Indian Heart Journal 70 (2018) S213–S220

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Prevalence and real-world assessment of central aortic blood pressure in adult patients with essential hypertension uncontrolled on single anti-hypertensive agents

Ranjan Kumar Sharma [a, *], Manish Verma [b], Ravi M. Tiwari [b], Abhay Joshi [b], Chirag A. Trivedi [b], Deepa R. Chodankar [b]

[a] Department of Cardiology, Nil Ratan Sircar Medical College and Hospital, 138, Acharya Jagadish Chandra Bose Road, Kolkata, West Bengal 700014, India
[b] Sanofi House, No 117-B, L & T Business Park, Saki Vihar Road, Powai, Mumbai, Maharashtra 400072, India

ARTICLE INFO

Article history:
Received 20 March 2018
Accepted 19 November 2018
Available online 8 December 2018

Keywords:
Brachial blood pressure
Central aortic pressure
Hypertension
India
Real-world study

ABSTRACT

Objective: To assess the prevalence of high central aortic pressure (CAP) in Indian patients with uncontrolled essential hypertension while on anti-hypertensive monotherapy. Also, to determine correlation between brachial blood pressure (BBP) and CAP, and ascertain if it is impacted by anti-hypertensive drug class and patients' age.

Methods: In this real-world, observational, prospective study, patients (30–70 years) with uncontrolled BBP (systolic BP [SBP] ≥140 mmHg or diastolic BP [DBP] ≥90 mmHg) were enrolled. Treatment was adjusted at Visit 1 (baseline), based on BBP and at treating physicians' discretion. Primary endpoint was proportion of patients with uncontrolled central aortic SBP (>125 mmHg) at baseline. Secondary endpoints were comparison of BBP and CAP across drugs classes and age groups at baseline and Visit 2 (End-of-study, ~8 weeks post-baseline), and proportion of patients with uncontrolled central SBP at end-of-study.

Results: Of 2030 patients screened, 1949 patients reported at baseline and 1740 patients completed end-of-study visit. Central SBP was >125 mmHg for 84.3% patients at baseline, and 48% patients at end-of-study. Interestingly, at end-of-study, 6.6% patients still had uncontrolled brachial SBP and controlled central SBP, while 13.6% patients had uncontrolled central SBP and controlled brachial SBP. At both visits, brachial SBP and central SBP showed positive correlation across most drug classes and age groups. At baseline, ACE inhibitors showed better efficacy than other drug classes. At end-of-study, BP control was better with fixed-dose combinations, though free–drug combinations were more frequently prescribed.

Conclusion: Measurement of CAP along with BBP can be vital in management of hypertension.

Ctri registration number: CTRI/2015/10/006302.

1. Introduction

Hypertension, defined as elevated systolic or diastolic blood pressure (SBP/DBP ≥140/90 mmHg according to JNC 7[1] and ≥130/80 mmHg according to ACC/AHA guidelines[2]) has causal association with cardiovascular events.[3,4]

Traditionally, the diagnosis and management of hypertension has been done based on brachial blood pressure (BBP), also considered as the surrogate marker for estimating cardiovascular risk.[5,6] However, emerging data shows that central aortic pressure (CAP) rather than BBP is a more sensitive marker of cardiovascular events such as stroke and myocardial infarction, and a better predictor of progression of hypertension, target-organ damage, and long-term cardiovascular outcomes.[7–9] Therefore, using CAP as a prognostic tool may help in efficiently managing patients with essential hypertension and achieve better clinical outcomes. Though, the current evidences indicate CAP as a valuable predictor

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ADR, adverse drug reaction; ARB, angiotensin II receptor blockers; BB, beta-blockers; BBP, brachial blood pressure; CAP, central aortic pressure; CI, confidence interval; DBP, diastolic blood pressure; DHP-CCB, dihydropyridine calcium channel blockers; FDC, fixed-dose combination; LCD, low ceiling diuretics; PP, per-protocol; SBP, systolic blood pressure; V1, Visit 1; V2, Visit 2.

* Corresponding author.
E-mail address: ranjankumars@yahoo.com (R.K. Sharma).

https://doi.org/10.1016/j.ihj.2018.11.013

of all-cause mortality and CV events; lack of widespread and routine use of CAP in clinical practice limits the prognostic utility of it.[10–12]

In order to bridge the gap in current knowledge, we evaluated the prevalence of CAP in uncontrolled, uncomplicated essential hypertension in Indian patients receiving anti-hypertensive monotherapy. Additionally, correlation between BBP and CAP, and effect of age and drug class, if any, on such correlation was evaluated.

2. Methods

2.1. Study design and enrolment criteria

This national, multicenter, observational, prospective, real-world, Sanofi-sponsored study was conducted between August 2015 and September 2016. In this study, 108 physicians randomly selected across India, actively recruited patients in a consecutive manner.

The study recorded data at two clinic visits; a baseline visit (visit 1) and end of study (visit 2) planned at 8 weeks (±15 days) after the visit 1.

The study included adult patients (aged 30–70 years), with uncontrolled essential hypertension (brachial SBP ≥140 mmHg or brachial DBP ≥90 mmHg) despite receiving anti-hypertensive monotherapy for at least a month and hence were prospective candidates for an add-on therapy.At the time of recruitment, an add-on anti-hypertensive therapy (fixed-dose combination [FDC] or free–drug combination) was prescribed. Pregnant women or patients with hypertensive emergencies, known cases of secondary hypertension or known cases of complications due to hypertension, were excluded.

2.2. Study endpoints

The primary endpoint was the proportion of patients with a central aortic SBP >125 mmHg at visit 1.[6,13,14] The secondary endpoints were the comparison of BBP and CAP across drugs classes and age groups at visit 1 and visit 2, and the proportion of patients with uncontrolled, uncomplicated hypertension as assessed by central SBP >125 mmHg at visit 2.

2.3. Data collection and study assessments

Data for visit 1 and visit 2 were recorded in the electronic case-report form. Treatment was adjusted at visit 1 and patients were followed-up at visit 2. The treatment decisions, including drug regimen and timings of doses, at visit 1 were based on BBP measurements and at treating physicians' discretion. Both visits to the clinic were conducted according to clinical practice. The CAP was measured using cuff-based oscillometry device (Pulsecor BP Plus, Uscom, Australia), which monitors supra-systolic oscillometric CAP.[15,16] The device measures BP and BP waveforms in the heart and in the arm that could previously only be measured by invasive cardiac catheterization. The BBP was measured in same manner as in routine clinical practice. Both CAP and BBP were measured in a sitting posture after ~5 min of rest, with the cuff placed on upper arm. Both readings were obtained at least in duplicates at an interval of 5–10 min, and the mean of two readings was used for analyses. As no product exposure was studied in particular and established anti-hypertensive agents were used, only a non-systematic collection of safety data was performed. Safety was to be assessed in terms of occurrence of adverse drug reactions (ADRs) with Sanofi products, coded using Medical Dictionary for Regulatory Activities version 18.0. Any reported ADR associated with Sanofi drug were to be closely monitored and followed-up by the pharmacovigilance department.

2.4. Statistical analyses

The sample size was estimated based on the SITE study[17] which included Indian patients with diabetes and hypertension. Assuming the prevalence of essential hypertension uncontrolled on an anti-hypertensive monotherapy as 77.1%, for an absolute precision of 2% measured with a 95% confidence interval (CI), 1696 evaluable patients were required. Considering a drop-out rate of 15%, the planned sample size was 2000 patients.

All patients in the study were included in the eligible population. All primary and secondary analyses were conducted on the evaluable population, defined as a subset of patients of the eligible population, having no major protocol deviations including non-conformity to the eligibility criteria.

Data were summarized using descriptive methods, and mean differences were presented with 95% CIs. The 95% CIs for proportion of patients with central SBP >125 mmHg at visit 1 and visit 2 were derived by Clopper and Pearson method. Paired *t*-test was used to compare the BBP and CAP for anti-hypertensive drug classes and age groups at both visits. Pearson's correlation coefficients between BBP and CAP were presented for each anti-hypertensive drug class and each age group separately for both visits. All statistical analyses were performed using SAS® version 9.2 (Cary, NC, USA).

2.5. Ethics

The study was conducted in accordance with the principles of 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments. The study complied with the guidelines for Good Epidemiology Practice and all applicable international guidelines, national laws, and regulations of India. Study protocol was approved by local Institutional Review Board/Independent Ethics Committee (Appendix A). All patients signed a written informed consent prior to study initiation.

3. Results

3.1. Patient disposition

A total of 2030 patients were screened from 95 sites by actively recruiting physicians in 37 cities across 15 states and one union territory of India. Twenty patients were recruited by 54 sites, <20 patients were recruited by 18 sites, and more than 20 patients were recruited by 23 sites. Of the, 1955 patients meeting the eligibility criteria; 1949 eligible patients had no major protocol deviations at visit 1. A total of 1740 patients completed the follow-up at visit 2 (Fig. 1). There were 14 subjects whose duration of hypertension was <1 month and range for hypertension duration was 7–15 days. The information were recorded and analysed. Based on investigator's judgment, this was categorized as 'minor' deviation and not a protocol violation; it did not affect the patient safety. Hence these subjects were included in the per-protocol population.

3.2. Demographics and baseline characteristics

Demographics and baseline characteristics are presented in Table 1. Prior to visit 1, patients were receiving mainly angiotensin II receptor blocker (ARB, n = 896, 46%). At visit 1, treatment was adjusted and dihydropyridine calcium channel blockers (DHP-CCB, n = 598, 30.7%) were most frequently prescribed (Table 1).

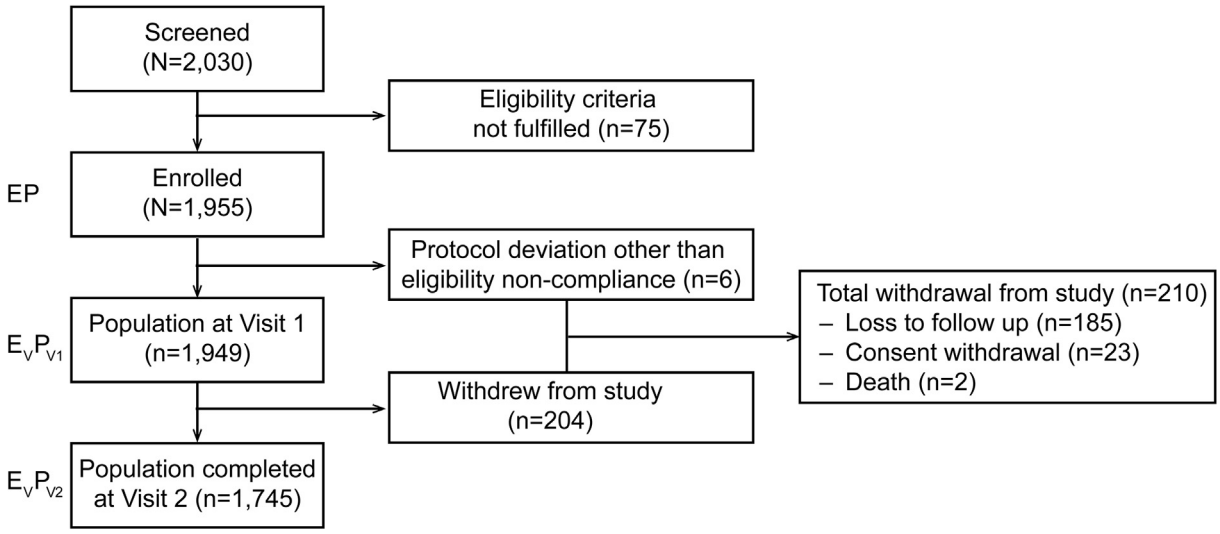

Fig. 1. Patient disposition. EP, eligible population; EvP, evaluable population. Patients were recruited from the following sites across India – East zone (Orissa, Assam, West Bengal, and Bihar; n = 20), North zone (Haryana, Delhi, Rajasthan, Jammu & Kashmir, Uttar Pradesh, and Punjab; n = 17), South zone (Kerala, Tamil Nadu, Telangana, and Karnataka; n = 31), West zone (Gujarat and Maharashtra; n = 27). $EvP_{V1,}$ 1949 eligible patients had no major protocol deviations at visit 1 and were included in EP population (EP_{V1}). $EvP_{V2,}$ 1740 patients completed the follow-up at Visit 2 and were termed as EP_{V2} (EP population at visit 2).

Table 1
Patient demographics and baseline characteristics.

Demographics/Baseline characteristics	Total (N = 1949)
Gender, n (%)	
Men	1051 (53.9)
Women	898 (46.1)
Age (years), mean (SD)	53.2 (10.5)
Age groups (years), n (%)	
30–40	287 (14.7)
41–50	500 (25.7)
51–60	621 (31.9)
61–70	541 (27.8)
Blood pressure (mmHg), mean[a] (SD)	
Brachial SBP	156.5 (14.5)
Brachial DBP	96.3 (8.6)
Central SBP	142.3 (19.0)
Central DBP	90.3 (13.4)
Duration of hypertension (years), median (range)	4.0 (0.0191–42.0)
Common medical history, n (%)	
Diabetes	741 (38.0)
Smoker	149 (7.6)
Dyslipidaemia	393 (20.2)
Coronary artery disease	71 (3.6)
Medications prior to V1 enrolment, n (%)	
ARB	896 (46.0)
DHP-CCB	474 (24.3)
BB	322 (16.5)
ACEI	225 (11.5)
Other drugs	32 (1.7)
Most common medications started at V1 enrolment, n (%)	
DHP-CCB	598 (30.7)
ACEI	382 (19.6)
ARB	380 (19.5)
BB	228 (11.7)
LCD, thiazides	168 (8.6)
ACEI + DHP-CCB	97 (5.0)
LCD, excluding thiazides	91 (4.7)
ARB + DHP-CCB	20 (1.0)

Drug classes having n > 20 (frequently prescribed) have been mentioned here. Data for other drug classes has not been given.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II antagonist; BB, beta-blocker; DBP, diastolic blood pressure; DHP-CCB, di-hydropyridine calcium channel blocker; mmHg, millimeter mercury; LCD, low-ceiling diuretics; N, total patients analysed; n, patients with outcome; SBP, systolic blood pressure; SD, standard deviation; V, visit.
[a] mean of the first and second blood pressure reading for patients with both readings present.

3.3. Patients with uncontrolled BP at visit 1 and visit 2

At visit 1, all patients in the per-protocol population had either elevated brachial SBP or brachial DBP (as per the inclusion criteria); after treatment adjustment, patients with uncontrolled BBP reduced to 51.8% (95% CI 49.0–54.0) at visit 2.

Uncontrolled central SBP (>125 mmHg) was reported in 84.3% (1643/1949); 95% CI 83.0–86.0) patients at visit 1 and in 48% (836/1740; 95% CI 46.0–50.0) patients at visit 2.

3.4. BBP and CAP: overall population and across drug classes

At visit 1, in the overall population, the mean difference between brachial SBP and central SBP (14.2 mmHg, 95% CI 13.611–14.797) and between brachial DBP and central DBP (5.9 mmHg, 95% CI 5.478–6.401) were significant and was reflected across individual drug classes (Fig. 2a, $p < 0.0001$). There was a moderate positive correlation (r range: 0.59 to 1.0) between brachial SBP and central SBP across most of the drug classes except centrally-acting anti-adrenergic agents ($r = -1.0$) (Supplementary Table 1). However, correlation could not be derived for non DHP-CCB due to small sample size.

At visit 1, mean brachial SBP/brachial DBP were 156.5/96.3 mmHg and mean central SBP/central DBP were 142.3/90.3 mmHg (Tables 1, 2). Patients treated with angiotensin converting enzyme inhibitors (ACEI) had the lowest mean central SBP (139.9 mmHg) among the individual drug classes (ARB, 142.9 mmHg; DHP-CCB, 141.3 mmHg; beta-blockers [BB], 144.4 mmHg) and significantly lower central SBP compared with BB (mean difference 4.5 mmHg, $p < 0.0345$). Similar trend was observed in central DBP, brachial SBP and brachial DBP, where BP was numerically lower with ACEI than other drug classes (Table 2).

At visit 2, in the overall population, the mean difference between brachial SBP and central SBP (9.9 mmHg, 95% CI 9.553–10.413) and between brachial DBP and central DBP (4.6 mmHg, 95% CI 4.287–5.025) were significant and was also reflected across individual drug classes and combination therapies (Fig. 2b, $p < 0.0001$ for all, $p = 0.0065$ for between brachial DBP and central DBP for LCDs other than thiazides). Among FDCs with few patients (n < 20), FDC ARB + DHP-CCB had significant mean difference between brachial

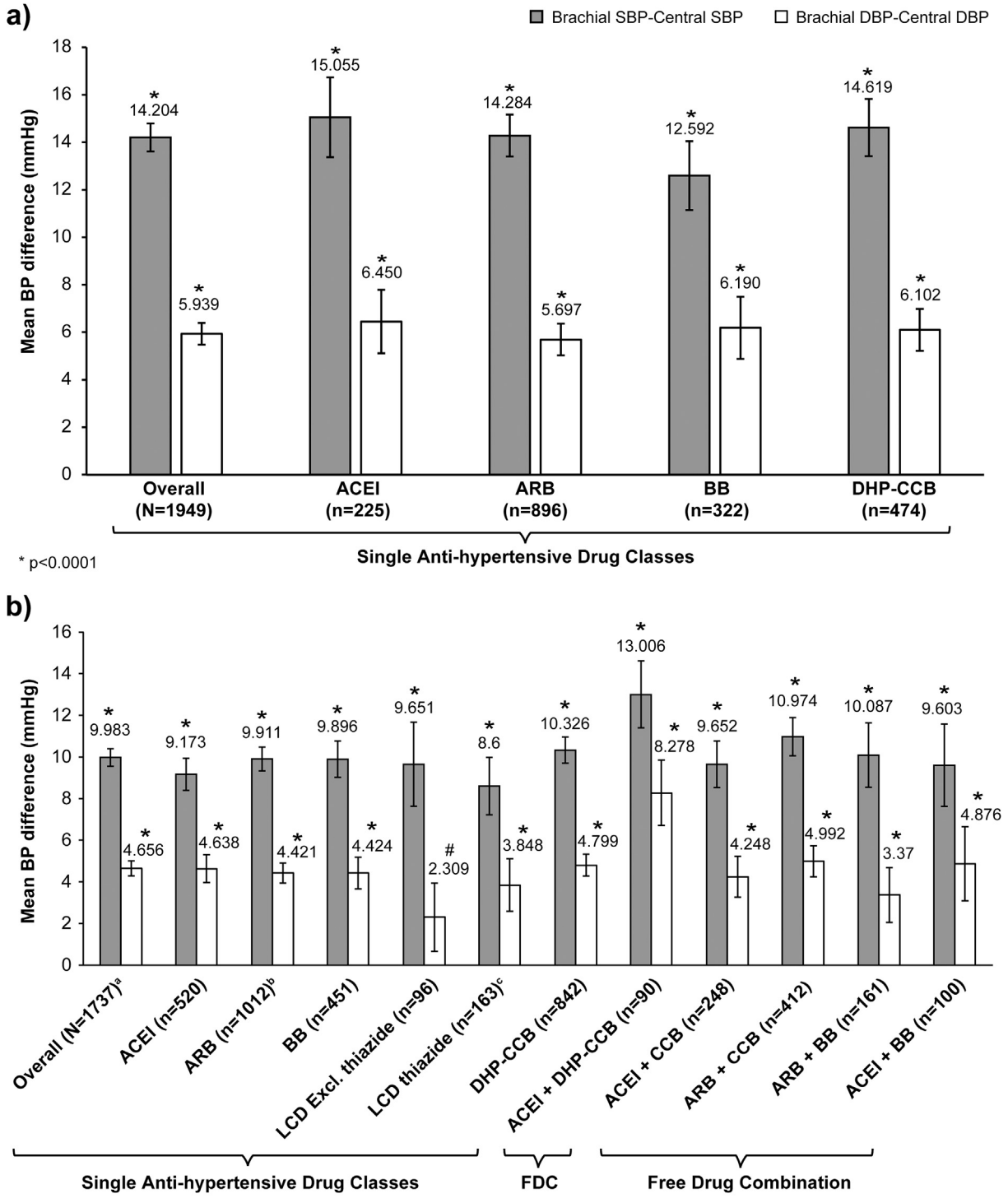

Fig. 2. Mean difference between brachial and central aortic BP for overall population and across drug classes at a) V1 and b) V2. a) N = 1736 for brachial and 1737 for central aortic BP. b) n = 1012 for brachial and 1013 for central aortic BP. c) n = 162 for brachial and 163 for central aortic BP. Drug classes having n > 20 (frequently prescribed) have been mentioned here. Data for other drug classes has not been given. Error bars indicate 95% confidence intervals. Mean of the first and second blood pressure reading was considered for patients with both readings present. If only single reading was taken then it was considered in the analysis. Patients with both readings missing were excluded from the analysis. At visit 2, the data for single drug classes, FDCs, and free-drug combinations is not mutually exclusive, but there is an overlap of patients. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; BP, blood pressure; DBP, diastolic blood pressure; DHP-CCB, di-hydropyridine calcium channel blocker; FDC, fixed-dose combination; LCD, low ceiling diuretics; SBP, systolic blood pressure; V, visit.

Table 2
Brachial and central aortic BP (systolic and diastolic) at V1 and V2 across anti-hypertensive drug classes.

Anti-hypertensive drug class	Mean (±SD)				
	N	Brachial SBP	Central SBP	Brachial DBP	Central DBP
Visit 1					
Overall	1949	156.5 (14.5)	142.3 (19.0)	96.3 (8.6)	90.3 (13.4)
ACEI	225	154.9 (14.7)	139.9 (18.7)	95.5 (7.3)	89.0 (12.7)
ARB	896	157.1 (15.0)	142.9 (19.1)	96.3 (9.0)	90.6 (13.3)
BB	322	156.9 (14.1)	144.4 (19.7)	97.0 (8.5)	90.8 (14.8)
DHP-CCB	474	155.9 (13.9)	141.3 (18.8)	96.4 (8.2)	90.3 (13.0)
Visit 2[a]					
Overall	1737[b]	136.1 (15.5)	126.1 (16.9)	85.7 (10.3)	81.0 (11.8)
Single anti-hypertensive drug classes					
ACEI	520	136.3 (15.6)	127.1 (17.0)	85.8 (10.9)	81.1 (12.7)
ARB	1013[c]	136.7 (15.5)	126.8 (17.0)	86.1 (10.3)	81.6 (11.9)
BB	451	137.7 (17.3)	127.8 (18.7)	86.3 (11.1)	81.9 (12.7)
DHP-CCB	842	136.1 (15.2)	125.8 (16.7)	86.0 (10.0)	81.2 (11.5)
LCD, excluding thiazides	96	138.4 (15.9)	128.8 (15.6)	85.5 (11.5)	83.2 (12.1)
LCD, thiazides	163[d]	133.3 (15.5)	124.7 (16.8)	85.0 (9.8)	81.1 (11.7)
Anti-hypertensive drug classes administered as FDC					
ACEI + DHP-CCB	90	132.8 (9.6)	119.8 (9.0)	83.8 (6.5)	75.5 (5.0)
Anti-hypertensive drug classes administered as free-drug combination					
ACEI + CCB	248	134.1 (15.4)	124.5 (16.9)	84.7 (10.5)	80.5 (11.8)
ARB + CCB	412	137.1 (14.1)	126.1 (15.8)	86.5 (9.6)	81.5 (11.1)
ARB + BB	161	139.5 (17.9)	129.4 (20.1)	86.2 (11.4)	82.8 (12.6)
ACEI + BB	100	136.6 (15.7)	127.0 (15.3)	84.9 (11.6)	80.0 (13.4)

Drug classes having n > 20 (frequently prescribed) have been mentioned here. Data for other drug classes has not been given.
Mean of the first and second blood pressure reading was considered for patients with both readings present. If only single reading was taken then it is considered in the analysis. Patients with both readings missing were excluded from the analysis.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II antagonist; BB, beta blocker; DBP, diastolic blood pressure; BP, blood pressure; CCB, calcium channel blocker; DHP-CCB, di-hydropyridine calcium channel blocker; FDC, fixed-dose combination; LCD, low ceiling diuretics; N, total patients analysed; SBP, systolic blood pressure; SD, standard deviation.
[a] At visit 2, the data for single drug classes, FDCs, and free–drug combinations is not mutually exclusive, but there is an overlap of patients.
[b] n = 1736 for brachial and 1737 for central aortic BP.
[c] n = 1012 for brachial and 1013 for central aortic BP.
[d] n = 162 for brachial and 163 for central aortic BP.

SBP and central SBP (13.6 mmHg, 95% CI 7.677–19.456, $p = 0.0002$) and between brachial DBP and central DBP (4.8 mmHg, 95% CI 0.489–9.045, $p = 0.0315$). Similar to visit 1, there was a moderate positive (r range: 0.51 to 1.0) correlation between brachial SBP and central SBP across most of the individual drug classes and FDCs (Supplementary Table 2). The correlations could not be derived for the remaining drug classes (high-ceiling diuretics, potassium-sparing agents, non DHP-CCB) and FDCs (ACEI + low-ceiling diuretics [LCD] thiazide) due to small sample size.

Following treatment adjustment, the mean brachial SBP was within normal range (133.3–138.4 mmHg) for individual drug classes. Noticeably, mean central SBP ranged close to normal at visit 2 (124.7–128.8 mmHg) in comparison to visit 1 (139.9–144.4 mmHg). Most FDCs (ACEI + DHP-CCB, ARB + LCD thiazide, ARB + DHP-CCB, and BB + DHP-CCB) except ACEI + LCD thiazide not only controlled brachial SBP, but also normalised central SBP. However, except ACEI + DHP-CCB, only few patients (n < 20) received the other FDCs. Free-drug combinations were more frequently prescribed than FDCs, and also helped in reducing brachial and central SBP (Table 2). Among the free–drug combinations, ACEI + CCB group had the least central SBP and brachial SBP (Table 2).

3.5. BBP and CAP: across age groups

A strong positive correlation between central SBP and brachial SBP was observed at visit 1 (r range: 0.70–0.73) and visit 2 (r range: 0.73–0.77) across all age groups except for patients in the 41–50 years age range that had moderate-to-strong correlation at visit 2 (r = 0.65).

At visit 1, brachial SBP was poorly controlled with increasing age, but no such trend was observed with central SBP across age groups (Supplementary Fig. 1a). At visit 2, both brachial SBP and central SBP remained consistent across all age groups, and well within the recommended BP cut-offs values (Supplementary Fig. 1b).

The mean difference between brachial SBP and central SBP at visit 1 across age groups was similar to that seen in overall population (~14 units), except for those in the 30–40 year age group where this difference was 12.6 units (Supplementary Fig. 2a). At visit 2, the mean difference between brachial SBP and central SBP across age groups was similar to overall population (~10 units) and decreased by 2–6 mmHg from visit 1 (Supplementary Fig. 2b).

3.6. Characteristics of patients with controlled or uncontrolled central SBP/brachial SBP at visit 2

Uncontrolled brachial SBP (≥140 mmHg) but controlled central SBP (≤125 mmHg) was reported in 6.6% (n/N = 114/1740) patients. These patients (mean ± standard deviation [SD]) age of 52.3 ± 9.6 years had history of hypertension for 3.0 years [median; range (0.0821–20.0 years)] and diabetes as the most common (46.5%, n/N = 53/114) comorbidity. The commonly prescribed treatments to these patients at Visit 1 included ARB (50.9%, n/N = 58/114), DHP-CCB (43.9%, n/N = 50/114), ACEI + DHP-CCB FDC (22.8%, n/N = 26/114), BB (21.9%, n/N = 25/114), and ACEI (15.8%, n/N = 18/114).

Uncontrolled central SBP (>125 mmHg) but controlled brachial SBP (<140 mmHg) was reported in 13.6% (n/N = 237/1740) patients. These patients (mean ± SD) age of 52.5 ± 10.0 years had history of hypertension for 4.0 years [median; range: (0.0191–30.0 years), and diabetes (40.9%, n/N = 97/237) and dyslipidaemia (24.5%, n/N = 58/237) as the most common comorbidities. The commonly prescribed treatments to these patients at Visit 1 included ARB (58.6%, n/N = 139/237), DHP-CCB (44.7%, n/N = 106/237), ACEI (32.9%, n/N = 78/237), BB (25.3%, n/N = 60/237), and LCD thiazide (11%, n/N = 26/237).

3.7. Safety

No ADRs with Sanofi products were reported in this study. Two deaths occurred during the study in patients who were not on any Sanofi product and which were attributed to an unknown cause.

4. Discussion

The study showed that CAP was largely uncontrolled in majority of patients with uncontrolled BBP who were being treated with prior anti-hypertensive monotherapy, thus predisposing these patients to an increased cardiovascular risk.[8] The uncontrolled CAP could be due to the fact that only BBP is considered by physicians to decide the treatment regimen that may be due to the cautious recommendations in the available guidelines on extensive clinical use of central BP.[18,19]

Central aortic pressure is a net effect of left ventricular contraction and peripheral vascular resistance and undergoes augmentation and peripheral amplification due to changes in the diameter and elasticity of arterial tree.[6] Augmentation increases the absolute aortic systolic pressure and is attributed to variation in cardiac ejection pattern, alteration in the various reflecting sites, arterial reservoir pressure, and an increased stiffness in aorta as well as in large arteries resulting from age or disease processes.[20] The peripheral amplification results in to a higher brachial SBP, up to 40 mmHg, than the central SBP; whereas, the diastolic and mean arterial pressures remain relatively constant.[6]

In this study, we have used the Pulsecor device to measure central BP among other devices that can estimate central aortic waveform with different methods of measurement.[6] Central SBP estimated by Pulsecor was found to be highly reproducible and comparable to that estimated by tonometry and showed a good correlation with that estimated by invasive method.[16,21]

It is evident from recent literature that measurement of CAP (rather than measurement of BBP alone) helps in evaluation of the actual pressure load imposed on the left ventricle.[5,22,23] Besides, the BP amplification (difference between central SBP and brachial SBP) has been established as strong indicator of cardiovascular risk.[24] Therefore, prognostic value of CAP has important implications in clinical setting. In this context, the 'LOW CBP' study initiated to determine whether CAP can be a therapeutic target in management of hypertension, will provide further proof to the importance of CAP.[25]

At visit 1, among the most commonly prescribed medications, patients treated with ACEI had the least BP. At visit 2, in general, free–drug combinations were more frequently prescribed than FDCs. Systemic reviews of retrospective and prospective clinical studies as well as meta-analysis[26] of randomized clinical studies in the hypertensive patients indicate that FDCs achieve better treatment adherence, patient compliance compared to free–drug combinations, but could not substantiate the BP-lowering efficacy and side effects of FDCs.[27] Previous studies have shown that anti-hypertensives have similar impact on BBP, however, substantially different impacts on CAP.[28] In a small (n = 30) randomized, double-blind, placebo-controlled trial, ACEI attained a significant decrease in central SBP than BB (average decrease of 5.2 mmHg, $p < 0.0001$) compared to brachial BP.[29] Moreover, the earlier small studies, meta-analysis, and a recent Japanese cross-sectional study have demonstrated that the vasodilatory antihypertensives (CCB, ARB, ACEI, alpha-blockers) lower CBP more than any non-vasodilatory class (diuretics and BB), but the brachial BP was lowered to the same level.[30,31] In the CAFE trial, conducted in 2199 patients with hypertension and receiving anti-hypertensive drugs (beta-blocker + LCD, CCB + ACEI) for 4 years in a controlled manner, despite similar brachial SBP between treatment groups (difference, 0.7 mmHg), there was substantial reduction in central SBP with ACEI + DHP-CCB *versus* beta-blocker + LCD (difference, 4.3 mmHg, $p < 0.0001$).[32] Another prospective randomised study (EXPLORE) showed that in 393 patients treated with anti-hypertensive drugs, central SBP decreased significantly more with ARB + DHP-CCB *versus* beta-blocker + DHP-CCB (difference in change from baseline, 4 mmHg, $p = 0.02$) after 24 weeks treatment, despite similar changes in brachial SBP between treatment groups after 4 weeks treatment.[33] However, any such conclusion could not be drawn in our study as patients at baseline were not treatment naïve, which precluded any comparison with respect to baseline BP measurements. Additionally, there was variability between the patients with respect to baseline characteristics in individual drug classes.

The mean difference between brachial SBP and central SBP at visit 1 and visit 2 was ~14 mmHg and ~10 mmHg, respectively in our study. This trend was consistent across age groups with minimum variability. Since CAP is known to be associated log-linearly with age, indicating it as a marker of vascular aging,[7] the lack of variability in CAP and BBP with age in our study fails to reflect the impact of arterial stiffness. An interesting observation from this study was the difference between brachial DBP and central DBP (~5 mmHg). There are limited literature available that indicate the difference between brachial DBP and central DBP essentially not varying more than 1–2 mmHg.[32,34] Our study is observational in nature and shows real-world pattern in India and may differ from the study designs of controlled trials and in the use of central BP measurement device. In our knowledge, there is no standard threshold of central DBP; therefore, the difference between brachial DBP and central DBP in our study is difficult to compare with other studies. There can be different reasons for the observed difference in DBP that need to be further looked into detail in future studies.

Previous studies have shown that different anti-hypertensive drugs have differential action and outcomes on central SBP and brachial SBP.[35,36] In our study, 13.6% patients had controlled brachial SBP but uncontrolled central SBP, and 6.6% patients had uncontrolled brachial SBP but controlled central SBP at visit 2, therefore supporting the available evidence. Considering CAP more precisely predicts cardiovascular events,[8,28] the central SBP uncontrolled patients may be at a high risk of cardiovascular events. Nonetheless, since this is a real-world observational study, where treatment groups were uncontrolled, the results may vary based upon their baseline characteristics.

It was observed in our study that treatment adjustment at visit 1 lowered central SBP from 84.3% to 48% and brachial SBP to 51.8%. Though, the treatment adjustment based on BBP at visit 1 improved the treatment outcome at visit 2 in terms of both BBP and CAP, the patients needed further treatment adjustment for better management of hypertension. Considering the findings and results from the 'BP guide' study, it might be important to account measurement of CAP while making treatment decisions to achieve better therapeutic outcomes.[34]

5. Conclusions

Overall, the findings of this study highlight the importance of measuring CAP along with BBP while making the treatment decisions with anti-hypertensives belonging to different drug classes. Any discrepancy between CSBP and BSBP readings may have a clinical implication in terms of vascular complications due to higher CSBP yet controlled BSBP, and hypotensive symptoms due to overtreatment based on higher BSBP yet controlled CSBP. This underlines the need of tailored treatment, based upon both CAP and BBP measurements. In future, with the support of robust clinical data, it will be plausible to make treatment decisions based on both

BBP and CAP for better management of hypertension in clinical settings.

6. Limitations

This study being observational in nature had important and pertinent limitations. First, none of the assessments were mandatory nor the treatment groups were uncontrolled. Therefore, the results need to be cautiously interpreted. Second, patient populations (overall and across drug classes) at both visits were not uniform with respect to baseline characteristics. Third, dosage and frequency of drugs varied among the populations making it difficult to draw conclusive inferences. Fourth, being a short-term study (2 months) the findings cannot be extrapolated to conventional hypertension treatment, where drugs are usually prescribed for a long-term. Fifth, non-invasive CAP estimation is device/technique-dependent,[37] hence caution needs to be exercised when extending the findings of this study while using other devices and techniques. Sixth, the sample size was calculated based on the SITE study.[17] The BP was measured in adult patients 30–70 years of age only, excluding patients of 18–29 years and >70 years. Hence, we acknowledge that the selection of patient within 30–70 years may have undermined the overall prevalence of CAP in adults. Future studies including patients with a broader age range will provide more evidence in this regard. Lastly, the cut-offs for BBP are well defined (140/90 mmHg), but the same is not true for CAP. Some studies have used the cut-off for CAP as ~125/90 mmHg, but further research is required.[6]

7. What is already known

Central aortic blood pressure is a more sensitive marker for cardiovascular events than brachial blood pressure.

8. What this study adds

This study reinforces the importance of measuring central aortic blood pressure along with brachial blood pressure while optimizing anti-hypertensive drug therapy.

CTRI Registration Number: http://ctri.nic.in/Clinicaltrials/login.php, identifier CTRI/2015/10/006302.

Funding and conflict of interest

The study was funded by Sanofi India Pvt Ltd. Dr Ranjan Sharma declares no conflict of interest. All other authors are employees of Sanofi.

Acknowledgment

We thank all the participating physicians for their contributions towards the registry. Editorial support in the preparation of this publication was provided by Tania Peshin of Tata Consultancy Services and paid for by Sanofi. Editorial support in the preparation of this publication was also provided by Anahita Gouri and Rohan Mitra of Sanofi, India. The authors, individually and collectively, are responsible for all content and editorial decisions and received no payment from Sanofi directly or indirectly (through a third party) related to the development/presentation of this publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2018.11.013.

References

1. The seventh report of the joint national committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. US Department of Health and Human Services, National Institutes of Health. Available from: https://www.nhlbi.nih.gov/files/docs/guidelines/express.pdf. Accessed on 25 Jan 2018.
2. Whelton PK, Carey RM, Aronow W, et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol*. 2017. https://doi.org/10.1016/j.jacc.2017.11.006.
3. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *J Am Med Assoc*. 2014;311(5):507–520.
4. Lewington S, Clarke R, Qizilbash N, et al. 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;360:1903–1913.
5. Sharman JE, Blizzard L, Kosmala W, et al. Pragmatic method using blood pressure diaries to assess blood pressure control. *Ann Fam Med*. 2016;14(1):63–69.
6. McEniery CM, Cockcroft JR, Roman MJ, et al. Central blood pressure: current evidence and clinical importance. *Eur Heart J*. 2014;35(26):1719–1725.
7. Cheng HM, Park S, Huang Q, et al. Vascular aging and hypertension: implications for the clinical application of central blood pressure. *Int J Cardiol*. 2017;230:209–213.
8. 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.
9. 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):183–190.
10. 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 Aug;31(15):1865–1871.
11. Huang C-M, Wang K-L, Cheng H-M, et al. Central versus ambulatory blood pressure in the prediction of all-cause and cardiovascular mortalities. *J Hypertens*. 2011;29(3):454–459.
12. Mitchell GF. Central pressure should not be used in clinical practice. *Artery Res*. 2015;9:8–13.
13. McEniery CM, Yasmin, McDonnell B, et al. Central pressure: variability and impact of cardiovascular risk factors: the Anglo-Cardiff Collaborative Trial II. *Hypertension*. 2008;51(6):1476–1482.
14. Saladini F, Santonastaso M, Mos L, et al. Isolated systolic hypertension of young-to-middle-age individuals implies a relatively low risk of developing hypertension needing treatment when central blood pressure is low. *J Hypertens*. 2011;29(7):1311–1319.
15. 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):2111–2115.
16. Park CM, Korolkova O, Davies JE, et al. Arterial pressure: agreement between a brachial cuff-based device and radial tonometry. *J Hypertens*. 2014 Apr;32(4):865–872.
17. Joshi SR, Saboo B, Vadivale M, et al. Prevalence of diagnosed and undiagnosed diabetes and hypertension in India–results from the Screening India's Twin Epidemic (SITE) Study. *Diabetes Technol Ther*. 2012;14(1):8–15.
18. Salvi P, Schillaci G, Parati G. Twenty-four-hour ambulatory central blood pressure: new perspectives for blood pressure measurement? *J Hypertens*. 2014;32(9):1774–1777.
19. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of hypertension (ESH) and of the European society of cardiology (ESC). *J Hypertens*. 2013;31(7):1281–1357.
20. Torjesen A, Wang N, Larson MG, et al. Forward and backward wave morphology and central pressure augmentation in men and women in the Framingham Heart Study. *Hypertension*. 2014;64(2):259–265.
21. 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):1743–1750.
22. Bulas J, Potočárová M, Murín J, et al. Central systolic hypertension in patients with well-controlled hypertension. *BioMed Res Int*. 2017;2017:8158974.
23. Sharman J, Stowasser M, Fassett R, et al. Central blood pressure measurement may improve risk stratification. *J Hum Hypertens*. 2008;22(12):838–844.
24. Ryuzaki M, Morimoto S, Niiyama M, et al. The relationships between the differences in the central blood pressure and brachial blood pressure and other factors in patients with essential hypertension. *Intern Med*. 2017;56(6):587–596.
25. Sharman JE, Stanton T, Reid CM, et al. Targeted LOWering of Central Blood Pressure in patients with hypertension: baseline recruitment, rationale and design of a randomized controlled trial (The LOW CBP study). *Contemp Clin Trials*. 2017;62:37–42.
26. Mallat SG, Tanios BY, Itani HS, et al. Free versus fixed combination antihypertensive therapy for essential arterial hypertension: a systematic review and meta-analysis. Hills RK, ed *PLoS One*. 2016;11(8), e0161285.

27. Bramlage P, Schmidt S, Sims H. Fixed-dose vs free-dose combinations for the management of hypertension—an analysis of 81 958 patients. *J Clin Hypertens*. 2018;20(4):705–715.
28. Ram CVS. Central aortic blood pressure assessment and cardiovascular risk. *Indian Heart J*. 2010;62(1):13–16.
29. Hirata K, Vlachopoulos C, Adji A, et al. Benefits from angiotensin-converting enzyme inhibitor 'beyond blood pressure lowering': beyond blood pressure or beyond the brachial artery? *J Hypertens*. 2005;23(3):551–556.
30. Miyashita H, Aizawa A, Hashimoto J, et al. Cross-sectional characterization of all classes of antihypertensives in terms of central blood pressure in Japanese hypertensive patients. *Am J Hypertens*. 2010;23(3):260–268.
31. Kostapanos M, McEniery CM, Wilkinson IB. Clinical relevance of central blood pressure – a critical review. *Vasa*. 2016;45(6):451–460.
32. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006;113(9):1213–1225.
33. Boutouyrie P, Achouba A, Trunet P, et al, EXPLOR Trialist Group. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. *Hypertension*. 2010;55(6):1314–1322.
34. Sharman JE, Marwick TH, Gilroy D, et al. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: principal findings of the BP GUIDE study. *Hypertension*. 2013;62(6):1138–1145.
35. Morgan T, Lauri J, Bertram D, et al. Effect of different antihypertensive drug classes on central aortic pressure. *Am J Hypertens*. 2004;17(2):118–123.
36. Protogerou AD, Papaioannou TG, Lekakis JP, et al. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part I: (Patho)-physiology, rationale and perspective on pulse pressure amplification. *Curr Pharmaceut Des*. 2009;15(3):267–271.
37. 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):1727–1740.