The Role of Central Aortic Pressure in the Management of High Blood Pressure

Objective of Presentation

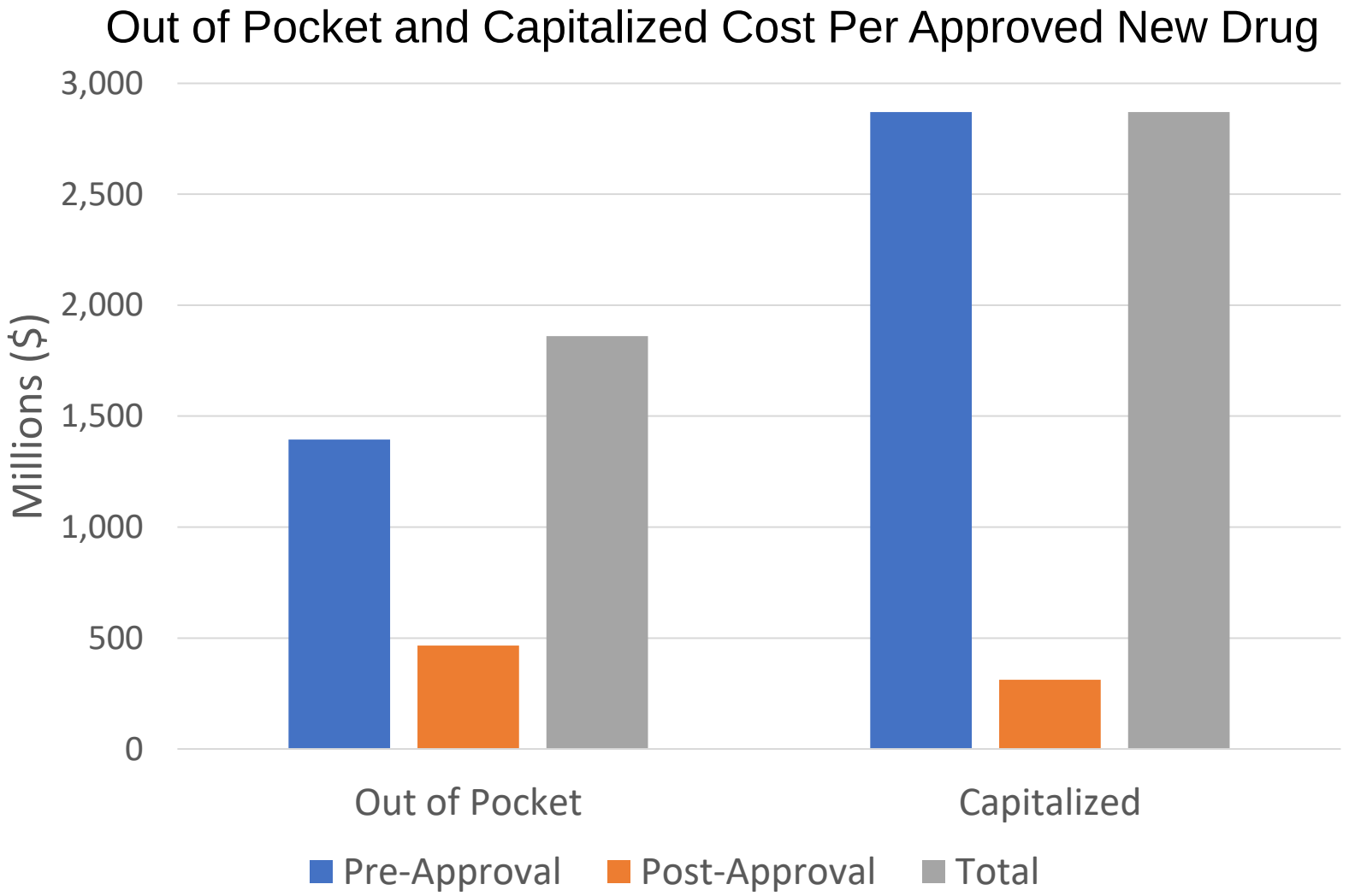
To outline the rationale for integrating central aortic pressure (cBP) monitoring into clinical development programs where arterial pressure is a primary outcome (e.g., products for hypertension) or an important secondary outcome (e.g., products for heart failure, pulmonary hypertension, chronic kidney disease).

Background

Incorporating Central Pressures

- 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 highly desirable.
- Incorporation of central aortic blood pressure (cBP) monitoring 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 from cBP provide the rationale for utilizing cBP in clinical trials from phase I to phase IV.

Total Cost Per Drug Approval



DiMasi et al. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Economics. 2016;47:20-33.

Drug Development Costs

Mean And Median Expected Research and Development Expenditure on New Therapeutic Agents Approved by the FDA (2009-2018)

Therapeutic Area	Sample Size	Median*	Mean*
Antineoplastic and immunomodulating agents	20	2,772 (2,052-5,366)	4,461 (3,114-6,001)
Alimentary tract and metabolism	15	1,218 (613-1,792)	1,430 (921-2,079)
Nervous system	8	766 (323-1,474)	1,077 (509-1,847)
Antiinfectives for systemic use	5	1,260 (260-2,128)	1,297 (672-1,859)
Dermatologicals	4	747	1,998
Cardiovascular system	3	339	1,152
Musculoskeletal system	3	1,052	937
Blood and blood-forming organs	2	793	793
Sensory organs	2	1,302	1,303
Other	1	1,121	1,121

*Expenditure in US$, millions (95% CI)

Given the high development costs, opportunities for improving development program decisions and increasing the probability of success should always be considered.

Wouters et al. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA. 2020;323(9):844-853. doi:10.1001/jama.2020.1166

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Clinical Trial Success Rates

Clinical Trial Success Rates by Phase and Therapeutic Area*

Source	Phase 1 to Approval, %	Phase 2 to Approval, %	Phase 3 to Approval, %	FDA Submission to Approval, %
Therapeutic-area–specific rates				
Oncology	3.4	6.7	35.5	81.7
Metabolism and endocrinology	19.6	24.1	51.6	80.4
Cardiovascular	25.5	32.3	62.2	84.5
Central nervous system	15	19.5	51.1	82.2
Autoimmune and inflammation	15.1	21.2	63.7	80.3
Ophthalmology	32.6	33.6	74.9	80.4
Infectious disease	25.2	35.1	75.3	84.9
Other	20.9	27.3	63.6	80.4

*adapted from Wouters et al

Given the modest probability of success from Phase 1 to 3, opportunities for improving development program decision making and increasing the probability of success should always be considered.

Wouters et al. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA. 2020;323(9):844-853. doi:10.1001/jama.2020.1166

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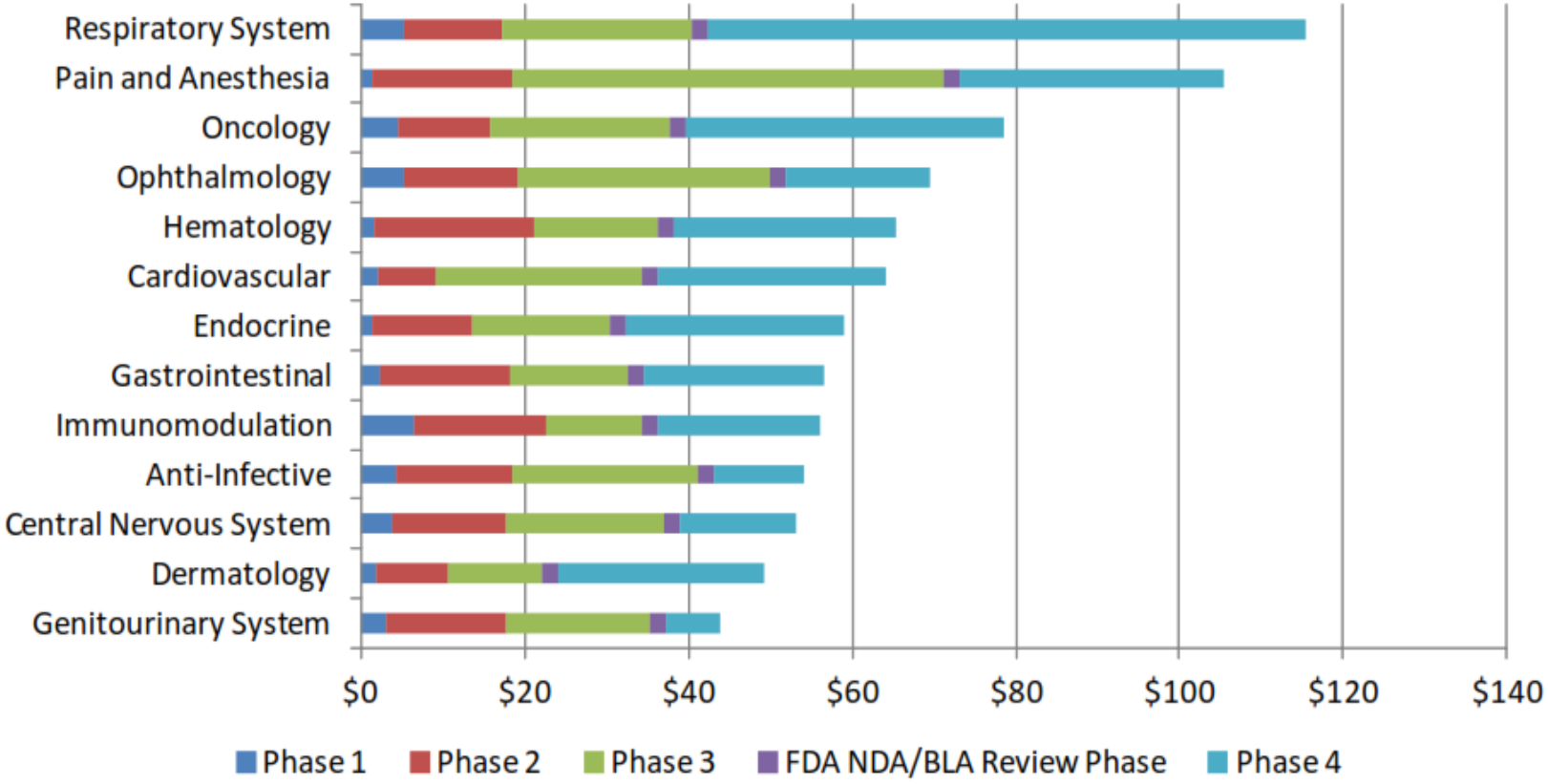
Costs of Drug Development Clinical Trials

Total Per-Study Costs (in $ Millions), by Phase and Therapeutic Area



Given the increased trial costs with increasing phase, opportunities for improving development program decision making and increasing the probability of success should be considered as early as possible.

Examination of clinical trial costs and barriers for drug development. US Department of Health and Human Services. 2014. https://aspe.hhs.gov/sites/default/files/private/pdf/77166/rpt_erg.pdf

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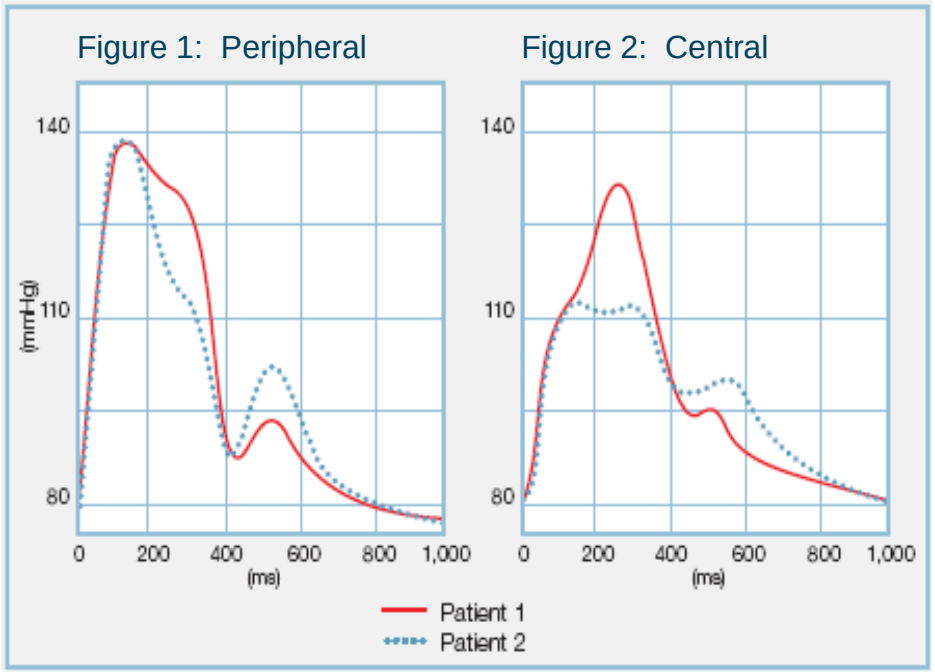
Non-Invasive Measurement of Central Aortic Pressure

- 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
- Calculations are performed through a generalized transfer function that corrects for pressure wave amplification in the upper limb
- Variables produced:
  - Central aortic systolic and diastolic pressures (cBP)
  - Central aortic pulse pressure (systolic minus diastolic pressure)
  - Augmentation pressure (difference between (a) reflected wave added to incident wave, and (b) incident pressure during systole)
  - Augmentation index (augmentation pressure divided by the pulse pressure)
- Peripheral (brachial) blood pressures (pBP) are highly correlated to central pressures
  - Brachial systolic pressure is higher than central aortic systolic pressure
  - Diastolic pressures are similar



The SphygmoCor® XCEL System

Dual Arterial Pressure Monitoring System

- Obtains brachial pressures immediately followed by measurement of central aortic pressures
- Brachial and central aortic pressure values obtained in the same session
- The only FDA cleared medical device for non-invasive central arterial pressure waveform analysis in adults

Arterial Waveform Capture

- A cuff is applied on the upper arm in the standard position
- The cuff is partially inflated to record the brachial waveforms
- These waveforms are detected by sensing changes in the pressure inside the cuff related to arterial pulsation
- The ascending aortic waveform is subsequently derived using a validated mathematical transfer function*

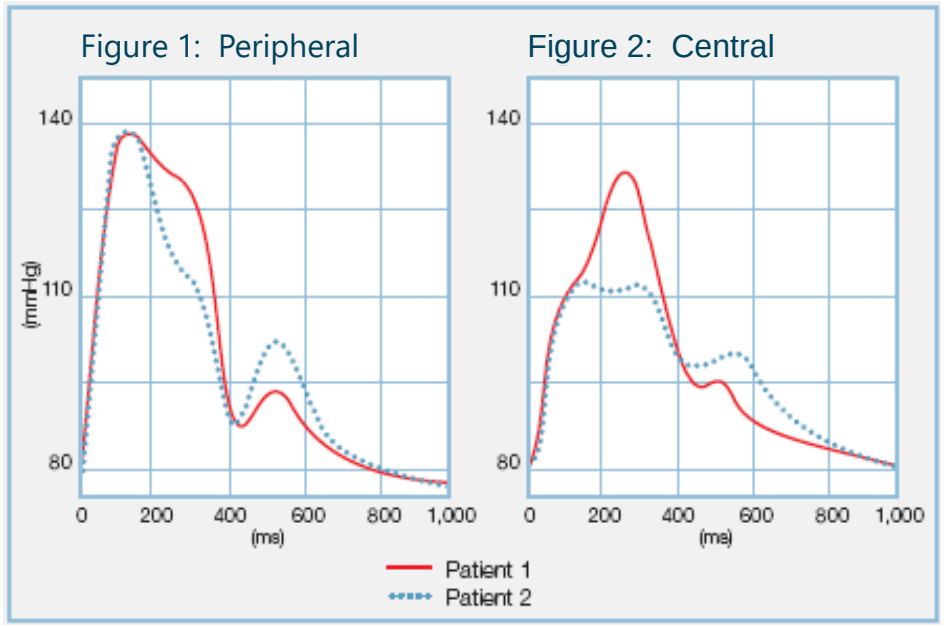
*Generalized transfer function cleared by FDA

Brachial Pressure Differs from Central Pressure

Brachial Cuff Pressure vs. Central Aortic Pressure

Two patients with IDENTICAL BRACHIAL CUFF pressures (Figure 1), but with significantly DIFFERENT CENTRAL/AORTIC arterial pressure waveforms (Figure 2).

- The difference in waveform shapes, due to differences in arterial stiffness and the effects of wave reflections, effects the aortic but not the brachial systolic and pulse pressures



Brachial and Central Aortic Pressure Measurements are Not Redundant and Provide Clinically Relevant and Complimentary Information

Incorporating Central Aortic Blood Pressure Monitoring in Clinical Development Programs

Incorporating Central Aortic Pressure – Why?

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

- Confirmation of hypertension at baseline and the precision (and reliability) of the baseline value
- Confirmation of blood pressure values at follow-up
- Additional endpoints for evaluation of therapeutic effect
- Informing dose selection during phase 2 dose-ranging trials
- Avoiding misleading information due to white coat hypertension.
- Improved patient selection and benefit risk with additional information that can directly impact patient safety
- Providing supportive and potentially key data improving the likelihood of regulatory approval
- Information from cBP may be incorporated into the prescribing information (package inserts)
  - Assisting in decisions that optimize patient dosing with the objective of improving both efficacious and safe product use
- Increasing opportunities for competitive advances with post-approval communication.

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.
- Inclusion/exclusion criteria based on threshold values may be improved in terms of subject qualification by considering cBP.
- Examples:
  - *Scenario A: Concurrent elevation in brachial and central pressures – confirmed hypertension*
  - *Scenario B: Minimal/borderline 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. Prespecified analysis stratifying subjects may be prudent.*
  - *Scenario C: Substantial divergence between brachial and central pressures. May suggest potential differential effect of intervention, which can be evaluated (pre-specified in SAP).*

Confirmation of Blood Pressure Values at Follow-Up

- The issues raised and potential solution proposed for baseline values and inclusion/exclusion criteria apply equally to follow-up (post-enrollment visits) measurements for which efficacy and safety is determined.
- Examples (particularly for end-point visit) :
  - *Scenario A: Large differences in absolute values. May indicate white coat hypertension.*
  - *Scenario B: Discordant changes from baseline in 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.*

Endpoints for Evaluation of Therapeutic Effect

- Published literature indicates 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.
- Example:
  - *Scenario: Drug in phase 2 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 2 studies or to proceed to phase 3.*

Informing Dose Selection During Phase II

- 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 3 program.
- Decisions in phase 2 can be considered the “sweet spot” in terms of economic decisions to proceed into the substantially more expensive and time-consuming phase 3 program.
  - Phase 2 dose ranging studies generally not powered for detecting difference among active doses.
  - Surrogate endpoints (often multiple endpoints) are utilized in phase 2 studies.
- In addition to dose, decisions may involve dose frequency (e.g., daily or bid).
- 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 (e.g., hypotension)
  (e) duration of effect

  All the above must be factored into the decisions that can broadly be categorized as either stopping development, implementing additional phase 2, or proceeding to phase 3.

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.
- Examples:
  - *Scenario A: brachial BP is elevated and cBP is normal or low at baseline.*
  - *Scenario B: brachial BP is significantly higher than baseline at follow-up visit, while cBP is the same as baseline visit.*

Information for Final Safety Evaluation

- Overtreatment (e.g., development of hypotension) is always a concern with the outcomes ranging from (a) symptoms without clinical consequences (presyncope), to (b) syncopal episodes with falls, to (c) end-organ damage (e.g., stroke, syncope, myocardial ischemia, elevated creatinine).
- Studies have documented worsening of end-organ function and increasing adverse events (including death) 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.
- Example:
  - *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 product profile range.*

Prescribing Information

- 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.
- Endpoints related to the primary endpoint (provided that the primary endpoint is positive and statistical issues are prespecified) have been and can be included in prescribing information regardless of whether the endpoint has been qualified (i.e., validated) by the FDA.
- 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.
- Companies that include informative cBP data in phase III trials will be at an advantage over those that have not included cBP monitoring.

Regulatory Approval and Post-Approval Communication

- 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 3 clinical trials, provide opportunities for regulatory agency discussions
- *Examples:*
  - *Supportive data and intended utility of the cBP variables*
  - *Competitive advantages relative to other compounds (including within the same drug class)*
  - *Post-approval communications*
- If such variables are prespecified in a successful development program leading to regulatory approval, external communication of cBP results can be disseminated and be within regulatory guidance and expectations.

Regulatory Guidance

Biomarkers

- Biomarkers are defined characteristics that are measured as indicators of health, disease, or a response to an exposure or intervention, including therapeutic interventions.
- Biomarkers can help diagnose a disease, or predict future disease severity or outcomes (e.g., measurements of blood pressure as an indicator of cardiovascular risks, measurements of blood glucose in diabetes).
- Biomarkers are used to identify the best treatment for a patient, to monitor the safety of a therapy, or to find out if a treatment is having the desired effect on the body.
- Many biomarkers used today have been developed to be used in a specific disease or as part of the development program for a specific medical product. Under the FDA's Biomarkers Qualification Program, biomarkers shown to be useful indicators across different development programs may be designated by the FDA as qualified biomarkers.

FDA Facts: Biomarkers and Surrogate Endpoints. https://www.fda.gov/about-fda/innovation-fda/fda-facts-biomarkers-and-surrogate-endpoints

Surrogate Endpoints

- Surrogate endpoints are used instead of clinical outcomes in some clinical trials. Surrogate endpoints are used when the clinical outcomes might take a very long time to study, or in cases where the clinical benefit of improving the surrogate endpoint, such as controlling blood pressure, is well understood.
- Clinical trials are needed to show that surrogate endpoints can be relied upon to predict, or correlate with, clinical benefit. Surrogate endpoints that have undergone this testing are called validated surrogate endpoints and these are accepted by the FDA as evidence of benefit (i.e., can be used as primary endpoint for basis of approval).
- Between 2010 and 2012, the FDA approved 45 percent of new drugs based on a surrogate endpoint.
- According to section 507(e)(9) of the FD&C Act the term 'surrogate endpoint' means a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, and:
  a) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or
  b) is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product in accordance with section 506(c).

FDA Facts: Biomarkers and Surrogate Endpoints. https://www.fda.gov/about-fda/innovation-fda/fda-facts-biomarkers-and-surrogate-endpoints. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

Surrogate Endpoints (examples)

Validated Surrogate Endpoint	Correlated Clinical Outcome
Systolic blood pressure (SBP)	Occurrence of stroke
Low density lipoprotein cholesterol (LDL) level	Occurrence of heart attack
Forced expiratory volume in 1 second (FEV1) *The amount of air that a person can blow out of his or her lungs in 1 second*	Improved breathing after taking medication for chronic lung diseases such as asthma
Human immunodeficiency virus (HIV) viral load *The amount of the human immunodeficiency virus that is present in the blood*	Development of an acquired immunodeficiency syndrome (AIDS) diagnosis

FDA Facts: Biomarkers and Surrogate Endpoints. https://www.fda.gov/about-fda/innovation-fda/fda-facts-biomarkers-and-surrogate-endpoints

Surrogate Endpoints

- “The acceptability of these surrogate endpoints for use in a particular drug or biologic development program will be determined on a case-by-case basis. It is context dependent, relying in part on the disease, studied patient population, therapeutic mechanism of action, and availability of current treatments.”
- “FDA encourages development of novel surrogate endpoints, and strongly encourages sponsors to seek advice from the relevant CBER or CDER division of such novel endpoints early in development by scheduling a PDUFA VI Type C SE meeting to discuss the use of a novel surrogate endpoint in their planned clinical trials.”
- “The acceptability of a surrogate endpoint for an individual drug or biologic development program will be determined on a case-by-case basis.”

FDA Facts: Biomarkers and Surrogate Endpoints. https://www.fda.gov/about-fda/innovation-fda/fda-facts-biomarkers-and-surrogate-endpoints. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

Surrogate Endpoints

- Surrogate endpoints that have not been “qualified” have been and will continue to be incorporated into clinical development programs.

- Surrogate endpoints can and have been used for patient selection, patient identification, dose-ranging and support of a primary endpoint.

Central Pressure Variables are Both Biomarkers and Surrogate Endpoints

Central Pressure as a Biomarkers

- Elevations in central aortic systolic pressure and augmentation index have both been recognized in multiple studies to be superior to brachial systolic pressure in risk of end-organ damage and adverse clinical outcomes.
- Central pressure variables can help diagnose a disease, or predict future disease severity or outcomes

Central Pressure as a Surrogate Endpoint

- Central pressure variables are consistent with section 507(e)(9) of the FD&C Act
  - The term ‘surrogate endpoint’ means a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, and:
    a) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or
    b) is reasonably likely to predict clinical benefit
- Central pressure variables can be used for patient selection, patient identification, dose-ranging and support of a primary endpoint.

Use of Non-Qualified Surrogate Endpoints in Approved Products

Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry

- "To date, **no biomarkers have been validated as surrogate endpoints** for clinical benefit in heart failure. For patients with symptomatic heart failure, it is generally possible to assess directly how individuals feel, function, and survive; therefore, biomarkers have little utility for evaluating drug efficacy in this setting. Biomarkers, however, can be used to characterize risk in patients with heart failure (e.g., NT pro-BNP, **left ventricular ejection fraction**), and such measures can be useful for prognostic enrichment. Moreover, **biomarkers have utility for early proof-of-concept studies and, in particular, studies that serve as the basis for dose selection**."*

*Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry 2019. https://www.fda.gov/media/128372/download

Non-Qualified Surrogate Endpoints Can Be Used in Patient Selection

Verquvo® (vericiguat tablets, guanylate cyclase stimulator)

Indication:

- VERQUVO is a soluble guanylate cyclase (sGC) stimulator, indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and **ejection fraction less than 45%.**

NOTE: LVEF is not a qualified biomarker or surrogate endpoint

Implications: Enriching studies with populations most likely to have the highest benefit-risk from drug administration improves the probability of success and is supported by the FDA. However, the approved label will restrict the indication to the population studied.

Promotion Acceptable for a Surrogate Endpoint based in Inclusion into Prescribing Information

Diovan® (valsartan, an angiotensin receptor blocker)

Indications:

- Treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
- Treatment of heart failure (NYHA class II-IV); Diovan significantly reduced hospitalization for heart failure
- Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction

Clinical Studies (section 14):

- Heart Failure Trial
  - There were two primary end points, both assessed as time to first event: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for intravenous inotropic or vasodilatory drugs for at least 4 hours.
  - **“In patients not receiving an ACE inhibitor, valsartan-treated patients had an increase in ejection fraction and reduction in left ventricular internal diastolic diameter (LVIDD)**.”

Implications: Information included in the prescribing information can be used in promotion when fair balance and appropriate context is used. For valsartan, this includes for LVEF and LVIDD in heart failure.

Summary

New Paradigm of Incorporating Central Pressures: Not a New Concept

Analogies to Advancement in Medical Evaluation

- Fasting blood glucose followed by introduction of HbA1C
- Electrocardiograms followed by introduction of echocardiogram
- COPD Guidelines: FEV_1 only, followed by incorporation of COPD exacerbations

Every-Day Analogies

- 2-factor identification
- Dead-bolt lock in addition to regular latch and lock

Common Sense Practice of Medicine

- BP measurement needs to be correct and confirmed
- Brachial pressures and central aortic pressures should be considered as part of management of all patients requiring blood pressure management, but particularly those with renal and/or cardiac disease

VISION: Brachial and central BP as essential and complimentary for BP management provided by the same device at the same time.

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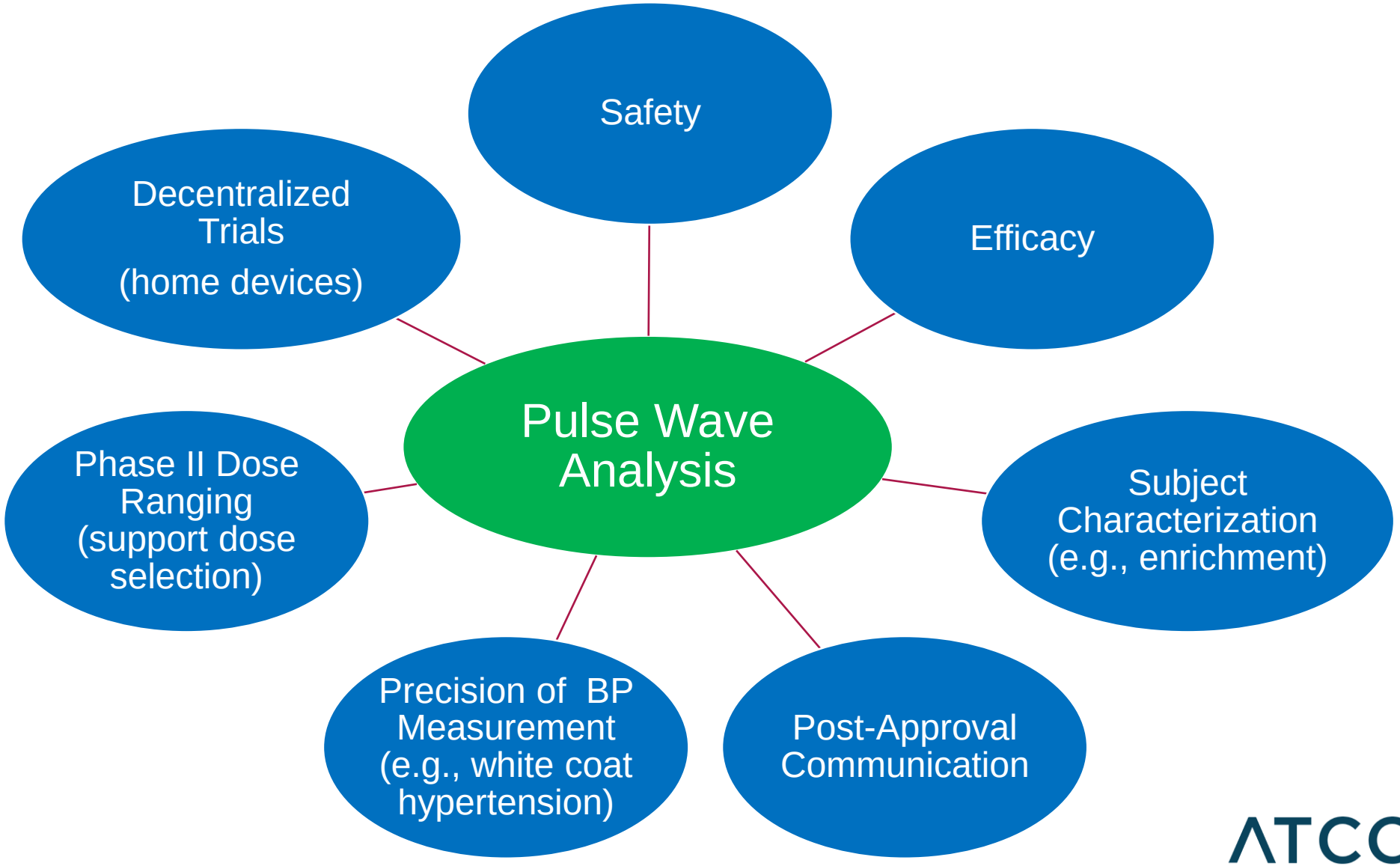
Incorporating PWA Can Improve Success and Efficiency of Drug & Device Development for Vascular Health



Conclusions

- For products targeting cardiovascular disease, incorporation of central aortic blood pressure measurement and monitoring into clinical trials can 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.