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Incorporating Non-Invasive Central Aortic Pressure Monitoring into Drug and Medical Device Development Clinical Trials for Cardiovascular Disease

Objective

The objective of this document is to discuss how and why central aortic pressure (cBP) monitoring should be integrated into clinical development programs where arterial pressures are a primary outcome (e.g., products for hypertension) or an important secondary outcome (e.g., products for heart failure, pulmonary hypertension, chronic kidney disease).

Background

Drug and medical device development costs increase exponentially as development programs advance to regulatory approval and commercialization. Development costs for cardiovascular pharmaceuticals can exceed one billion dollars. Opportunities to improve decision making during development, improve the likelihood of regulatory success, improve the safe and efficacious use of products, and increase commercial viability are always sought and considered. Incorporation of central aortic blood pressure (cBP) into the development program provides opportunities to improve key decisions along the development pathway for cardiovascular products, particularly those targeting hypertension. Numerous properties and data about cBP provide the rationale for utilizing cBP in clinical trials from phase I to phase IV. The data presented in this document focuses on hypertension; however, additional data and publications exist describing the use of cBP in other cardiovascular diseases and therapeutic areas.

Management of hypertension through cuff measurement of peripheral (brachial artery) pressures has dramatically but incompletely improved the ability of health care providers and their patients to control hypertension and reduce associated end-organ damage. Multiple issues likely contribute to the ongoing socioeconomic burden of hypertension despite the availability of multiple effective medications and widespread educational efforts. Such issues include, but are not limited to, case finding (early diagnosis), continuity and continued follow-up of care, affordability of care, medication adverse effects, medication compliance and challenges in modifying lifestyle behavior.

An underappreciated but clinically relevant area to consider is the precision and reliability of current monitoring which is based on brachial blood pressure measurements, including patient and health care provider factors. Cheng and colleagues placed the issue in context and noted that cuff brachial blood pressure measurement "is not so much a surrogate, but a compromised measure that is recorded because of technical limitations."[1] The reference is to cuff pressures being a surrogate for central (i.e. aortic) blood pressures, which represent the actual pressures that are transmitted to organs effected by hypertension (e.g. heart, brain, kidney) due to the closer proximity of the ascending aorta to vital organs. Non-invasive pulse wave analysis (PWA) is a technique that transforms the data from peripheral arterial pressure waveforms obtained into an

evaluation of central aortic pressures. Peripheral (brachial) blood pressures are highly correlated to central pressures; however, significant variability exists such that central pressures cannot be reliably inferred from brachial pressures.[2]

The technology for non-invasive assessment of central aortic pressures through PWA is currently available and approved by the United States Food and Drug Administration (FDA). In recognition of the clinical utility of PWA, a Current Procedural Terminology (CPT) code has been established. The SphygmoCor XCEL system is a dual arterial pressure monitoring medical device consisting of brachial blood pressure and central aortic pressures (using partial cuff inflation to record the outgoing brachial waveform), which can be obtained in the clinic in the same patient session with as little as 10 additional seconds to a typical brachial blood pressure assessment. The SphygmoCor XCEL is the only FDA cleared medical device for non-invasive central arterial pressure waveform analysis for all adults. The SphygmoCor System incorporation of PWA was developed as complementary to brachial pressure measurements to help guide treatment decisions designed to prevent or reduce long-term target organ damage and cardiovascular events resulting from increased aortic pressure. CardieX is close to completing development on additional dual arterial pressure monitoring devices for home use (Pulse), clinical practice (Pulse MD) and a wearable medical device (Conneqt Band). CardieX envisions their medical grade devices as being part of a comprehensive medical ecosystem with the capabilities of exchanging and sharing vascular health data among patients, their families, health care providers and health care systems.

Why Should Central Aortic Blood Pressure Monitoring be Part of Cardiovascular Product (Drug and Medical Device) Development Clinical Trials?

There are multiple reasons to incorporate monitoring of central aortic cBP measurement into drug and medical device development trials, particularly but not exclusively in the development of interventions for hypertension. This section of the document highlights key areas to consider when using cBP in clinical trials from phase I through IV for pharmaceuticals and in "pilot" and "pivotal" trials for medical devices. The rationale is based on the physiology of arterial pressure and the well-described pathophysiologic consequences of poorly regulated arterial pressure. Data supporting the reasons outlined consider peer-reviewed publications documenting data that associate the risk of end-organ damage with elevated cBP (Section IV) and the data outlining threshold values for normal and elevated cBP (Section V). Defining thresholds allow for cBP to be understood and used in a manner similar to peripheral BP. The advantages of incorporating cBP into clinical development programs (i.e., clinical trials) can be summarized as follows:

1. Confirmation of hypertension at baseline

    *   Clinical trials incorporate optimal measurement procedures (e.g., quiet room, sitting upright, cuff at the level of the right atrium, multiple measurements) for baseline assessment. However, optimal measurement processes in protocols may still have either suboptimal implementation or be influenced by unrecognized subject specific factors. Inaccurate baseline values can potentially invalidate all post-intervention results within a subject; therefore, confirmation of hypertension and the absolute BP values is essential. In addition, inclusion/exclusion criteria based on threshold values may be improved in terms of subject qualification by considering cBP. Examples include the following:

        Scenario A: Concurrent elevation in brachial and central pressures – confirmed hypertension
        Scenario B: Minimal elevation in brachial pressure that minimally satisfies inclusion criteria (e.g.,

subject must have Stage 2 hypertension). Elevation of central pressure confirms acceptability. Low central pressure suggests that the subject may not be an optimal candidate.

2. Confirmation of blood pressure values at follow-up

   - The previous section referred to baseline values and inclusion/exclusion criteria. The issues raised and potential solution proposed apply equally to follow-up (post-enrollment visits) measurements for which efficacy and safety is determined. Examples are as follows:

     Scenario A: Concurrent elevation in brachial and central pressures – confirmed hypertension
     Scenario B: Discordant cBP and pBP values when measurement procedures are correct (e.g., no change in pBP but decline in cBP). The implication is that the therapeutic intervention may be having a differential effect, which has been documented in the past in other trials comparing drugs in different classes. Without cBP, a false interpretation (e.g., no efficacy) could be concluded, when a true drug effect exists.

3. Endpoints for evaluation of therapeutic effect

   - Published literature (Sections IV and V) indicate that cBP may distinguish thresholds or associations with end-organ damage that might not be observed within a given peripheral BP (pBP) range. Central pressures provide additional and potentially independent information regarding risk of end-organ damage (or probability of reduced risk) and clinical outcomes. This information can be utilized is clinical trials. An example is as follows:

     Scenario: Drug in phase II shows minimal change in pBP that does not provide adequate information for assessment of go/no go decision. A clear effect (or absence of effect) on central pressures allows for a more informed decision as to whether to proceed with additional phase II studies or to proceed to phase III.

4. Informing dose selection during phase II dose ranging trials

   - A critical decision in drug development is dose selection. Often 3 to 5 doses are evaluated in phase II in order to proceed with 1 to 2 doses in the pivotal phase III program. The decision may also involve dose frequency (e.g., daily or bid). The additional information from central aortic pressures permits more informed decision regarding (a) confirmation of therapeutic effect when the effect and effect size is unclear or variable, (b) magnitude of therapeutic effect), (c) different therapeutic effect than anticipated, (d) signals as to expected adverse effects related to hypotension, and (e) duration of effect. All of the above must be factored into the decisions that can broadly be categorized as either stopping development, implementing additional phase II, or proceeding to phase III.

   - Based on the above potential uses, cBP should be considered as a clinically relevant biomarker in phase II to help guide decisions for phase III.

5. Avoiding misleading information due to white coat hypertension.

   - White coat hypertension is extremely common. Procedures outlined in clinical trial protocols and investigator training will decrease but unlikely to eliminate the phenomena. cBP can provide informative information. The scenario where this becomes a consideration is when pBP is elevated and cBP is normal or low.

6. Information for final safety evaluation

   - Overtreatment (development of hypotension) is always a concern with the outcomes ranging from symptoms without clinical consequences (presyncope) to syncopal episodes with falls to end-organ damage (e.g., stroke, syncope, myocardial ischemia). Several studies have noted that worsening of end-organ function and increasing adverse events (including death) are associated with more aggressive treatment and low blood pressure. Episodic and infrequent hypotension may only occur in a small subset that are predisposed (e.g., elderly, unrecognized autonomic dysfunction, left and right ventricular failure) and could lead to either failure to achieve regulatory approval or have prominent labeling (warnings, precautions, contraindications). cBP data can provide early signals and evidence that may determine that a higher dose should either be considered or not be brought forward into phase III.

   - An example of what could occur is as follows:
     Scenario: Large declines in cBP indicative of risk for adverse events in the setting where the pBP declines are considered acceptable and within the target range.

7. Prescribing information

   - It is anticipated that cBP monitoring will be increasingly recognized as clinically relevant and utilized by health care providers and consumers.

   - With increasing acceptance and incorporation into pivotal clinical trials, cBP information may be included in prescribing information. Companies that consider cBP in phase III trials will be at an advantage over those that have not considered cBP monitoring.

   - The FDA recognizes and encourages companies to identify population characteristics and responses to interventions that improve the overall benefit-risk profile of drugs and medical devices. Such information has been and will continue to be included in prescribing information.

   - Based on current data and assuming that cBP is part of a clinical development program, information from cBP could be incorporated into the prescribing information (package inserts) to health care providers and such information may lead to decisions that optimize patient dosing (increasing or decreasing dose) with the objective of improving both efficacious and safe use of the product.

8. Regulatory approval and post-approval communication.

   - The incorporation of novel endpoints from cBP that are clinically and physiologically related to the primary outcome of a development program (e.g., hypertension, heart failure), especially for phase III clinical trials, provide opportunities for regulatory agency discussions (e.g., supportive data and intended utility of the cBP variables), competitive advantages, and post-approval communications. It is likely that if such variables are prespecified in a successful development program leading to regulatory approval that external communication of cBP results can be disseminated and be within regulatory guidance and expectations.

Central Aortic Pressure as A Predictive Measure of Cardiovascular Risk

Peripheral (brachial) blood pressure elevation has been proven to be a prominent risk factor for vascular-related end-organ damage, morbidity, and mortality.[3]. Reductions in blood pressure has been definitively

demonstrated to reduce vascular end-organ damage, morbidity, and mortality.[9-1]. A comprehensive meta-analysis encompassing 306,273 participants from 74 trials demonstrated that blood pressure lowering pharmacotherapy reduced mortality and cardiovascular disease based on a threshold (baseline) systolic blood pressure > 140 mm Hg.. They further noted that pharmacotherapy was not associated with any benefit in primary prevention at systolic blood pressures below 140 mm Hg although there may be additional protection in patients with coronary artery disease. A recent study (SPRINT)[14] suggests that the thresholds for initiation of pharmacotherapy should be lower and is referred to in hypertension management guidelines.[11,1]. With reference to systolic blood pressure, the 2017 Guidelines for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults recommend follow-up monitoring and lifestyle modifications at lower pressures (i.e., systolic blood pressures 120 to 139 mm Hg) and recommend pharmacotherapy at lower thresholds where a patient has known risk factors for cardiovascular disease (i.e., 130 to 139 mm Hg).[12]

Threshold values have been defined that represent the targets for initiation of treatment (lifestyle treatments such as diet and exercise, and pharmacotherapy) and values have been defined for the goals of treatment. However, sparse data has been published on how and what target values should be used for recommending reductions in pharmacotherapy.

End-organ damage associated with hypertension is related to central pressures and is physiologically intuitive, as such pressures are directly transmitted to vital organs. Central systolic pressures are highly but incompletely correlated to peripheral systolic pressures with correlation coefficients of up to 0.97 although a published review from 2014 indicated a range from 0.6 to 0.9.[13-15] Despite the high correlation, prediction of aortic systolic pressures based on brachial systolic pressures cannot be reliably inferred as demonstrated by McEniery et al using data from over 10,000 subjects participating in the Anglo-Cardiff Collaborative trial.. The study by McEniery reinforces the issue that both central and peripheral pressures are closely related but not interchangeable.

Multiple studies including several meta-analyses have evaluated cBP variables with some studies suggesting that cBP may have a higher predictive value for cardiovascular events relative to peripheral blood pressure, but all have demonstrated that non-invasive cBP is at least as predictive as peripheral blood pressure.[16-2]. A meta-analysis conducted by Wang et al indicated that central blood pressure appears to have a higher predictive value for end-organ damage.[2]. In a study of 1,169 participants, the group of patients with a normal/high-normal peripheral BP with central systolic blood pressure (cSBP) values that were less than the 95% confidence interval (CI) of healthy participants with optimal BP values (45% of those with a normal/high normal BP), had no evidence of target organ changes.[23] In patients with a normal/high-normal BP with cSBP values that exceeded optimal threshold values, left ventricular mass index was increased and estimated glomerular filtration rate was decreased. The report demonstrated that central pressure may have higher predictive value for end-organ damage related to hypertension.[23]

Wang and colleagues evaluated the relationship of central and peripheral pressures to end-organ damage in 1,272 subjects.[21] Carotid intima-media thickness and glomerular filtration rate were more strongly related to central pressures than peripheral pressures. A total of 130 participants died with 37 dying from a cardiovascular cause. Peripheral and central blood pressure predicted all-cause and cardiovascular mortality. With adjustment for age, sex, heart rate, body mass index, current smoking, glucose, lipids, carotid-femoral pulse wave velocity, left ventricular mass, intima-media thickness, and glomerular filtration rate, only cSBP consistently independently predicted cardiovascular mortality (hazard ratio=1.30 per 10 mmHg increase).21

Vlachopoulos et al reported a meta-analysis of 11 studies that incorporated central hemodynamics and had followed 5,648 subjects for a mean of 45 months.[24] The age- and risk-factor-adjusted pooled relative risk of

total CV events was 1.088 (95% CI 1.040– 1.139) for a 10 mm Hg increase of cSBP, 1.137 (95% CI 1.063 –1.215) for a 10 mmHg increase of central pulse pressure, and 1.318 (95% CI 1.093 –1.588) for a 10% absolute increase of central augmentation index (AIx). When compared with brachial pulse pressure, central pulse pressure was associated with marginally but not significantly higher relative risk of clinical events (p = 0.057).[24]

A more recent meta-analysis assessed 24 prospective studies with 146,986 individuals.[25] The adjusted pooled hazard ratio of total cardiovascular events was 1.10 (95% confidence interval [CI] 1.04–1.16) for a 10 mmHg increase of cSBP, 1.12 (95% CI 1.05–1.19) for a 10 mmHg increase of central pulse pressure and 1.18 (95% CI 1.09–1.27) for a 10% increase of central augmentation index. The hazard ratio of all-cause mortality was 1.22 (95% CI 1.14–1.31) for a 10 mmHg increase of central pulse pressure and 1.19 (95% CI 1.05–1.34) for a 10% increase of central augmentation index. The authors concluded central hemodynamic variables are independent predictors of cardiovascular disease and all-cause mortality.[25]

A prospective study published in 2021 evaluated the predictive value of cSBP for cardiovascular events in 13,461 patients using available central blood pressure measurements and follow-up data from administrative databases.[26] A total of 1,327 major adverse cardiovascular events occurred during follow-up (median approximately 9 years). The hazard ratio for risk of major adverse cardiovascular events was 1.16 (95% CI 1.09-1.22) for cSBP and 1.15 (95%CI 1.09-1.22) for brachial sBP for a one standard deviation increase. Modeling data evaluating area under the curve for risk indicated a slightly higher risk using cSBP vs. brachial sBP that was statistically but not clinically significant.

McEniery and colleagues have performed a systematic review and individual participant data meta-analysis from 15 studies for the purpose of evaluating central aortic pressures for the prediction of cardiovascular events.[27] The report is perhaps the most comprehensive and statistically detailed meta-analysis on the subject to date. At this time, the report is under peer-review and has been provided to CardieX with permission from the authors. Study-specific associations of central and peripheral systolic (SBP) and pulse pressure (PP), and augmentation index (AIx) with cardiovascular (CV) events, were determined using Cox proportional hazard models, and random effect models to estimate pooled effects. Of 22,433 participants, 908 had a myocardial infarction, 641 a stroke and 1,844 a CV event. The pooled hazard ratio (HR) [95% CI] for combined CV events per SD increase in SBP, after adjustment for physiological confounders and cardiovascular risk factors, was 1.16 [1.06, 1.26] for peripheral sBP (SD 21.0 mmHg) and 1.20 [1.09, 1.33] for central sBP (SD 21.8 mmHg). Adjustment of central sBP for peripheral sBP was also associated with an increased HR for CV events (1.17 [1.00, 1.37]). In summary, central sBP was predictive of CV events even after adjustment for physiological confounders including adjustment for brachial sBP and is therefore an independent predictor of CV events.

The substantial data in multiple peer-reviewed publications demonstrate an increased risk for cardiovascular events with elevated central pressures, particularly cSBP and it is therefore reasonable to conclude that reductions in hypertension based on cSBP will be associated with reduced CV events, as has been proven with brachial blood pressure. Furthermore, the predictive value of cSBP is at least as high and in some studies higher than peripheral systolic blood pressure. Given the knowledge, experience, and correlations of peripheral and central systolic pressures, it is intuitive that an objective of treatment should be to lower central systolic pressures to values (or thresholds) that correspond to the targets set for peripheral systolic pressures for the purpose of reducing vascular risk.

Threshold Values for Central Systolic Blood Pressure

Management decisions for the treatment of hypertension are based on specific values for systolic and diastolic brachial pressures regardless of age and gender. The 2017 ACC/AHA Guidelines for the Prevention, Detection,

Evaluation, and Management of High Blood Pressure in Adults specify the following: normal BP: < 120/80 mm Hg, elevated BP >120 – 129/<80 mm Hg, Stage 1 hypertension: 130 – 139/80 – 89 mm Hg, and Stage 2 hypertension >140/90 mm Hg.[12]

Table 1: Current staging of hypertension by NICE, ESH/ESC and ACC/AHA. Adapted from NICE, ESH/ESC and ACC/AHA guidelines.

	Systolic BP	Diastolic BP
NICE (2019)		
Normotension	<140	<90
Stage 1 Hypertension	≥140	≥90
Stage 2 Hypertension	≥160	≥100
Severe hypertension	≥180	or ≥120
ESH/ESC (2018)		
Optimal	<120	<80
Normal	120-129	80-84
High Normal	130-139	85-89
Grade 1 Hypertension	140–159	and/or 90–99
Grade 2 Hypertension	160–179	and/or 100–109
Grade 3 hypertension	≥180	and/or ≥110
ACC/AHA (2017)		
Normotension	<120	and <80
Elevated BP	120–129	and <80
Stage 1 Hypertension	130–139	or 80–89
Stage 2 Hypertension	≥140	or ≥90

ACC, American College of Cardiology; AHA, American Heart Association; BP, blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; NICE, National Institute for Health and Care Excellence

Expert recommendations based on agreed upon thresholds are provided for brachial BP goals for adults with confirmed hypertension as follows:[12]

- With known cardiovascular disease (CVD) or 10-year atherosclerotic CVD (ASCVD) event risk of 10% or higher, a BP target of <130/80 mm Hg is recommended.

- Without additional markers of increase CVD risk, a BP target of <130/80 may be reasonable.

Given the high correlation to brachial pressures and the predictive value for CV events, thresholds for management decisions based on central systolic pressures can be determined.

Cheng and colleagues published an analysis demonstrating central aortic BP<110/80 mmHg as optimal, 110-129 / 80-89 mm Hg as prehypertension (corresponding to "elevated" and Stage 1 hypertension in the 2017 Guidelines) and >130/90 mm Hg as hypertension (corresponding to Stage 2 hypertension in the 2017 Guidelines).[1] The analysis utilized a derivation cohort and then validated the results against a second independent cohort (validation cohort). In the derivation cohort (1,272 individuals and a median follow-up of 15 years), the authors determined diagnostic thresholds for central blood pressure by using guideline-endorsed cut-offs for brachial blood pressure with a bootstrapping method (resampling by drawing randomly with replacement) and an approximation method. The thresholds from the derivation cohort were tested in 2,501 individuals with median follow-up of 10 years (validation cohort) for prediction of cardiovascular outcomes.[1]

The analyses (derivation and validation cohort) yielded similar threshold values for central aortic pressures. Relative to optimal (central BP < 110/80 mmHg), the risk of cardiovascular mortality in subjects with hypertension (central BP > 130/90 mm Hg) was clinically and statistically elevated (hazard ratio: 3.08, 95% confidence interval 1.05 to 9.05). Modeling demonstrated that central BP > 130/90 mm Hg was associated with the largest contribution to the prediction of cardiovascular events.

The authors discussed the clinical relevance of central pressures and noted "...in current international guidelines, the classification of cuff BP values disregards age, sex, and other cardiovascular risk factors. In our multivariate model, the results were consistent after accounting for these factors. In line with current clinical practice and considering the higher clinical events in the aged population, we now propose diagnostic thresholds of CBP without age and sex specification."[1] In reference to spurious systolic hypertension and white coat hypertension, the authors recognized the clinical utility of measuring central aortic BP in that the diagnosis can be inferred based on a high cuff (brachial) BP and low/normal central BP.[1]

Takase and colleagues evaluated the distribution of central blood pressure values in a population study of Japanese subjects.[14] This cross-sectional study involved 10,756 subjects without overt cardiovascular disease. In the cohort, 7,348 subjects received no antihypertensive, antidiabetic or lipid-lowering drug treatment, and were used for the analysis. The cSBP values in those without cardiovascular risk factors other than hypertension was 125.8±37.2 (mean±2 SD, n=3,760) mm Hg. The values obtained from subjects with no cardiovascular risk factors were 112.6±19.2 (n=1,975) mm Hg for optimal and 129.2±14.9 mm Hg for normal brachial blood pressure categories (n=697). The reference values of optimal and normal cSBP categories were reported as 112.6+19.2 mm Hg and 129.2+14.9 mm Hg.[14] The study provides further support for cSBP reference values and threshold values based on risk and is corroborative data for the threshold of >130 mm Hg as published by Cheng et al.[1]

North American Artery is a professional society whose purpose is to "encourage, support, and understanding of vascular structure and function and its application to clinical medicine, research, and pharmaceutical and medical device development". The organization includes national and international experts in the field of hypertension. The organization sponsored a symposium on the clinical use of PWA in which a central aortic systolic value of 124 mm Hg was recommended as a reasonable upper limit of normal based on data that demonstrated a corresponding brachial systolic pressure of 140 mm Hg.[28] While slightly more stringent than the value noted above, it is still similar to what was proposed by the other investigators.

Based on the totality of the data, a threshold for the diagnosis of hypertension (corresponding to Stage 2 Hypertension in the 2017 guidelines) is proposed to be > 130/90 mm Hg; however, justification is available to consider a threshold of >125 mm Hg.

Threshold values for management decisions are supported by the aforementioned reports, but target goals are also desirable for the widespread utility of central pressures as a complementary approach to blood pressure management. Incorporating cSBP into brachial BP treatment goals should lead to more precise and reliable patient management. The previous studies have documented what is considered optimal central pressures, which can be considered the target goal. Several other reports exist that corroborate the values noted.[23,2]

Booysen et al reported an upper threshold for cSBP of 112 mm Hg in a study of 1,169 participants.[23] In patients with a normal/high-normal BP with cSBP values that were less than 95% confidence interval of healthy participants with optimal BP values (45% of those with a normal/high normal BP), no target organ changes were noted. In patients with a normal/high-normal BP with cSBP values that exceeded optimal threshold values, left ventricular mass index was increased and estimated glomerular filtration rate was decreased. The report demonstrated that central pressure may have higher predictive value for end-organ damage related to hypertension.[23] Lamarche and colleagues recently reported a prospective study that examined the predictive value of central systolic blood pressure for cardiovascular events.[26] The study included 13,461 participants available central BP and follow-up data from administrative databases but without cardiovascular disease or antihypertensive medication. A total of 1,327 major adverse cardiovascular events occurred during follow-up (median approximately 9 years). Central and brachial systolic pressures of 112 mm Hg (95% CI 111.2–114.1) and 121 mm Hg (95% CI 120.2–121.9) were identified as optimal BP thresholds.[26] The data indicate that a target goal for central systolic pressure should be 112 mm Hg, which would be consistent with the previously described reports.

Yu et al investigated the prevalence of central hypertension and its association with end-organ damage in 1,983 elderly people.[29] Brachial hypertension was defined as ≥140/90 mmHg or using antihypertensive medications. Central hypertension was defined by central BP ≥130/90 mmHg or using antihypertensive medications. Both normal brachial and central pressures occurred in 28.4% of subjects, concordant brachial and central hypertension occurred in 67.9%, isolated brachial hypertension (normal central pressures) in 2.3% (consistent with white coat hypertension group), and isolated central hypertension in 1.4% of subjects (consistent with masked hypertension group). Measures of end-organ damage were significantly associated with the concordant hypertensive group (left ventricular hypertrophy: adjusted odds ratios [95% confidence interval] = 2.03 [1.55, 2.68], left ventricular diastolic dysfunction: 2.29 [1.53, 3.43], urinary albumin-creatinine ratio >30 mg/g: 1.97 [1.58, 2.44]), compared to isolated brachial hypertension or isolated central hypertension. The study results demonstrated that groups can be distinguished based on concordance and discordance of hypertension using threshold values of 140/90 mm Hg (brachial pressure) and 130/90 (central aortic pressure) for risk evaluation and treatment decisions.[2] While the discordant groups were a minority of the population, the data indicate that both measurements of central and peripheral pressures should be reviewed given that treatment decisions often constitute a life-commitment to pharmacotherapy.

In summary, threshold values that represent a decision point for medication prescription for hypertension can be determined based on published data from multiple studies involving an overall large population. A central systolic pressure of >130 mm Hg (possibly >125 mg) should be considered clinically equivalent to the brachial systolic pressure threshold of >140 mm Hg (Stage II hypertension as per the 2017 AHA guidelines). Furthermore, a normal central systolic pressure of 112 mm Hg can be considered as clinically equivalent to a brachial pressure of 120 mm Hg for the purpose of establishing treatment goals.

Summary and Conclusions

The following is a summary of the key discussion points:

- Drug and medical device development costs increase exponentially as development programs advance to regulatory approval and commercialization. Incorporation of central aortic blood pressure (cBP) into the development program provides opportunities to improve key decisions along the development pathway for cardiovascular products, particularly those targeting hypertension.

- Numerous properties and data about cBP provide the rationale for utilizing cBP in clinical trials from phase I to phase IV.

  - Central aortic systolic pressure is highly correlated to brachial systolic pressures; however, central systolic pressures cannot be reliably inferred from brachial pressures

  - Elevated central aortic pressure predicts cardiovascular events and mortality in addition to structural changes (e.g., left ventricular hypertrophy, carotid intima-media thickness and reduced glomerular filtration rate). The risk of adverse CV outcomes with elevated central pressure is at least as high and possibly higher than with brachial pressure. A recent meta-analysis, which incorporated multiple baseline factors including brachial systolic pressure, demonstrated that central systolic pressure is independently predictive of cardiovascular events and therefore provides additional risk information.

  - Based on the extensive published data on prediction of risk, the correlations of central and brachial systolic pressures, the improvement of health outcomes resulting from lowering elevated brachial systolic pressure, it is clinically appropriate to conclude that lowering of elevated central systolic pressures will reduce the risk of cardiovascular events and morality.

  - Threshold values for the diagnosis of elevated central arterial pressures have been defined and have been referenced to the threshold values for the diagnosis of hypertension based on brachial pressures and for target goals of treatment.

- Measurements of central arterial pressures can be incorporated into the current approaches to hypertension management as the dual arterial pressure SphygmoCor XCEL device, the only FDA cleared medical device for non-invasive central arterial pressure waveform analysis for all adults, can provide both brachial and central aortic pressures in the same clinic setting.

- Incorporation of PWA into product development clinical trials for cardiovascular disease (particularly hypertension) has the following advantages:

  a. Confirmation of hypertension at baseline and the precision (and reliability) of the baseline value

  b. Confirmation of blood pressure values at follow-up

  c. Additional endpoints for evaluation of therapeutic effect

  d. Informing dose selection during Phase II dose ranging trials

  e. Avoiding misleading information due to white coat hypertension.

  f. Improved patient selection and benefit risk with additional information that can directly impact patient safety

g. Providing supportive and potentially key data improving the likelihood of regulatory approval

h. Information from cBP may be incorporated into the prescribing information (package inserts) to health care providers and such information leads to decisions that optimize patient dosing (increasing or decreasing dose) with the objective of improving both efficacious and safe use of the product.

i. Increasing opportunities for competitive advances with post-approval communication.

Drug and medical device development costs increase exponentially as development programs advance to regulatory approval and commercialization. For products targeting cardiovascular disease, incorporation of central aortic blood pressure measurement and monitoring into clinical trials has the potential to improve key decisions during development (go/no go, endpoints, population characteristics, benefit-risk profile, dosing, etc.) and enhance the likelihood of both regulatory and commercial success.

Based on current technology, the availability of a non-invasive dual arterial pressure measurement system, the compelling clinical rationale and the extensive clinical published research, incorporation of central aortic pressure monitoring into clinical trials, which is complementary to continued reliance on brachial pressure monitoring should be part of drug and medical device development programs for hypertension and other cardiovascular disorders.

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