the basis of several lines of evidence questioning the accuracy of cuff BP, a series of interconnected individual participant meta-analyses were performed to interrogate this issue. There were several key findings. Firstly, 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. Thirdly, 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 prehypertension to stage 1 hypertension. These data do not weaken the firmly established evidence on the critical role of cuff measured BP for assessing cardiovascular risk, but the findings do indicate the need to improve accuracy standards of cuff BP devices.

Potential c~~C~~linical implications

A key aspiration identified to address the global burden of disease related to high BP is improved diagnosis and characterization of the hypertensive phenotype (84). Our findings relate directly to this goal because a fundamental problem with BP accuracy was identified that affects most (but not all) cuff BP devices~~, with a key problem being the underestimation of the actual risk related to BP~~. Despite strong correlations between cuff BP and intra-arterial BP, from the cuff BP devices examined, 16 out of 22 significantly underestimated intra-arterial brachial SBP (**Figure 1~~2~~, panel A**) and 15 out of 18 significantly underestimated pulse pressure (**Figure 1~~2~~, panel C**), with the mean difference in the magnitude of underestimation often exceeding 10 mmHg. Translating these error margins to the traditional classification of BP based on intra-arterial SBP readings, cuff BP correctly identified prehypertension and stage 1 hypertension only in about half the participants, whether based on intra-arterial brachial or aortic SBP (**Table 1, panels A and B**). ~~Most of the misclassification of intra-arterial brachial BP was due to underestimation by cuff BP; for example, 36% of people with stage 1 hypertension were misclassified as having prehypertension, and 31% of people with stage 2 hypertension were misclassified as having stage 1 hypertension (**Table 1, panel A**).~~ Concordance with revised intra-arterial brachial BP thresholds (based on cuff BP percentile rank) was improved from 50% to 66% in the prehypertension range (**Tables 1 and 2**). This analysis also resulted in less propensity toward systematic underestimation of risk using cuff BP among the categories of prehypertension and stage 1 hypertension, and instead a relatively even distribution was observed towards both over- and under-estimation of correct classification of intra-arterial BP (**Table 2**). The true implications of these findings with respect to identification of risk related to BP in clinical practice will need to be gauged in future studies. ~~speculate that these cuff BP~~

~~inaccuracies could inadvertently underlie the concept of "residual cardiovascular risk" despite BP control~~ (85)~~.~~

~~Although the broader clinical impact of cuff BP underestimation is not able to be tested within this current analysis, the natural consequence of lower recorded BP in clinical practice is a downgrading of risk projection, leading to less incentive for initiation (or uptitration) of therapy or lifestyle intervention, and a forgone opportunity to reduce cardiovascular risk. This outcome would have wide reaching potential for adverse health and economic effects at the population level.~~(5,86) ~~Then again, a~~An argument could be raised against our findings being a major clinical problem because hypertension 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 could be valid if there were consistent systematic error(s), but in fact there was little uniformity and wide inter-device variability with respect to SBP, DBP and PP accuracy. To definitively clarify the issue, separate analysis on the accuracy of BP devices used in all the seminal clinical trials would need to be undertaken. In any case, a reasonable degree of confidence in cuff BP being representative of intra-arterial brachial or aortic SBP is provided with readings <120/80 mmHg or ≥160/100 mmHg (**Table**~~**s**~~ **1** ~~**and 2**~~).

Cuff BP validation standards

Guidance on validation protocols for cuff BP devices is provided by several scientific bodies,(33,87-91) however, there are many procedural differences between guidelines on features such as sample size, acceptable margin of error and pass criteria (92). When comparing BP device performance with the reference standard (which can be intra-arterial BP or, most

often, mercury sphygmomanometry), differences of 0 – 5 mmHg are considered to be "very accurate," whereas differences >15 mmHg are "very inaccurate."(89) 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 mmHg and only 5% of differences fall outside 15 mmHg (33). 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 – 5 mmHg, and >20% were >15 mmHg from intra-arterial SBP (**Figure 43**), which 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, and this is an area of future research need.

A novel finding with respect to the use of mercury sphygmomanometry as a reference standard in BP validation protocols is that this method was not without 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 (Online Table 16). 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 casts 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 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, which is applicable to BP device validation protocols in which cuff BP is compared against intra-arterial BP at the radial (93), brachial (10), or aortic (55) level. Improvement of BP device accuracy standards is desirable (29).

Strengths and limitations

Individual level data were acquired from a wide variety of studies employing high-quality techniques and spanning several decades of investigations, altogether 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. Further, although intra-arterial BP is regarded as the reference standard measurement of BP (94,95), inaccurate BP is still possible via numerous sources of error if operators do not follow appropriate techniques (e.g. catheter handling and dynamic response),(96) or variability in BP between the recording of cuff and intra-arterial measurements, or if measures being compared are recorded sequentially rather than simultaneously, or within contralateral rather than ipsilateral arterial sites. Reassuringly, the sensitivity analyses showed no significant difference between the studies that received the maximum quality rating for experimental design taking into consideration the above 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, as

such, there was a bias towards overweight, middle-to-older-aged men. Therefore, the findings cannot be widely generalized.

Conclusions

Cuff BP is the cornerstone method for hypertension management and physicians need to have confidence in its accuracy. The most important finding of the present study with respect to hypertension management was the inaccuracy of cuff BP when compared with intra-arterial brachial BP (underestimated SBP and PP; overestimated DBP) and aortic BP (wide variability for SBP; overestimated DBP; underestimated PP). These deviations substantially influenced BP classification according to clinical guideline criteria~~, with underestimation of cardiovascular risk being of largest concern to daily practice~~. While accepting the very important clinical role of cuff BP in general medicine, it is expected that the inadequacies identified within this work could be improved with better (more accurate) non-invasive cuff BP methods to estimate brachial or aortic BP. Notionally, this should then lead to reduced cardiovascular disease burden through enhanced clinical diagnosis and management of hypertension.

Perspectives

Competency in Medical Knowledge: There is substantial variability of cuff BP device accuracy for measurement of intra-arterial brachial or aortic BP. This theoretically has clinical implications, however, further studies are required to confirm this hypothesis.

Translational Outlook: Development of new methods of BP measurement with improved accuracy is desirable. These methods should undergo robust validation to ensure high levels of accuracy.

References

1. 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;386:2287-323.
2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. 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;360:1903-13.
3. Kannel WB. Role of blood pressure in cardiovascular disease: the Framingham Study. Angiology 1975;26:1-14.
4. 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;45:142-61.
5. Jones DW, Appel LJ, Sheps SG, Roccella EJ, Lenfant C. Measuring blood pressure accurately: new and persistent challenges. JAMA 2003;289:1027-30.
6. 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;277:739-45.
7. Liszka HA, Mainous AG, 3rd, King DE, Everett CJ, Egan BM. Prehypertension and cardiovascular morbidity. Annals of family medicine 2005;3:294-9.
8. 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;373:2103-16.
9. 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;52:1675-1680.
10. Hunyor SN, Flynn JM, Cochineas C. Comparison of Performance of Various Sphygmomanometers with Intra-Arterial Blood-Pressure Readings. Br Med J 1978;2:159-162.
11. Cheng HM, Wang KL, Chen YH et al. Estimation of central systolic blood pressure using an oscillometric blood pressure monitor. Hypertens Res 2010;33:592-9.
12. 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;7:313-8.
13. 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;11:138-144.
14. Kavanagh-Gray D. Comparison of central aortic and peripheral artery pressure curves. Can Med Assoc J 1964;90:1468-71.
15. Kollias A, Lagou S, Zeniodi ME, Boubouchairopoulou N, Stergiou GS. Association of Central Versus Brachial Blood Pressure With Target-Organ Damage: Systematic Review and Meta-Analysis. Hypertension 2016;67:183-190.
16. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 2010;31:1865-71.

17. 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;62:1780-7.
18. Millasseau S, Agnoletti D. Non-invasive estimation of aortic blood pressures: a close look at current devices and methods. Curr Pharm Des 2015;21:709-18.
19. Sharman JE, Laurent S. Central blood pressure in the management of hypertension: soon reaching the goal? J Hum Hypertens 2013;27:405-11.
20. Mitchell GF. Central pressure should not be used in clinical practice. Artery Research 2015;9:8-13.
21. Sharman JE. Central pressure should be used in clinical practice. Artery Research 2015;9:1-7.
22. Cameron JD. Comparison of noninvasive devices for assessing central blood pressure parameters: what to compare, when and why. J Hypertens 2013;31:27-31.
23. Narayan O, Casan J, Szarski M, Dart AM, Meredith IT, Cameron JD. Estimation of central aortic blood pressure: a systematic meta-analysis of available techniques. J Hypertens 2014;32:1727-40.
24. Davies JI, Band MM, Pringle S, Ogston S, Struthers AD. Peripheral blood pressure measurement is as good as applanation tonometry at predicting ascending aortic blood pressure. J Hypertens 2003;21:571-6.
25. Cheng HM, Lang D, Tufanaru C, Pearson A. Measurement accuracy of non-invasively obtained central blood pressure by applanation tonometry: a systematic review and meta-analysis. Int J Cardiol 2013;167:1867-76.
26. 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;289:2560-72.
27. 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;313:1657-65.
28. 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.
29. 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;In Press.
30. Sprafka JM, Strickland D, Gomez-Marin O, Prineas RJ. The effect of cuff size on blood pressure measurement in adults. Epidemiology 1991;2:214-7.
31. Temmar M, Jankowski P, Peltier M et al. Intraaortic pulse pressure amplification in subjects at high coronary risk. Hypertension 2010;55:327-32.
32. Tummers B. DataThief III manual v. 1.1. 2005.
33. 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:S43-S62.
34. Riley RD, Lambert PC, Staessen JA et al. Meta-analysis of continuous outcomes combining individual patient data and aggregate data. Stat Med 2008;27:1870-93.
35. 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;27:169-76.

36. 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;27:674-9.
37. Davies JE, Shanmuganathan M, Francis DP, Mayet J, Hackett DR, Hughes AD. Caution using brachial systolic pressure to calibrate radial tonometric pressure waveforms: lessons from invasive study. Hypertension 2010 55:e4.
38. Ding FH, Li Y, Zhang RY, Zhang Q, Wang JG. Comparison of the SphygmoCor and Omron devices in the estimation of pressure amplification against the invasive catheter measurement. J Hypertens 2013;31:86-93.
39. Gould L, Shariff M. Comparison of the left ventricular, aortic and brachial arterial first derivative. Vasc Surg 1969;3:34-9.
40. Liang F, Yin Z, Fan Y, Chen K, Wang C. In vivo validation of an oscillometric method for estimating central aortic pressure. Int J Cardiol 2015;199:439-441.
41. 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;30:581-6.
42. 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;105:1858-63.
43. !!! INVALID CITATION !!! (9-11,39,42,44-57).
44. Aakhus S, Torp H, Haugland T, Hatle L. Noninvasive Estimates of Aortic Root Pressures - External Subclavian Arterial Pulse Tracing Calibrated by Oscillometrically Determined Brachial Arterial Pressures. Clin Physiol 1993;13:573-586.
45. Bhatt SD, Hinderliter AL, Stouffer GA. Influence of Sex on the Accuracy of Oscillometric-Derived Blood Pressures. J Clin Hypertens 2011;13:112-119.
46. 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;103:879-86.
47. Bos WJW, Van Goudoever J, Wesseling KH et al. Pseudohypertension and the measurement of blood pressure. Hypertension 1992;20:26-31.
48. Costello BT, Schultz MG, Black JA, Sharman JE. Evaluation of a brachial cuff and suprasystolic waveform algorithm method to noninvasively derive central blood pressure. Am J Hypertens 2015;28:480-6.
49. 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;30:1533-9.
50. Lin AC, Lowe A, Sidhu K, Harrison W, Ruygrok P, Stewart R. Evaluation of a novel sphygmomanometer, which estimates central aortic blood pressure from analysis of brachial artery suprasystolic pressure waves. J Hypertens 2012;30:1743-50.
51. Lowe A, Harrison W, El-Aklouk E, Ruygrok P, Al-Jumaily AM. Non-invasive model-based estimation of aortic pulse pressure using suprasystolic brachial pressure waveforms. J Biomech 2009;42 2111-5.
52. 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;65:1141-6.
53. Nagle FJ, Naughton J, Balke B. Comparisons of direct and indirect blood pressure with pressure-flow dynamics during exercise. J Appl Physiol 1966;21:317-20.

54. Nakagomi A, Okada S, Shoji T, Kobayashi Y. Aortic pulsatility assessed by an oscillometric method is associated with coronary atherosclerosis in elderly people. Blood Press 2016:1-8.
55. 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;22:410-415.
56. Ott C, Haetinger S, Schneider MP, Pauschinger M, Schmieder RE. Comparison of two noninvasive devices for measurement of central systolic blood pressure with invasive measurement during cardiac catheterization. J Clin Hypertens (Greenwich) 2012;14:575-9.
57. Park CM, Korolkova O, Davies JE et al. Arterial pressure: agreement between a brachial cuff-based device and radial tonometry. J Hypertens 2014;32:865-872.
58. 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;19:280-7.
59. 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;31:77-85.
60. Rajani R, Chowienczyk P, Redwood S, Guilcher A, Chambers JB. The noninvasive estimation of central aortic blood pressure in patients with aortic stenosis. J Hypertens 2008;26:2381-8.
61. Saul F, Aristidou Y, Klaus D, Wiemeyer A, Losse B. Comparison of Invasive Blood-Pressure Measurements with Indirect Oscillometric Wrist and Upper Arm Values. Z Kardiol 1995;84:675-685.
62. Smulyan H, Siddiqui DS, Carlson RJ, London GM, Safar ME. Clinical utility of aortic pulses and pressures calculated from applanated radial-artery pulses. Hypertension 2003;42:150-5.
63. Smulyan H, Sheehe PR, Safar ME. A preliminary evaluation of the mean arterial pressure as measured by cuff oscillometry. Am J Hypertens 2008;21:166-71.
64. Smulyan H, Mukherjee R, Sheehe PR, Safar ME. Cuff and aortic pressure differences during dobutamine infusion: a study of the effects of systolic blood pressure amplification. Am Heart J 2010;159:399-405.
65. 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.
66. Takazawa K, Kobayashi H, Shindo N, Tanaka N, Yamashina A. Relationship between radial and central arterial pulse wave and evaluation of central aortic pressure using the radial arterial pulse wave. Hypertens Res 2007;30:219-28.
67. 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;30:908-16.
68. Weber F, Lindemann M, Erbel R, Philipp T. Indirect and direct simultaneous, comparative blood pressure measurements with the Bosstron 2 (R) device. Kidney Blood Press Res 1999;22:166-171.
69. Weber T, Wassertheurer S, Rammer M et al. Validation of a brachial cuff-based method for estimating central systolic blood pressure. Hypertension 2011;58:825-32.

70. Williams B, Lacy PS, Yan P, Hwee CN, Liang C, Ting CM. 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;57:951-61.
71. Berliner K, Yildiz M, Garnier B, Lee DH, Fujiy H. Blood Pressure Measurements in Obese Persons - Comparison of Intra-Arterial and Auscultatory Measurements. Am J Cardiol 1961;8:10-&.
72. Freis ED, Sappington RF, Jr. Dynamic reactions produced by deflating a blood pressure cuff. Circulation 1968;38:1085-96.
73. Gelman ML, Nemati C. A new method of blood pressure recording that may enhance patient compliance. JAMA 1981;246:368-70.
74. Gould BA, Hornung RS, Kieso HA, Altman DG, Cashman PM, Raftery EB. Evaluation of the Remler M2000 blood pressure recorder. Comparison with intraarterial blood pressure recordings both at hospital and at home. Hypertension 1984;6:209-15.
75. Hayashi S, Yamada H, Bando M et al. Augmentation index does not reflect risk of coronary artery disease in elderly patients. Circ J 2014;78:1176-82.
76. Melamed R, Johnson K, Pothen B, Sprenkle MD, Johnson PJ. 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;17:179-83.
77. 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;23:283-97.
78. Omboni S, Parati G, Groppelli A, Ulian L, Mancia G. Performance of the AM-5600 blood pressure monitor: comparison with ambulatory intra-arterial pressure. J Appl Physiol (1985) 1997;82:698-703.
79. Raftery EB, Ward AP. The indirect method of recording blood pressure. Cardiovasc Res 1968;2:210-8.
80. Roberts LN, Smiley JR, Manning GW. A comparison of direct and indirect blood-pressure determinations. Circulation 1953;8:232-42.
81. 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;77:1297-305.
82. Sagiv M, Ben-Sira D, Goldhammer E. Direct vs. indirect blood pressure measurement at peak anaerobic exercise. Int J Sports Med 1999;20:275-8.
83. Vardan S, Mookherjee S, Warner R, Smulyan H. Systolic hypertension. Direct and indirect BP measurements. Arch Intern Med 1983;143:935-8.
84. 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 [Epub Ahead of Print].
85. Blacher J, Evans A, Arveiler D et al. Residual cardiovascular risk in treated hypertension and hyperlipidaemia: the PRIME Study. J Hum Hypertens 2010;24:19-26.
86. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 2000;343:16-22.
87. American National Standard Non-invasive sphygmomanometers - Part 2: Clinical validation of automated measurement type. ANSI/AAMI/ISO 81060-2:2009. Arlington, Virginia: AAMI, 2009.

88. 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;15:23-38.
89. 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;7:3-17.
90. Tholl U, Anlauf M. [Conscientious evaluation of measuring accuracy. Hypertension League provides approval seals for automatic blood pressure units]. MMW Fortschr Med 1999;141:45.
91. White WB, Berson AS, Robbins C et al. National standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. Hypertension 1993;21:504-9.
92. Beime B, Deutsch C, Gomez T, Zwingers T, Mengden T, Bramlage P. Validation protocols for blood pressure-measuring devices: status quo and development needs. Blood Press Monit 2016;21:1-8.
93. O'Callaghan WG, Fitzgerald DJ, O'Malley K, O'Brien E. Accuracy of indirect blood pressure measurement in the elderly. Br Med J (Clin Res Ed) 1983;286:1545-6.
94. 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;54:375-83.
95. Perloff D, Grim C, Flack J et al. Human blood pressure determination by sphygmomanometry. Circulation 1993;88:2460-70.
96. Gardner RM. Direct blood pressure measurement--dynamic response requirements. Anesthesiology 1981;54:227-36.

Figure legends

Central Illustration. Summary findings from individual participant data meta-analyses of cuff blood pressure (BP) 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 or ≥160/100 mmHg to predict intra-arterial brachial or aortic BP. Improved accuracy is recommended in the BP range from prehypertension (≥120/80 to <140/90 mmHg) to stage 1 hypertension (≥140/90 to <160/100 mmHg), where concordance with intra-arterial BP was not strong.

~~**Figure 1. Forest plot of intra-arterial aortic and brachial BP difference.** Pooled mean difference and 95% confidence interval for meta-analysis 1, the comparison of intra-arterial aortic and brachial systolic blood pressure (SBP, panel A), diastolic BP (DBP, panel B) and pulse pressure (PP, panel C).~~

Figure 1~~2~~. Forest plot of brachial cuff and intra-arterial brachial BP difference. Pooled mean difference and 95% confidence interval for meta-analysis 2, the comparison of brachial cuff and intra-arterial brachial systolic blood pressure (SBP, panel A), diastolic BP (DBP, panel B) and pulse pressure (PP, panel C).

Figure 2~~3~~. Forest plot of brachial cuff and intra-arterial aortic BP difference. Pooled mean difference and 95% confidence interval for meta-analysis 3, the comparison of brachial cuff and intra-arterial aortic systolic blood pressure (SBP, panel A), diastolic BP (DBP, panel B) and pulse pressure (PP, panel C).

Figure 34. Individual brachial cuff and intra-arterial BP 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 mmHg 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 mmHg (dotted line (orange)) and ±15 mmHg (dot-dashed line (red)). The solid black horizontal line represents a BP difference = 0 mmHg.

Table 1. 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	**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~~**Brachial cuff blood pressure**~~ ~~**Normal**~~	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~~**Brachial cuff blood pressure**~~	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 (6)	795 (78)		107 (16)

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 ~~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. ~~According to JNC 7, normal BP <120/80 mmHg; prehypertension 120-139/80-89 mmHg; stage 1 hypertension 140-159/90-99 mmHg and stage 2 hypertension ≥160/100 mmHg.~~ 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.

Table 2. 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 based on revised intra-arterial thresholds.

A		**Intra-arterial brachial blood pressure**			
n=668		**Normal**	**Prehypertension**	**Stage 1 hypertension**	**Stage 2 hypertension**
Cuff blood pressure		SBP <124.5 and DBP <74	SBP 124.5- <150 and/or DBP 74– <85	SBP 150- <167 and/or DBP 85– <91	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 SBP <120 and DBP<80	<24th	302 (74)	97 (25)	6 (1)	1 (0)
Prehypertension SBP 120-139 and/or DBP 80 – 89	24th - <59th	89 (15)	364 (61)	133 (22)	10 (2)
Stage 1 hypertension SBP 140-159 and/or DBP 90 – 99	59th – <86th	14 (3)	108 (27)	245 (56)	67 (14)
Stage 2 hypertension SBP ≥160 or DBP ≥100	≥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.