CardioDynamics
THE ICG COMPANY

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RE: Formal Request for CMS Reconsideration of Thoracic Electrical Bioimpedance (TEB) for Expanded Coverage for Hypertension

Dear Drs. Jacques and Ulrich, and Mr. Lyman:

Thank you again for your willingness to collaboratively discuss reconsideration of Thoracic Electrical Bioimpedance (TEB) coverage, as outlined in the Centers for Medicare & Medicaid Services (CMS) Manual Section 20-16. CardioDynamics is the primary manufacturer of TEB devices in the world today. Since 1997, we have developed a substantial customer base, including approximately 10,000 CMS physician providers who use TEB (commonly referred to as impedance cardiography or ICG) technology as an important tool in patient management. These CMS providers have voiced considerable concern about the restriction of TEB coverage for hypertension as a result of the 2004 National Coverage Determination (NCD). CMS has indicated a need for additional evidence demonstrating TEB's clinical application in hypertension before it could provide national and broadened coverage for hypertension.

New evidence supporting TEB's impact on health outcomes in hypertension is now available. The evidence is of high quality and generalizable to the CMS beneficiary population. The purpose of this letter is to formally request that CMS reconsider TEB coverage in hypertension and issue an NCD with the following language: *"TEB is covered for the management of hypertensive patients on one or more antihypertensive drugs who are not at goal blood pressure. TEB is covered for hypertension that is essential or secondary, benign or malignant, or with or without comorbidities."*

This request is for expansion of coverage under the current benefit category, diagnostic tests. The evidence supporting TEB's clinical application in hypertension is included in this document and attachments and consists of 23 studies of 2,483 subjects, including:

- Primary evidence from two randomized controlled trials (2 studies of 268 subjects)
- Secondary evidence on TEB's:
    - Diagnostic / prognostic role in hypertension (9 studies of 1,564 subjects)
    - Therapeutic monitoring role in hypertension (9 studies of 305 subjects)
    - Therapeutic-decision-making role in hypertension (3 studies of 346 subjects)

Additionally, we have provided background information on TEB technology, TEB validity, and the importance of hemodynamic considerations in hypertension.

We appreciate your careful consideration of this request and maintain a strong desire to work collaboratively with CMS to establish an appropriate and consistent NCD for TEB in hypertension.

Regards,

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President

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TEB Technology Overview

Overview of Hemodynamics

"Hemodynamics" refers to the forces affecting the flow of blood throughout the body. Human beings cannot survive without adequate oxygenation, and the primary function of the cardiopulmonary system is to deliver oxygen and nutrients to meet the metabolic demands of the body and then to remove metabolic waste products. A healthy body constantly regulates cardiac output, the amount of blood pumped each minute by the heart, to maintain adequate tissue perfusion. In disease states, however, hemodynamic imbalances occur and the body is forced to compensate, often severely, for cardiovascular dysfunction. Most cardiac drugs administered in the setting of acute or chronic cardiovascular dysfunction directly or indirectly affect one of the four determinants of cardiac output:

Component	Definition
Preload	Volume of blood in the ventricle at the end of diastole (relaxation)
Contractility	Rate of shortening of myocardial muscle fibers
Afterload	Force heart must overcome to expel blood into the vasculature
Heart Rate	Number of heart beats per minute

Knowledge of the level of cardiac output and its components allows clinicians to make judicious decisions regarding diagnosis, prognosis, and treatment. It has been well established that both trained and untrained physicians alike are unable to estimate cardiac output through physical assessment alone.[1, 2, 3, 4, 5] The inability of clinicians to accurately assess hemodynamic status from physical examination is the basis for the measurement of hemodynamic parameters in clinical practice.

Invasive Hemodynamic Monitoring

Measurements of cardiac output by the thermodilution technique have been available since the 1970's. However, this measurement is highly invasive, utilizing a flow-directed, pulmonary artery catheter (also known as right heart catheterization or Swan-Ganz® catheterization), which exposes the patient to risk of complications. In addition, this technique is costly and requires a skilled physician and a sterile environment for catheter insertion. As a result, it has been used only in a very narrow strata of critically ill and high-risk patients in whom the knowledge of hemodynamics outweighed the risks of the procedure. In the United States, it is estimated that more than one million pulmonary artery catheter monitoring procedures (CPT 93501) are performed annually, most often in perioperative cardiac and vascular surgical patients, acutely decompensated heart failure, cardiogenic shock, multi-organ failure, and trauma. Use of invasive techniques to assess patients with nonhospitalized patients with chronic cardiovascular conditions is not considered practical or appropriate.

Noninvasive Hemodynamic Monitoring

In theory, a noninvasive way to monitor hemodynamics would provide exceptional clinical value because data similar to invasive hemodynamic monitoring methods could be obtained at much lower cost and no risk. While there is obvious benefit in patients who would otherwise require invasive monitoring, the largest number of patients who could benefit from noninvasive monitoring would be those in whom invasive hemodynamic monitoring is neither possible nor worth the risk or

cost. This includes outpatients with chronic diseases that involve hemodynamic disturbances and who are receiving treatments that directly and indirectly alter hemodynamics.

TEB Methodology

Thoracic electrical bioimpedance (TEB), more commonly referred to as impedance cardiography (ICG), has been researched since the 1940's. Because the Centers for Medicare and Medicaid Services (CMS) describes the procedure as "TEB" instead of "ICG", TEB will be used to describe the technology in this document. With TEB, the placement of four specially designed and FDA 510(k) cleared disposable sensors are used to transmit and detect electrical and impedance changes in the thorax, which are used to measure and calculate hemodynamic parameters.[6]

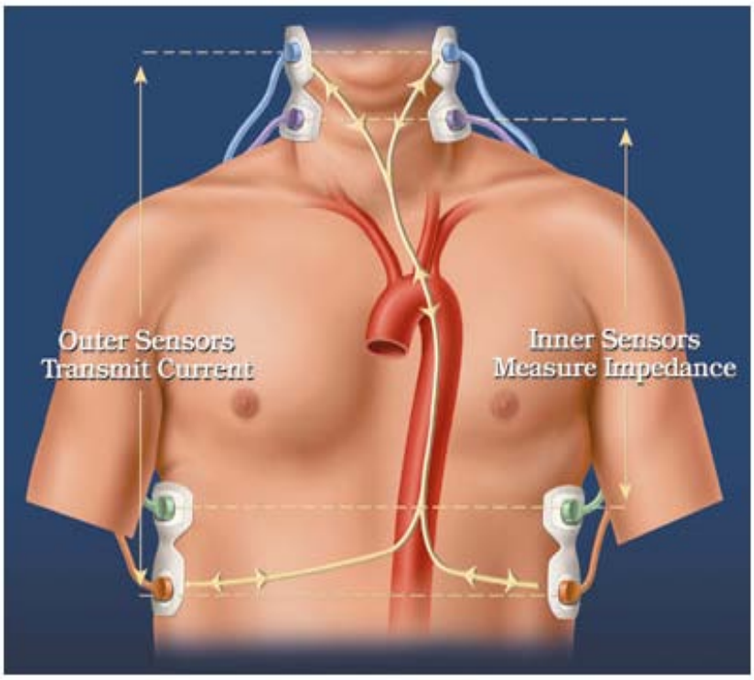

Figure 1. TEB Method

- Alternating Current is Transmitted Through the Chest Through the Outer Sensors
- Current Seeks Path of Least Resistance: The Blood Filled Aorta
- TEB Device Measures the Baseline Impedance (Resistance) to this Current Through the Inner Sensors
- With Each Heartbeat, Blood Volume and Velocity in the Aorta Change
- TEB Device Measures the Corresponding Change in Impedance
- TEB Device Uses the Baseline and Changes in Impedance to Measure and Calculate Hemodynamic Parameters

Waveform Analysis

Electrical and impedance signals are automatically processed to determine ECG and ICG waveform characteristics. These waveform characteristics are called fiducial points (shown in Figure 2), and are used to measure and calculate hemodynamic parameters, such as cardiac output, stroke volume, systemic vascular resistance, velocity index, thoracic fluid content, and systolic time ratio (listed in Table 1). As part of TEB report interpretation, physicians review the ECG and ICG waveforms to confirm the quality of the signals and reliability of the waveform measurements. Unstable waveforms or unreliable measurements can lead to poor results with both ECG and ICG.

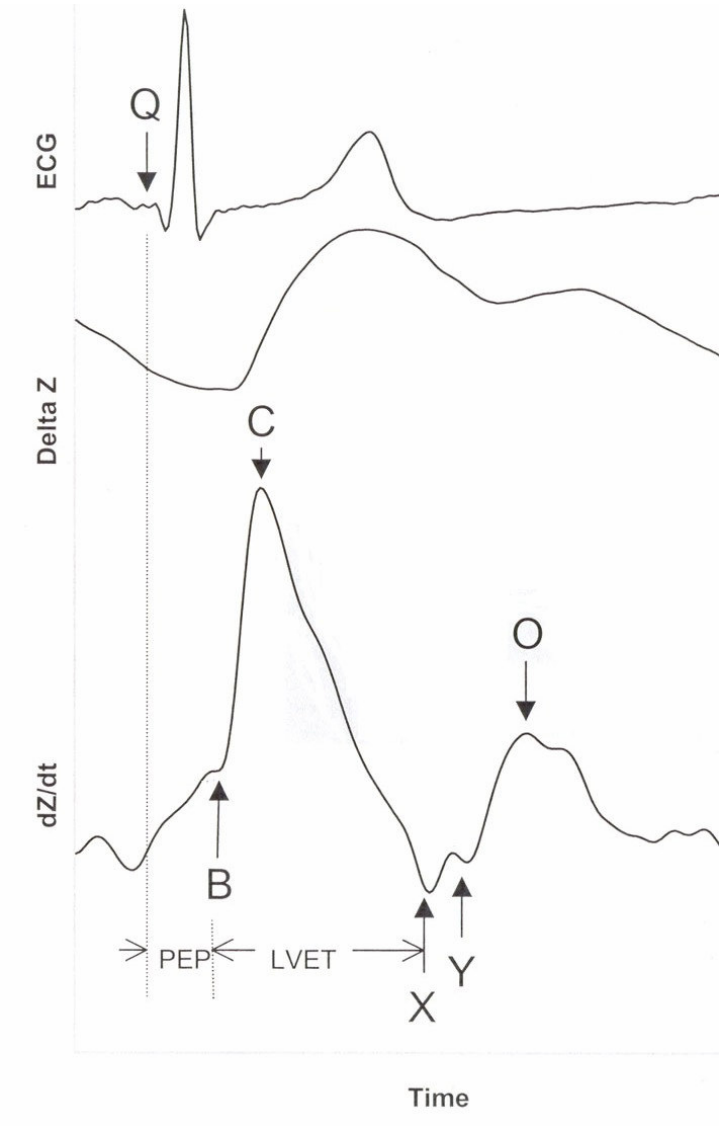

Figure 2. ECG and Impedance Waveform Characteristics with Representative Cardiac Cycle Events; Q = ventricular depolarization, B = opening aortic & pulmonic valves, C = maximal slope; X = Closure aortic valve; Y = Closure of pulmonic valve; O = Opening mitral valve / rapid filling of ventricles.

Table 1. TEB parameter description

Parameter	Abbrev	Definition	Normal Range
Blood Flow			
Cardiac Output	CO	Amount of blood pumped by the left ventricle each minute	Varies based on body size
Cardiac Index	CI	Cardiac output normalized for body surface area	2.5 - 4.2 L/min/m^2
Stroke Volume	SV	Amount of blood pumped by the left ventricle each heartbeat	Varies based on body size
Stroke Index	SI	Stroke volume normalized for body surface area	35 - 65 mL/beat/m^2
Resistance			
Systemic Vascular Resistance	SVR	The resistance to the flow of blood in the vasculature (often referred to as "Afterload")	Varies based on body size
Systemic Vascular Resistance Index	SVRI	Systemic vascular resistance normalized for body surface area	1680 – 2580 dynes sec m^2 / cm^5
Contractility			
Acceleration Index	ACI	Peak acceleration of blood flow in the aorta.	Males: 70 – 150 / 100 / sec^2 Females: 90 – 170 / 100 / sec^2
Velocity Index	VI	Peak velocity of blood flow in the aorta	33 - 65 / 1000 / s
Left Cardiac Work Index	LCWI	Left cardiac work normalized for body surface area	3.0 - 5.5 kg m / m^2
Systolic Time Ratio	STR	The ratio of the electrical and mechanical systole	0.3 - 0.5
Pre Ejection Period	PEP	The time from the beginning of electrical stimulation of the ventricles to the opening of the aortic valve (electrical systole)	Varies based on heart rate, preload, and contractility
Left Ventricular Ejection Time	LVET	The time from the opening to the closing of the aortic valve (mechanical systole)	Varies based on heart rate, preload, and contractility
Fluid Status			
Thoracic Fluid Content	TFC	The electrical conductivity of the chest cavity, which is primarily determined by the intravascular, intraalveolar, and interstitial fluids in the thorax	Males: 30 – 50 / kOhm Females: 21 - 37 / kOhm

Background Evidence on TEB Accuracy and Reproducibility

Accuracy

Multiple published studies demonstrate that current TEB technology (BioZ®, CardioDynamics, San Diego, CA) is accurate compared to invasive techniques such as thermodilution and direct Fick.

Table 2. Published Studies Comparing BioZ to Invasive Methods of Cardiac Output Estimation

Author (year)	Population	Parameter	Comparison	R Value	Bias	Precision
Albert (2003) [7]	Heart failure in intensive care unit (n = 33)	Cardiac output	TEB–TD	0.89	-0.46	1.38
Drazner (2002) [8]	Heart failure in catheterization laboratory (n = 59)	Cardiac output	TEB-Fick TD-Fick TEB-TD	0.73 0.81 0.76	0.74 0.75 0.03	1.1 0.95 1.1
Sageman (2002) [9]	Post CABG (n = 20)	Cardiac index	TEB-TD	0.92	0.07	0.40
Van de Water (2003) [10]	Post CABG (n = 53)	Cardiac output	TEB-TD	0.81	-0.17	1.09
Yung (2004) [11]	Pulmonary hypertension (n = 42)	Cardiac output	TEB-Fick TD-Fick TEB-TD	0.84 0.89 0.80	-0.24 0.19 -0.43	0.87 0.76 1.01

Bias calculation = TEB – reference measurement; CABG = coronary artery bypass graft surgery; Fick = direct Fick method; TEB = thoracic electrical bioimpedance; n = number of patients; NR = not reported; r value = Pearson's correlation coefficient; TD = bolus thermodilution method.

Reproducibility

Additionally, TEB is more reproducible than thermodilution in patients in a stable physiologic state, and is therefore better able to discern changes in hemodynamics. In the study by Van De Water, the correlation of cardiac output by TEB to itself was significantly greater than when thermodilution was compared to itself on serial measurements (Table 3). This is also reflected in the smaller bias and significantly lower standard deviations among individual cardiac output measurements.

Table 3. Reproducibility of TEB and Thermodilution Measurements (Van De Water 2003)

Comparison	Correlation (R^2)	Bias (L/min)	Std Dev (L/min)	P-Value
Thermodilution				
CO_{TD} 2 vs. CO_{TD} 1 (n = 53)	0.69	-0.13	1.02	< 0.001
CO_{TD} 3 vs. CO_{TD} 2 (n = 53)	0.71	0.16	1.01	< 0.001
CO_{TD} 3 vs. CO_{TD} 1 (n = 53)	0.69	0.03	1.07	< 0.001
Thoracic Electrical Bioimpedance				
CO_{TEB} 2 vs. CO_{TEB} 1 (n = 53)	0.95	0.08	0.44	< 0.001
CO_{TEB} 3 vs. CO_{TEB} 2 (n = 53)	0.96	-0.06	0.39	< 0.001
CO_{TEB} 3 vs. CO_{TEB} 1 (n = 53)	0.95	0.02	0.43	< 0.001

TD=thermodilution; TEB=thoracic electrical bioimpedance

Other studies have also shown the high intraday and interday reproducibility of TEB in stable outpatients with heart failure[12] and coronary disease.[13] These data form the basis of expected interday variability and provide a reliable guide to whether a patient has actually experienced a change in hemodynamics that is outside of expected physiologic variation.

Thoracic Fluid Content

Thoracic fluid content, the reciprocal of total thoracic impedance, is highly correlated with amount of fluid in the chest cavity, whether intravascular or extravascular. Studies validating the diagnostic value of absolute and relative changes in thoracic impedance / thoracic fluid content measurements include:

- Fluid reductions during thoracentesis and pericardiocentesis[14,15]
- Fluid increases with infused blood and saline, and during lung lavage during surgery[16,17]
- Fluid shifts during lower body negative pressure maneuver, validated versus central venous pressure[18]
- Blood and plasma volumes in heart failure patients, validated versus radioactive isotope testing[19]
- Extravascular fluid overload in patients with and without pulmonary edema[20,21]
- Fluid reductions in response to diuretic therapy [22,23]

TEB Products and Clinical Users

TEB Products

CardioDynamics has received FDA 510(k) clearance to market devices that monitor noninvasive hemodynamic parameters. CardioDynamics currently markets the TEB devices shown in Figure 3.

BioZ Monitor
510(k) K974725, K001100, & K011439

BioZ Module for GE Medical Systems
510(k) K010164

BioZ Dx
510(k) K041294 & K051228

Figure 3. CardioDynamics TEB Products

TEB Users

CardioDynamics has approximately 4,000 TEB devices in clinical use in the United States. These devices are used in leading hospitals and physicians offices by an estimated 10,000 physicians. Over 90% of these devices are for outpatient use, predominantly in cardiology, internal medicine, and family practice offices. CardioDynamics estimates that our "BioZ" brand of TEB has greater than 95% market share of TEB devices in the United States.

History of CMS Coverage and Coding of TEB

Coverage History

TEB was evaluated by CMS in 1989 and 1992. In 1992, a full technology assessment was completed. Both times, CMS rendered a noncoverage decision for TEB. In 1998, in what the CMS website identifies as "the original consideration of TEB coverage" (CAG-00001N), CMS covered TEB for six indications, including "suspected or known cardiovascular disease". The 1998 Decision Memorandum stated:

> *"One manufacturer, Cardiodynamics, has submitted substantial documentation on the medical effectiveness of their device which answers the questions we had raised during previous assessments (in 1989 and 1992). The manufacturer submitted over 70 peer-reviewed studies on more than 5,000 patients, conducted by 600 researchers at 275 institutions. We also performed an independent review of the medical literature and found no substantial problems in proceeding with coverage."*

As a result of working together in 1998, CMS highlighted CardioDynamics as a model company for their accelerated review process. Importantly, CMS considered hypertension evidence in its initial evaluation. Many of the 70 peer-reviewed studies provided to CMS were relevant to the use of TEB for hypertension management. During the evaluation process, CardioDynamics, along with invited expert physicians, met with CMS representatives to review clinical evidence. During the ongoing discussions, there was agreement that TEB was appropriate for use in situations when physicians were prescribing hemodynamic-altering medications, such as beta blockers, calcium channel blockers, ACE inhibitors (and other drugs affecting the renin angiotensin system), vasodilators, inotropes, and diuretics. CMS officials indicated that stating the indication as "suspected or known cardiovascular disease" would enable physicians to use TEB when treating patients for conditions requiring hemodynamic-altering drugs. The specific conditions for treatment included hypertension, heart failure, left ventricular hypertrophy, cardiomyopathies, and pulmonary disease – for outpatients as well as for emergent and critically ill patients. The 1998 decision memo defined TEB coverage as such. Additionally, when the American Medical Association created a CPT level I HCPCS code for TEB in 2001, they submitted a document to CMS illustrating clinical application of TEB including a hypertension clinical vignette. To CardioDynamics' knowledge, at no time after the 1998 decision memo was the inclusion of hypertension within the indication of "known or suspected cardiovascular disease" an issue. Consistent with the 1998 decision memorandum, the vast majority of contractors implemented coverage policies that included hypertension ICD-9 codes.

Between 1998 and 2001, no evidence was published that questioned the validity or clinical application of CardioDynamics' BioZ TEB device. On the contrary, during that time frame a significant amount of positive evidence was generated, including a randomized controlled trial from the Mayo Clinic in refractory hypertension (uncontrolled blood pressure on 2 or more medications) showing a 70% improvement in achieving goal blood pressure with TEB-guided management. Without new evidence suggesting that the use of TEB for suspected or known cardiovascular disease was ineffective or had negative impact on health outcomes, CardioDynamics believes there was no rationale for removal of this coverage indication.

However, CMS accepted a request submitted in December 2001 from a single CMS carrier for a reconsideration of TEB to "reevaluate the scope of the existing policy and to consider adding the management of hypertension". The CMS review resulted in a decision memo (CAG-00001R) on August 7, 2003, and an NCD effective January 23, 2004, which removed the "suspected or known cardiovascular disease" indication, changed "fluid management" indication to "fluid management for congestive heart failure", left the other indications largely unchanged, and included the following language on coverage of TEB for hypertension:

> *"Contractors have discretion to determine whether the use of TEB for the management of drug-resistant hypertension is reasonable and necessary. Drug-resistant hypertension is defined as failure to achieve goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic."*

In the opinion of CardioDynamics and physician experts with whom we discussed the decision, there was sufficient evidence from the Mayo Clinic Trial to support national coverage of TEB for hypertension not at goal blood pressure on two or more medications (the entry criteria for that specific study). While the Mayo Clinic Trial was conducted in patients with "refractory" hypertension, defined as patients not at goal BP on two or more medications, CMS specified carrier discretion for coverage of the more restrictive "resistant" hypertension, defined as the failure to achieve goal blood pressure in patients on three or more medications. Moreover, placing the burden of the decision regarding hypertension coverage on each individual carrier has resulted in inconsistent coverage decisions based on the varied experiences of medical directors and sources they consulted. For example, a patient with resistant hypertension living in Connecticut and working in New York would be covered if TEB was performed by a physician near his home but not if performed for the same condition by a physician near his work.

The issues related to the inconsistent coverage across the individual carriers and the disagreement over which hypertensive patients might benefit from TEB led to a meeting in June 2004 at the National Heart Lung Blood Institute (NHLBI) that was requested by the Secretary of Health and Human Services, Mr. Tommy Thompson. Experts invited by NHLBI and CardioDynamics met to discuss the evidence and rationale for TEB clinical application in hypertension. While some experts believed that there was sufficient evidence supporting TEB's use in hypertension, other experts and CMS indicated a desire to see additional evidence demonstrating TEB's clinical application in hypertension before extending national TEB coverage for hypertension. Some of the requested components of a new clinical trial included: 1) a greater number of subjects than the 104 subjects in the Mayo Clinic Trial; 2) a multicenter trial; 3) evaluation of use of TEB by generalists vs. hypertension specialists; and 4) a mechanism to measure whether patient compliance to medications affected outcomes. There was also a discussion of appropriate endpoints for TEB studies and whether long-term, population-based studies were required to obtain additional prognostic information on the use of TEB parameters. Because blood pressure itself is an accepted surrogate outcome for morbidity and mortality, there was broad consensus that blood pressure reduction would serve as an appropriate endpoint for TEB studies.

In two letters from CardioDynamics to Ms. Gay Burton dated July 2, 2004, CardioDynamics informally requested that CMS:

1. Reconsider coverage of TEB and issue a revised NCD with national coverage (vs. the current "contractor discretion" status) and change the definition of coverage to those who have failed to reach goal blood pressure on two or more antihypertensive medications (vs. the current "three or more drugs including a diuretic" status).
2. Clarify that:
    a. For carriers covering TEB for drug-resistant hypertension, any hypertension ICD-9 code could qualify as "drug-resistant" as long as the patient was on three or more medications.
    b. For carriers covering TEB for drug-resistant hypertension, "full doses" of drugs would be defined as the maximum tolerable doses for the patient.

On September 10, 2004, CardioDynamics received a letter from Dr. Louis Jacques, Director, Division of Items and Devices, Coverage and Analysis Group. The letter stated that:

1. CMS did not believe that the evidence CardioDynamics submitted provided sufficient evidence to reconsider TEB coverage for hypertension.
2. CMS would communicate to its contractors that:
    c. "There is no ICD-9 code specifying drug-resistant hypertension. Accordingly, any hypertension code may be submitted with a claim for the use of TEB in the context of drug resistant hypertension."
    d. "Full doses are the maximum tolerated doses for the individual patient as determined by the treating physician."

Currently, approximately two-thirds of the CMS carriers cover TEB for resistant hypertension in some form, although many of these carriers do not list hypertension ICD-9 codes that allow electronic submission and payment for the procedure. Instead, they require burdensome manual submission of records to process payment for TEB for resistant hypertension, or require the submission to be rejected and then appealed. Both of these procedures create significant obstacles for physicians who wish to perform TEB for resistant hypertension.

In August 15, 2005, representatives from CardioDynamics met informally with CMS officials to discuss the new evidence supporting coverage of TEB in hypertension and the process for CMS to formally reconsider coverage. We appreciate the collaborative manner in which CMS representatives considered the new evidence, asked clarifying questions, and provided feedback on CardioDynamics' projected formal reconsideration request.

<u>Coding History</u>

In the original CMS decision memorandum, CMS established that a set of existing CPT codes be utilized for the TEB procedure:

93720 Plethysmography, full body, with interpretation and report
93721 Plethysmography, tracing only, without interpretation and report
93722 Plethysmography, full body, interpretation and report only

In April 1999, CMS announced the effective date of coverage to be July 1, 1999, and modified the decision memorandum to instruct carriers and providers to use the codes previously established for TEB as an experimental procedure under HCPCS Level II coding:

M0302	Global code, technical and professional included
M0302-26	Professional component only
M0302-TC	Technical component only

To remain consistent with the Medicare-approved indication of TEB for determination of need for inotropic therapy, in September 2000, the Durable Medical Equipment Regional Carriers (DMERC) modified their policy to allow noninvasive hemodynamic studies to be used in place of invasive hemodynamic studies for coverage of inotropic drugs administered through external infusion pumps, effective July 1, 1999.

In November 2001, CMS accepted the American Medical Association recommendation for provision of a Level I HCPCS procedure code for TEB (CPT code). Federal Register publication 42 CFR Part 405 announced that effective January 1, 2002, the previous procedure code M0302 would be inactive and that CPT code 93701 would become active. The new CPT code has three components based on services rendered:

93701	Global, technical and professional included
93701-26	Professional component only
93701-TC	Technical component only

In November 2001, the Outpatient Prospective Payment System (OPPS) Fee Schedule first listed CPT 93701 as a reimbursable procedure. Hospitals performing TEB testing as an outpatient procedure were directed to bill using Ambulatory Payment Classification 0099 (same as 12 lead resting ECG).

Currently, per the Federal Register notice on TEB coverage in 2001, CMS allows frequency of the procedure as medically necessary. A statement regarding use with Critical Care Services (CPT 99291 and 99292) clarifies that, "separate payment for this service will not be made when provided in conjunction with critical care services. If critical care services are not performed, the professional component may be billed."

For 2006, the national average reimbursement for the procedure is $44.34, which is calculated as the Medicare Conversion Factor of $37.90 x Relative Value Units (RVU) of 1.17.

Table 4. Coding for TEB

	Global	**Technical**	**Professional**
CPT	93701	93701-TC	93701-26
RVU	1.17	1.00	0.17

Proposed Coverage Language

According to title XVIII of the Social Security Act § 1869(f)(1)(B), in order to be covered by Medicare, an item or service must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." Under § 1862(a)(1)(A), an item or service may be considered reasonable and necessary if it improves net health outcome(s). In addition, to be considered reasonable and necessary, the technology must, if FDA-regulated, have been approved or cleared by the FDA for at least one indication and the technology causes an equal or greater improvement in net health outcome(s) than any established alternatives used to treat the same indication in the same population in the same clinical setting.

CardioDynamics' TEB devices have received FDA 510(k) clearance and there is strong evidence that use of CardioDynamics' TEB results in a net improvement in health outcomes for hypertension patients. The evidence is of high quality and is generalizable to the CMS beneficiary population. Therefore, CardioDynamics requests that CMS issue expanded coverage for TEB in hypertension through an NCD with the following language:

> *"TEB is covered for the management of hypertensive patients on one or more antihypertensive drugs who are not at goal blood pressure. TEB is covered for hypertension that is essential or secondary, benign or malignant, or with or without comorbidities."*

Proposed Benefit Category, Site of Service, and Coding

Benefit Category
Diagnostic Tests (other)

Site of Service
TEB is currently covered as either a hospital or outpatient service.

Procedural Coding

CPT codes

93701	Global, technical and professional included
93701-26	Professional Component only
93701-TC	Technical component only

APC codes

Hospitals performing TEB testing as an outpatient procedure are currently directed to bill using Ambulatory Payment Classification 0099 (Electrocardiogram).

Appropriate ICD 9 Codes for Patients with Hypertension

401 Series	*Essential Hypertension*
401.0	Essential hypertension; Malignant
401.1	Benign essential hypertension
401.9	Unspecified essential hypertension
402 Series	*Hypertensive Heart Disease*
402.00	Hypertensive heart disease; Malignant; Without congestive heart failure
402.01	Hypertensive heart disease; Malignant; With congestive heart failure
402.10	Hypertensive heart disease; Benign; With congestive heart failure
402.11	Hypertensive heart disease; Benign; With congestive heart failure
402.90	Hypertensive heart disease; Unspecified; Without congestive heart failure
402.91	Hypertensive heart disease; Unspecified; With congestive heart failure
403 Series	*Hypertensive Renal Disease*
403.00	Hypertensive renal disease; Malignant; without mention of renal failure
403.01	Hypertensive renal disease; Malignant; with renal failure
403.10	Hypertensive renal disease; Benign; without mention of renal failure
403.11	Hypertensive renal disease; Benign; with renal failure
403.90	Hypertensive renal disease; Unspecified; without mention of renal failure
403.91	Hypertensive renal disease; Unspecified; with renal failure

404 Series	*Hypertensive Heart and Renal Disease*
404.00	Hypertensive heart and renal disease; Malignant; w/o mention of congestive heart failure or renal failure
404.01	Hypertensive heart and renal disease; Malignant; with congestive heart failure
404.02	Hypertensive heart and renal disease; Malignant; with renal failure
404.03	Hypertensive heart and renal disease; Malignant; with congestive heart failure and renal failure
404.10	Hypertensive heart and renal disease; Benign; w/o mention of congestive heart failure or renal failure
404.11	Hypertensive heart and renal disease; Benign; with congestive heart failure
404.12	Hypertensive heart and renal disease; Benign; with renal failure
404.13	Hypertensive heart and renal disease; Benign; with congestive heart failure and renal failure
404.90	Hypertensive heart and renal disease; Unspecified; w/o mention of congestive heart failure or renal failure
404.91	Hypertensive heart and renal disease; Unspecified; with congestive heart failure
404.92	Hypertensive heart and renal disease; Unspecified; with renal failure
404.93	Hypertensive heart and renal disease; Unspecified; with congestive heart failure and renal failure

405 Series	*Secondary Hypertension*
405.01	Secondary hypertension; Malignant; Renovascular
405.09	Secondary hypertension; Malignant; Other
405.11	Secondary hypertension; Benign; Renovascular
405.19	Secondary hypertension; Benign; Other
405.91	Secondary hypertension; Unspecified; Renovascular
405.99	Secondary hypertension; Unspecified; Other

Rationale to Consider TEB in Hypertension Management

Summary

- Only 31% of hypertensive patients in the United States have controlled blood pressure
- 44% of those ≥60 years of age who are aware, told to control their blood pressure, and actively treated for hypertension do not have their blood pressure controlled
- Hypertension is a leading risk factor for stroke, ischemic heart disease, heart failure, and renal disease
- High blood pressure is caused by disturbances in hemodynamics, including a high cardiac output, high systemic vascular resistance, or varying degrees of both
- Antihypertensive medications reduce blood pressure by reducing cardiac output, systemic vascular resistance, or both

Hypertension Definition

Hypertension is currently defined as a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medications.[24] Essential hypertension has no definitive etiology, but a variety of risk factors appear to contribute to its development. Hypertension is a major public heath concern in the United States and is a major risk factor for stroke, ischemic heart disease, heart failure, renal disease, and stroke.[25]

Hypertension Control

Table 5 displays data from the National Health and Nutrition Examination Survey (NHANES) that reveals the lack of progress in controlling blood pressure to <140/90 mm Hg in the United States since 1988.[26]

Table 5. NHANES Blood Pressure Control Trends

	NHANES II (1976-1980)	**NHANES III (Phase I, 1988-1991)**	**NHANES III (Phase 2, 1991-1994)**	**NHANES 1999-2000**
Blood Pressure Control	10%	29%	27%	31%

The general lack of improvement exists in spite of the large amount of patient and physician education and over 100 antihypertensive medications available in the marketplace. According to the NHANES survey there are 30 million adults over 60 years of age with hypertension. Of the 30 million with hypertension, 19 million have been diagnosed with hypertension, have been told to control their hypertension, and have had antihypertensive medications instituted. Of the 19 million actively-treated patients, 8.5 million (44%) are not controlled to BP<140/90 mm Hg and are thus at increased risk for cardiovascular events.

Hypertension as a Risk Factor

A meta-analysis of one million patients reported that each 2 mm Hg systolic BP reduction over a ten-year period would result in 10% reduction in stroke mortality and 7% reduction in ischemic heart disease or other cardiovascular disease mortality.[27] The linear reduction in risk was evident for both systolic and diastolic blood pressure, across all age groups, and to blood pressure levels as low as 115/75 mm Hg. Therefore, small decreases in blood pressure are clinically significant.

Current Pharmacological Treatment for Hypertension

Increasing awareness of hypertension and convincing patients of the need to make lifestyle modifications are vital to reduce the overall incidence and improve control of hypertension. However, these issues will not likely be addressed through drugs, devices, or diagnostic tests such as TEB. For that reason, the use of TEB is applicable in patients who have been diagnosed with hypertension and for whom the decision to initiate pharmacological therapy has already been made. In those patients, a lack of treatment options is not the primary reason for lack of blood pressure control. On the contrary, a multitude of treatment options exist. Hypertension guidelines identify multiple drug choices for uncomplicated hypertension, as well as compelling indications for comorbid conditions and specific indications for specific agents. However, no treatment approach is universally accepted and thus there is great variation the drug agents and doses chosen by physicians. In any case, it is clear that inadequate pharmacological regimen selection is the most significant opportunity for improvement in the treatment of hypertension.[28, 29]

Hypertension and Hemodynamics

Blood pressure has two hemodynamic components – cardiac output and systemic vascular resistance. Regardless of the pathophysiology of hypertension, elevated mean arterial pressure can only manifest through elevated cardiac output, elevated vascular resistance, or a combination of the two.[30, 31]

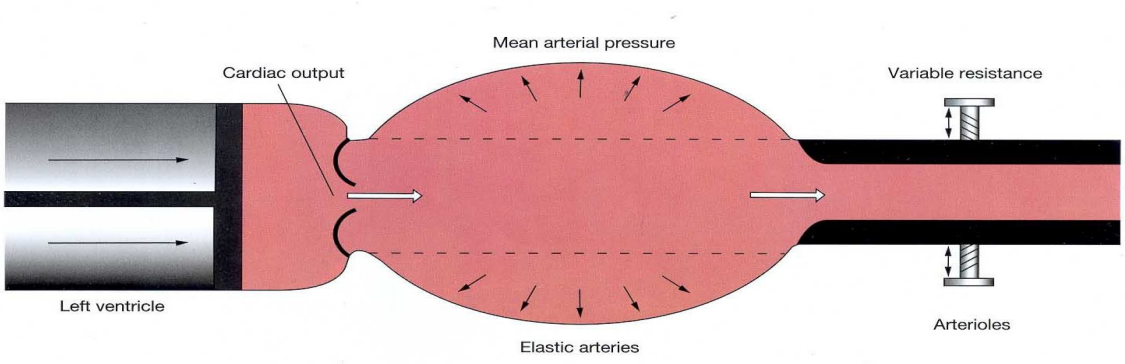

Figure 4. Physiologic Model of Cardiac Output, Arterial Pressure, and Systemic Vascular Resistance

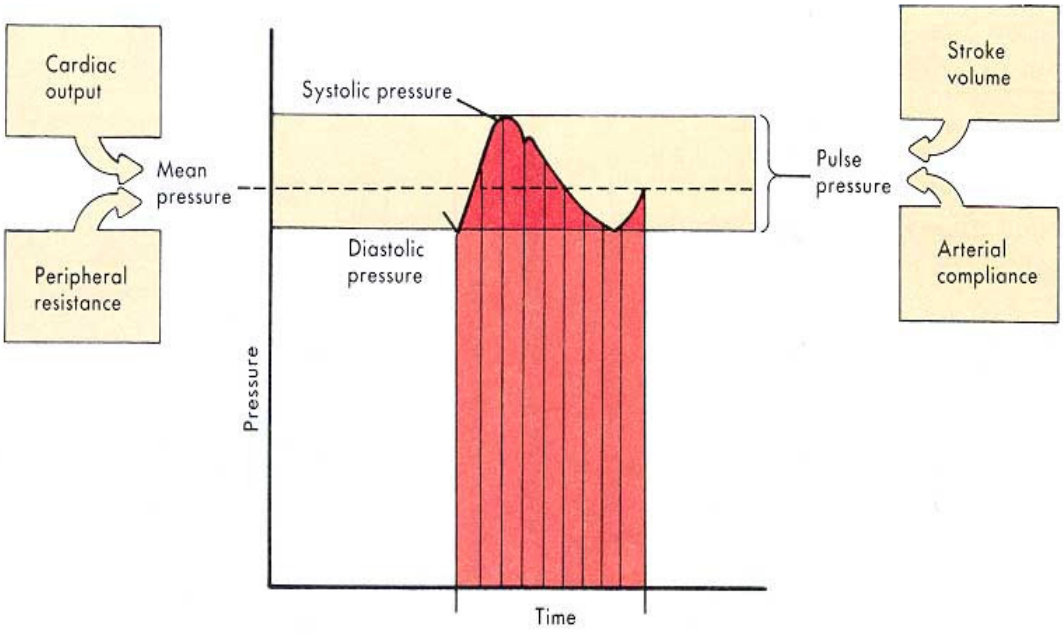

Figure 5. Relationship of Hemodynamic Factors and Arterial Pressure

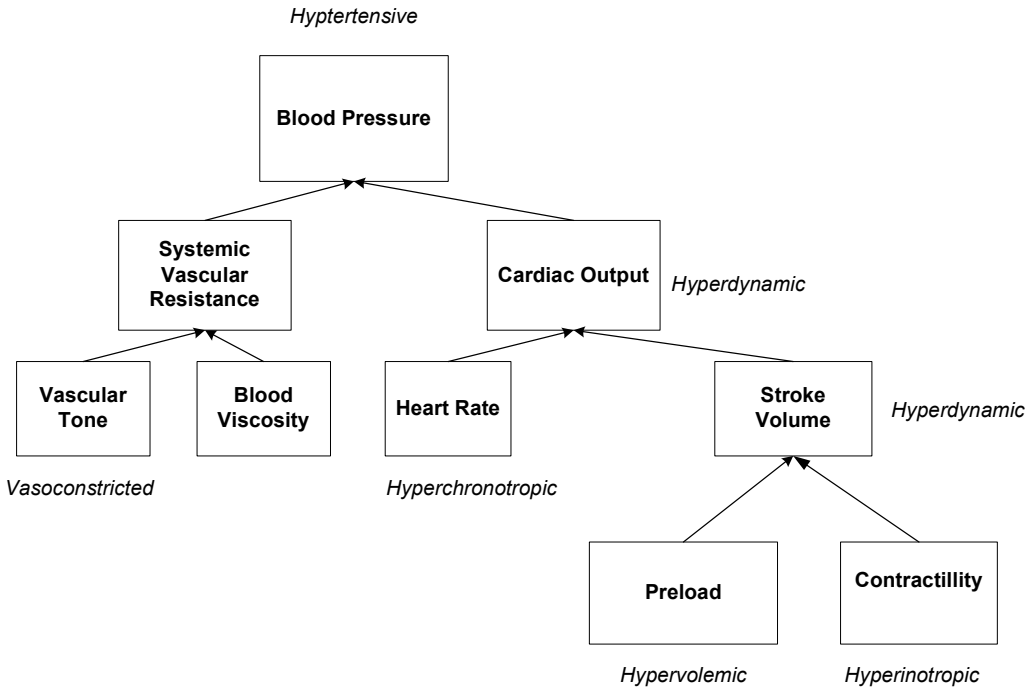

Figure 6. Potential Hemodynamic Causes of Hypertension

The specific hemodynamic alterations in patients with hypertension are not predictable, differ across patient types, and can change over time. However, both the initial and sustained reductions in blood pressure are accomplished by antihypertensive medications that reduce cardiac output, systemic vascular resistance, or both.[32, 33]

Rationale for the Use of Hemodynamics in Hypertension Management

A hemodynamic model of hypertension has been reviewed extensively by leaders in the field.[34, 35, 36, 37, 38, 39] While experts acknowledge the hemodynamic origins of hypertension, the measurement of cardiac output and systemic vascular resistance in the treatment of hypertension was not typically considered before the availability of TEB. The primary reason for this was the requirement for invasive hemodynamic monitoring with its associated costs and risks, or noninvasive echocardiography with its associated costs and operator-dependent results. We are unaware of any significant trial utilizing invasive- or echocardiographic-hemodynamic studies to guid treatment of hypertension. However, prior to successful commercialization of TEB, the potential benefit of hemodynamics in the treatment of hypertension was often described by authorities in the field:

> *"In hypertension there are three main requirements for the measurement of cardiac output. The first is to verify the existence of a hemodynamic state…Secondly, information on cardiac output is needed to understand the mechanisms operating in hypertension and to enable one to estimate the level of peripheral resistance…Thirdly, in investigating the mechanism of hypotensive agents, knowledge of cardiac output is essential."*[40]

> *"The hemodynamic dysregulation that occurs in the development and progression of hypertension may contribute not only to elevated arterial blood pressure, but may also act in concert with the higher pressure levels to induce structural and functional cardiovascular changes. The anatomic and physiologic cardiovascular changes, which are not fully reversed by antihypertensive therapy, provide the substrate for subsequent complications. A greater understanding of the sequential hemodynamic pathophysiology of hypertension may permit the development of more effective treatment strategies. Although unproved, physiologically based treatment vs. conventional approaches, which are targeted at correcting underlying hemodynamic abnormalities in hypertension, may more effectively interrupt the sequence of events leading to cardiac morbidity and mortality."*[41]

> *"Although the clinical relevance of measuring cardiac output in patients is not fully understood, knowledge of cardiac output could be of considerable value in elucidating the pathophysiology of hypertension and the mechanism of action of therapeutic interventions. The ability of follow systemic vascular resistance, in addition to blood pressure, might also be of prognostic value…This ability offers great potential to investigators and clinicians to enhance our understanding of the pathophysiology of hypertension, assess the mode of action and efficacy of new treatments, and increase diagnostic and prognostic accuracy."* [42]

Secondary Evidence for TEB Coverage for Hypertension

Summary

- TEB has a diagnostic and prognostic role to differentiate the various hemodynamic profiles of hypertension and identify risk (9 studies in 1,564 subjects)
- TEB has a therapeutic monitoring role to evaluate the effectiveness of pharmacologic and nonpharmacologic treatments for hypertension (9 studies in 305 subjects)
- TEB-guided decision-making has shown to aid blood pressure reduction in observational studies (3 studies in 346 subjects)

Note: A comprehensive review of the diagnostic, prognostic, and therapeutic evidence using hemodynamics in hypertension (including TEB) has been published.[43]

TEB Diagnostic and Prognostic Application in Hypertension

TEB has been used in multiple studies to identify and characterize hemodynamic profiles in hypertensive subjects.

- In one study,[44] TEB was used to evaluate noninvasive hemodynamic characteristics of subjects with and without hypertension. A total of 19 healthy nonhypertensive and 136 hypertensive subjects were evaluated. Hemodynamic parameters measured with TEB included cardiac index, stroke index, systemic vascular resistance index, total arterial compliance index, and thoracic fluid content. These were compared with subject type, blood pressure value, demographics, and medications. The blood pressure levels of healthy and hypertensive subjects were 117/71 and 154/90 mm Hg, respectively ($P < 0.0001$). Hypertensive subjects had significantly lower stroke index, cardiac index, total arterial compliance index, and thoracic fluid content and significantly higher systemic vascular resistance index. Subjects with stage two hypertension had higher systemic vascular resistance index (4149 v 3418 dyne sec cm^{-5} m^2, $P<0.01$) and lower total arterial compliance index (0.61 v 0.53 mm Hg/mL/m^2, $P<0.05$) than those with stage 1 hypertension. Compared to subjects with controlled hypertension, normal subjects had significantly lower systemic vascular resistance index (1996 v 2746 dyne sec cm^{-5} m^2, $P<0.0001$) and significantly higher cardiac index (3.23 v 2.63 L/min/m^2, $P<0.001$), SI (48.2 v 37.4 mL/m^2, $P<0.0001$), total arterial compliance index (1.08 v 0.85 mm Hg/mL/m^2, $P<0.01$), and thoracic fluid content (29.1 v 24.1 /kOhm, $P<0.0001$). The parameters of total arterial compliance index, systemic vascular resistance index, and cardiac index demonstrated only modest correlation with systolic blood pressure, supporting the authors' hypothesis that TEB provides additional information regarding cardiovascular risk beyond that available from blood pressure levels alone (Figure 7 below shows the significant scatter when systolic BP is plotted against systemic vascular resistance index). Importantly, in the 54 subjects with blood pressure <140/90 mm Hg, systemic vascular resistance index, a measure of arterial constriction and vascular risk, varied significantly. In fact, despite "normal" blood pressure values, 32 of those 54 subjects (59.3%) had elevations in systemic vascular resistance index (>2483 dyne sec cm^{-5} m^2). TEB demonstrated significantly different hemodynamic profiles between hypertensive and nonhypertensive subjects and documented significant individual

variation within various blood pressure groups. As the various classes of medications for blood pressure control target different hemodynamic substrates, hemodynamic measurements with TEB can be helpful in diagnostic, prognostic, and therapeutic decision-making in hypertensive subjects.

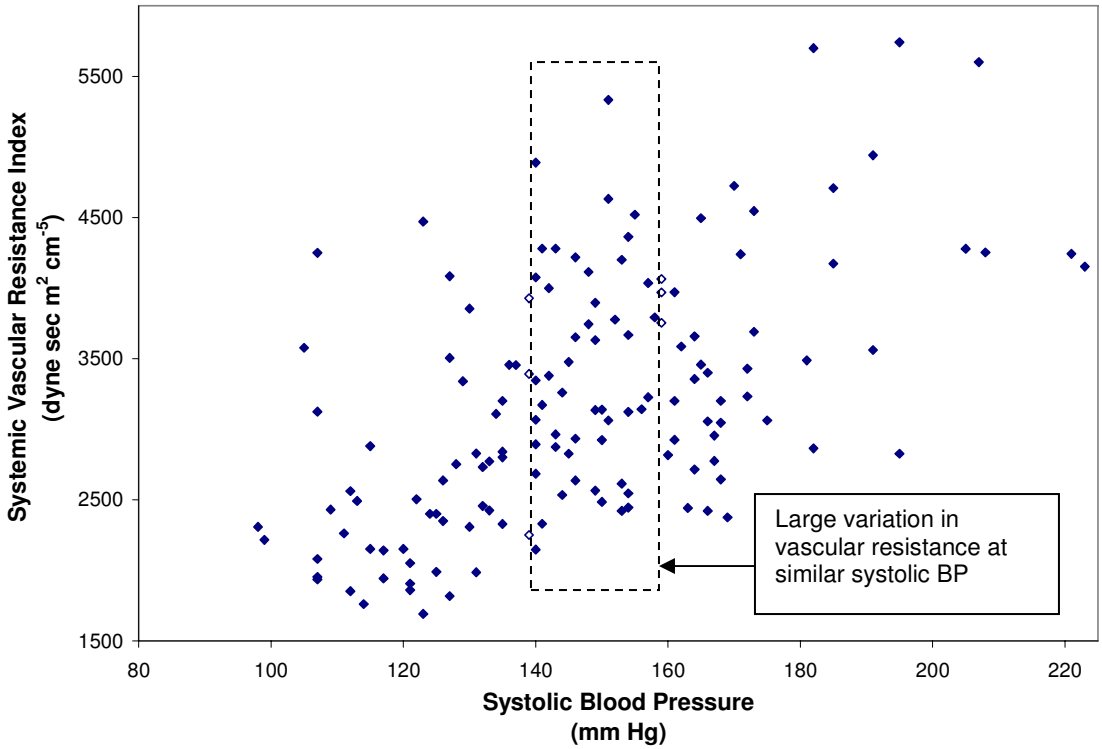

Figure 7. Scatter Plot of the Variability of Systemic Vascular Resistance Index Versus Systolic Blood Pressure (N=155, R = 0.62, R^2 = 0.38, P<0.0001)

TEB has also been used to:

- Compare age-related changes in hemodynamics in stable blood pressure levels in 636 subjects from the third to seventh decade.[45] TEB was used to identify increases in systemic vascular resistance of nearly 50% and decreases in cardiac index of 27%.
- Evaluate the age-related hemodynamic mechanism of increased mean arterial pressure in 119 subjects. In younger patients, elevation of mean arterial pressure was associated with a parallel decrease in pulse pressure and stroke index. In older patients, higher mean arterial pressure was associated with higher pulse pressure and reduced arterial compliance (measured as the stroke volume to pulse pressure ratio) and increased arterial stiffness, the reciprocal of arterial compliance.[46]
- Compare gender-related differences in hemodynamics in 105 subjects (52 women and 53 men).[47] Compared with women, men with lower daytime blood pressure had a 12% higher systemic vascular resistance index and a 14% lower cardiac index, whereas men with higher daytime blood pressure had a 25% higher vascular resistance and a 21% lower cardiac index.

These and other studies using TEB show that within any given population, hemodynamic values may show trends, but in the individual patient there is significant variation across the population. The heterogeneity of hemodynamic findings within various cohorts is evidence that the specific hemodynamic values of the individual patient cannot be predicted reliably on the basis of age, gender, or ethnicity. Because hemodynamic values cannot be identified by blood pressure levels or clinical assessment alone, objective measures such as TEB are required to evaluate hemodynamic factors in patients with hypertension.

TEB has been used in multiple studies to provide diagnostic information related to ventricular structure and to provide prognostic information in hypertensive subjects beyond blood pressure levels alone.

- One study[48] evaluated the ability of brain natriuretic peptide (BNP) and N-terminal BNP (NT-BNP) testing and TEB hemodynamics to detect the presence of left ventricular dysfunction in patients with hypertension. A convenience sample of 193 subjects undergoing echocardiography who had a history of hypertension or current systolic blood pressure ≥140 mm Hg were enrolled and retrospectively evaluated. Patients with known left ventricular dysfunction were excluded. Diagnosis of left ventricular function was determined by the presence of systolic or diastolic dysfunction, valvular or wall motion abnormalities, or left ventricular hypertrophy. A total of: 189 men and four women were enrolled, age 68.8 +/- 11.7 years. Multivariate regression analysis of history and symptoms, BNP, and TEB parameters identified significant predictor variables for left ventricular function including cardiac index (P = .005), left cardiac work index (P=0.008), BNP (P=0.017), arrhythmia (P=0.023), angina (P=0.034), and systemic vascular resistance (P =0.048). Receiver operating characteristic (ROC) analysis determined the area under the ROC curve of BNP (0.60), NT-BNP (0.67), TEB velocity index (0.66), TEB combined with BNP (0.70), and TEB combined with NT-BNP (0.73). In this hypertensive population, TEB, BNP, and NT-BNP were useful to identify the presence of left ventricular dysfunction.

TEB has also been used to:

- Compare hemodynamic variables in 118 subjects between pre-menopausal and post-menopausal women and their association to left ventricular structure.[49] Post-menopausal women had lower cardiac output and higher systemic vascular resistance for any given blood pressure level compared to pre-menopausal women. These significant changes in cardiac output and systemic vascular resistance occurred without significant changes in blood pressure levels, suggesting that the underlying hemodynamic parameters may provide more prognostic information than mean arterial pressure alone.
- Identify race-related differences in hemodynamics and association to left ventricular structure in 171 subjects.[50] African-American men and women had increased levels of systemic vascular resistance, decreased cardiac output, and associated left ventricular remodeling compared to Caucasians at similar blood pressure values. Hemodynamic differences may account for poorer prognosis of African-Americans than Caucasians at similar blood pressure values.
- Profile risk in 52 subjects for ischemic vs. hemorrhagic stroke.[51] In this population of hypertensive stroke patients admitted to the intensive care unit, TEB showed elevated vascular resistance and depressed cardiac output and stroke volume. In the ischemic stroke

group, higher vascular resistance was associated with in-hospital death, whereas in the hemorrhagic stroke group, lower vascular resistance was associated with in-hospital death.

- Predict symptomatic response to antihypertensive therapy in 15 subjects after liver transplantation.[52] Hypertension is common after liver transplantation, and this study showed that treated patients with high cardiac output and normal systemic vascular resistance were more likely to develop symptomatic vasodilation as a result of standard vasodilator therapy. Use of TEB would allow profiling of these patients and a more tailored approach to selecting antihypertensive treatment, such as selection of a beta blocker versus a vasodilator.

TEB Use to Measure Effects of Therapy

A variety of studies illustrate the use of TEB in assessing the hemodynamic mechanisms of blood pressure changes due to pharmacologic and nonpharmacologic interventions. TEB has been used to:

- Compare the effects of a cardioselective beta blocker (atenolol) to those of a beta blocker with intrinsic sympathomimetic activity (pindolol) in 57 subjects.[53] Pindolol therapy was associated with a 12% decrease in systemic vascular resistance compared to minimal change with atenolol. Atenolol-related improvement in blood pressure resulted from decreases in heart rate and cardiac index.
- Compare in 26 subjects the differential hemodynamic effects of combination therapy with verapamil/trandolapril (calcium channel blocker and ACE inhibitor) to metoprolol/hydrochlorothiazide (beta blocker and diuretic) after 6 months of therapy.[54] The combination of reduced diastolic blood pressure to a greater degree than metoprolol / hydrochlorothiazide and lowered systemic vascular resistance by about 15% compared to minimal change with metoprolol / hydrochlorothiazide. Metoprolol / hydrochlorothiazide was associated with a significant reduction in cardiac output compared to baseline, which was not seen with calcium channel blocker and ACE inhibitor.
- Compare the mechanism of blood pressure lowering (cardiac output and systemic vascular resistance) of a novel antihypertensive agent (rilmenidine) and hydrochlorothiazide in 40 subjects.[55] Both agents reduced blood pressure through a decrease in cardiac output.
- Assess in 28 subjects the hemodynamic effects of clonodine. Clonodine reduced systemic vascular resistance in the short term and cardiac output as well in the longer-term study.[56]
- Compare the divergent hemodynamic effects of dihydropyridine (felodipine) and phenylalkylamine (verapamil) calcium channel blockers in 15 subjects.[57] Acutely, felodipine caused a larger blood pressure decrease through a larger decline in systemic vascular resistance than the corresponding effects produced by verapamil.
- Evaluate the hemodynamic mechanism of blood pressure reduction of angiotensin converting enzyme inhibitors and prostaglandin inhibitors in 19 subjects who were either salt-sensitive or salt-insensitive.[58]
- Compare the hemodynamic mechanism of blood pressure reduction in 30 subjects undergoing diet (salt restriction) and exercise changes.[59] Diet and exercise resulted in changes in blood pressure through different hemodynamic mechanisms.
- Assess the hemodynamic effects of sodium restriction in 13 subjects.[60] During sodium restriction, TEB-derived stroke volume decreased in association with fall in diastolic blood

pressure. In addition, the increase in overall thoracic impedance (the reciprocal of thoracic fluid content) was consistent with a decrease in extracellular fluid volume.

- Illustrate in 77 subjects the gender differences in the hypertensive response to caffeine.[61] Men who show hypertensive responses to caffeine increase their systemic vascular resistance while women primarily increase stroke volume and cardiac output.

Non-TEB Hemodynamic Prognostic Application in Hypertension

A variety of studies are available that demonstrate that invasive and echocardiographic hemodynamic measures of vascular resistance and total arterial compliance (calculated as echo-derived stroke volume divided by pulse pressure) provide independent prognostic variables in hypertensive subjects.[62, 63, 64, 65] These studies are not direct evidence for TEB. However, TEB provides accurate measurement of stroke volume, and pulse pressure measurements are readily available. Therefore, if the studies were replicated with TEB there is a high probability that the results would be replicated.

TEB Use in Observational Studies to Aid Therapeutic Decision-Making

TEB has been used in several observational studies to aid in blood pressure reduction and control.

One retrospective case series study[66] demonstrated improved blood pressure control in 21 subjects previously uncontrolled with standard therapy. Blood pressure at entry was 157.2 $\pm$ 13.9 / 78.7 $\pm$ 9.9 mm Hg. Subjects were treated for 215 $\pm$ 85 days, 5.0 $\pm$ 2.0 visits. After TEB-guided treatment, 12/21 (57.1%) achieved sustained blood pressure control ($p<0.001$). Blood pressure was lowered to 141.6 $\pm$ 22.0 ($p<0.001$) / 77.1 $\pm$10.7 mm Hg ($p>0.05$). Antihypertensive agents increased from 2.0 $\pm$ 0.0 to 2.5 $\pm$ 0.7 ($p<0.05$). In subjects with uncontrolled blood pressure on two antihypertensive agents, TEB-guided pharmacologic decision-making resulted in significant reduction in blood pressure and improvement in blood pressure control.

In a prospective cohort study available only in abstract form, investigators used TEB to guide the hypertension management of 322 uncontrolled hypertensive subjects on two or more antihypertensive medications, treated for an average of 12.5 years.[67] Each subject's blood pressure level with historical, non-TEB-managed treatment was used as the comparison. Using TEB-guided decision-making, 63% of the patients achieved blood pressure control with one therapeutic iteration. Manuscripts describing the diagnostic characteristics of the full cohort[68] and the effects of therapy in the first 100 subjects[69] have been published, although neither of the manuscripts are in the English language. Therefore, we are not requesting that CMS evaluate these manuscripts.

Lastly, a published case report of three hypertensive subjects demonstrated the practical value of using TEB in the outpatient management of hypertension.[70]

Primary Evidence for Coverage of TEB for Hypertension

Summary

- In the Mayo Clinic Trial,[71] TEB-guided therapy resulted in greater blood pressure reduction and blood pressure control in patients with uncontrolled hypertension (average 171/89 mm Hg) on 2 or more medications who were being treated in a specialist setting (104 subjects, one center). TEB-guided therapy resulted in a 4/4 mm Hg greater blood pressure reduction and a 70% improvement (56% vs. 33%) in blood pressure control to <140/90 mm Hg.
- In the CONTROL Trial,[72] TEB-guided therapy resulted in greater blood pressure reduction and blood pressure control in patients with uncontrolled hypertension (average 148/88 mm Hg) on one to three antihypertensive medications who were being treated in a generalist setting (164 subjects, eleven centers). TEB-guided therapy resulted in an 8/7 mm Hg greater blood pressure reduction and a 35% improvement (77% vs. 57%) in blood pressure control to <140/90 mm Hg. The results of the CONTROL Trial have been accepted for publication in a peer-reviewed journal.

Mayo Clinic Trial

Taler SJ, et al. Resistant hypertension: Comparing hemodynamic management to specialist care. Hypertension. 2002;39:982-988.

Methods: This trial evaluated the utility of serial hemodynamic parameters in the selection and titration of antihypertensive medication in resistant hypertensive patients using TEB in a three-month intensive treatment program. Resistant hypertension patients (n=104) were randomized to either drug selection based on serial TEB hemodynamic measurements with a predefined algorithm or drug selection directed by a hypertension specialist.
Results: Blood pressure was lowered by intensified drug therapy in both treatment groups (169/87 to 139/72 mm Hg hemodynamic group versus 173/91 to 147/79 mm Hg specialist care group, $p<0.01$ for systolic and diastolic blood pressure), using similar number of antihypertensive medications. Blood pressures were reduced to a greater degree in the hemodynamic care arm, resulting in improved control rates (56% hemodynamic versus 33% specialist care for control defined as blood pressure <140/90 mm Hg, $p<0.05$). Hemodynamic-guided therapy resulted in greater reductions in systemic vascular resistance measurements. Although the number of patients taking diuretics did not differ between groups, final diuretic dosage was higher in the hemodynamic cohort.
Conclusion: This randomized trial demonstrates superior blood pressure control using a treatment algorithm based on serial hemodynamic measurements compared with clinical judgment alone. These results show that measurements of thoracic fluid volume can identify occult volume expansion as a mediator of antihypertensive drug resistance and use of impedance measurements to guide advancing diuretic dose and adjustment of multidrug antihypertensive treatment.

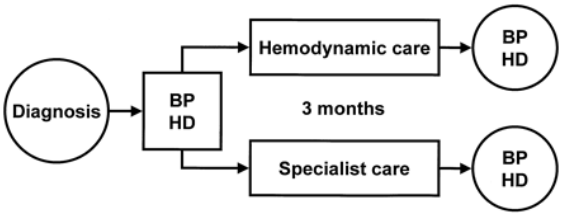

Figure 8. Mayo Clinic Trial: Study Design; BP=blood pressure; HD=TEB hemodynamics

Table 6. Mayo Clinic Trial: Characteristics Before and After Treatment; DDD=defined daily dose

Characteristics	Hemodynamic Care (n=50)	Specialist Care (n=54)
Before treatment		
Age, y	67±2	64±2
Weight, kg	91.5±3.2	95.9±4.0
Body mass index, kg/m^2	31.4±1.0	32.7±1.2
Office blood pressure sitting, mm Hg	169±3/87±2	173±3/91±2
Heart rate sitting, bpm	66±1*	72±2
Serum creatinine, μmol/L	115±9	115±9
No. of medications	3.6±0.1	3.6±0.1
Total medications DDD	5.3±0.3	5.2±0.3
Diuretic DDD	1.1±0.1	1.2±0.2
Cardiovascular comorbidities		
Diabetes mellitus	16 (32)	18 (33)
Hyperlipidemia	27 (54)	25 (46)
Target organ damage		
Stroke or TIA	5 (10)	5 (9)
Coronary artery disease	15 (30)	10 (19)
Congestive heart failure	3 (6)	3 (6)
Left ventricular hypertrophy	9 (18)	10 (19)
Peripheral vascular disease	9 (18)†	3 (6)
Abdominal aortic aneurysm	4 (8)	2 (4)
Secondary/contributing causes		
Renal artery stenosis	6 (12)	8 (15)
Primary aldosteronism	3 (6)	4 (7)
Obstructive sleep apnea	9 (18)	11 (20)
After 3 months of treatment		
Office blood pressure sitting, mm Hg	139±2/72±1‡*	147 ±2/79±1‡
Heart rate sitting, bpm	68±1†	72±2
Serum creatinine, μmol/L	141±9‡	133±9§
No. of medications	4.3±0.1‡	4.1±0.1‡
No. of nurse visits	6.2±0.2	6.2±0.3
Total medications DDD	6.1±0.4§	5.7±0.3§
Diuretic DDD	2.1±0.2‡*	1.4±0.1§
Control to ≤140/90 mm Hg	28/50 (56)†	18/54 (33)
Control to ≤150/90 mm Hg	40/50 (80)†	33/54 (61)

Values are mean±SEM or n (%).
*$P<0.01$ vs specialist care; †$P<0.05$ vs specialist care; ‡$P<0.01$ vs entry; and §$P<0.05$ vs entry.

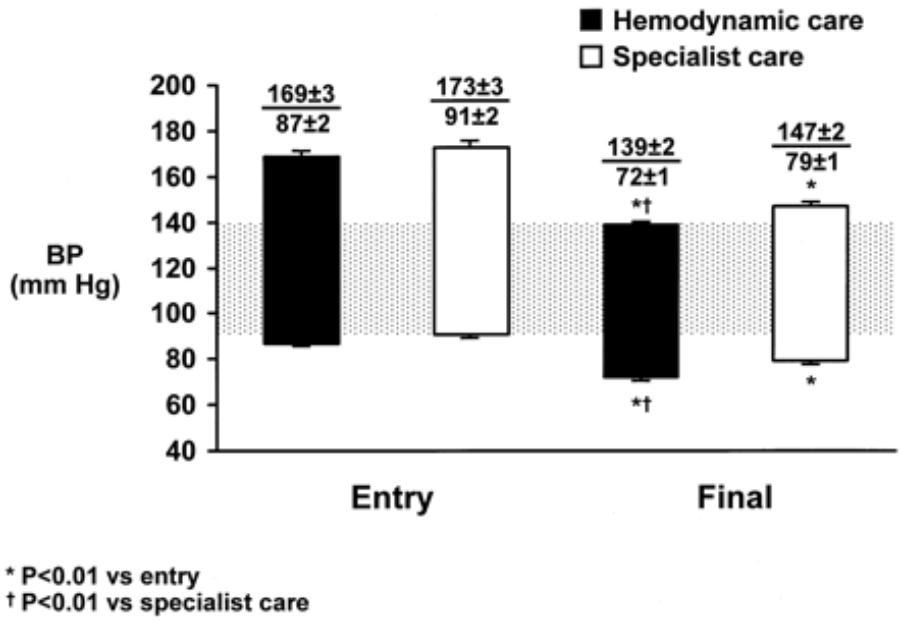

Figure 9. Mayo Clinic Trial: Blood Pressure at Entry and Final

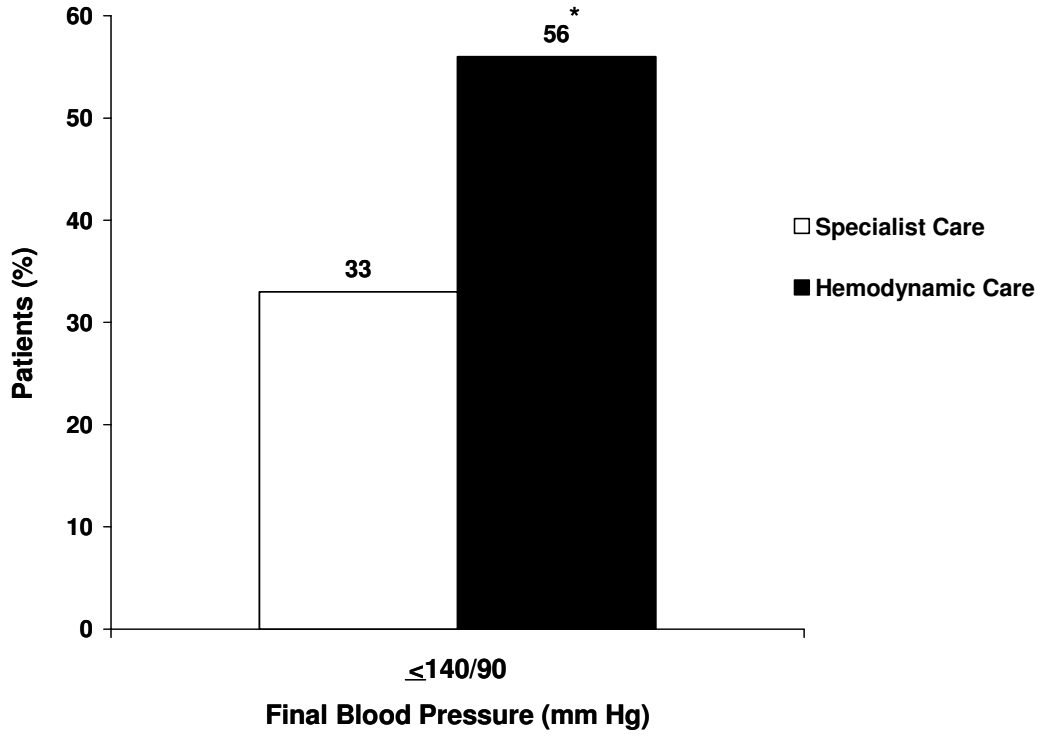

Figure 10. Mayo Clinic Trial: Blood Pressure Control Rates at Final; *=p<0.05 vs. Specialist Care

CONTROL Trial

The results of the CONTROL Trial were presented in May of 2005 at the American Society of Hypertension and published in abstract form in the *American Journal of Hypertension*. The full manuscript describing the study results has been accepted for publication in a peer-reviewed journal.

Smith R, Levy P, Ferrario C. Efficacy of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels (CONTROL). Am J Hypertens. 2005. 18;(5 part 2):94A.

Methods: Uncontrolled hypertensive patients on one to three medications were randomized by 3:2 ratio to either a Standard Arm or Hemodynamic Arm that utilized TEB (BioZ®, CardioDynamics). Each patient completed five study visits with a two-week washout period followed by three months of treatment. A total of 164 patients from 11 centers completed the study, 95 in the Standard Arm and 69 in the Hemodynamic Arm.
Results: At baseline and post-washout, there were no differences between Arms in number of medications, demographic, blood pressure, or hemodynamic characteristics. Systolic blood pressure reductions in the Hemodynamic Arm were greater than in the Standard Arm: from baseline (19 mm Hg vs. 11 mm Hg, $p<0.01$) and post-washout (25 mm Hg vs. 19 mm Hg, $p<0.05$). Diastolic blood pressure reductions were also greater in the Hemodynamic Arm from baseline (12 mm Hg vs. 5 mm Hg, $p<0.001$) and post-washout (17 mm Hg vs. 10 mm Hg, $p<0.001$). The Hemodynamic Arm achieved goal blood pressure (<140/90 mm Hg) more frequently (77% vs. 57%, $p<0.01$) and a more aggressive blood pressure level (<130/85 mm Hg) more frequently (55 vs. 27%, $p<0.0001$). Patients in the Hemodynamic Arm had a greater drop in systemic vascular resistance index from baseline (433 vs. 219 dyne sec m^2 cm^{-5}, $p<0.05$) and post-washout (599 vs. 369 dyne sec m^2 cm^{-5}, $p<0.05$). The Hemodynamic Arm maintained superiority in three key subgroups: patients who were older, on thiazide diuretics, or had isolated systolic hypertension. At end of study there was no difference in the number of antihypertensive medications utilized in the two arms. There were, however, more patients in the Hemodynamic Care Arm on angiotensin II receptor blockers (46 vs. 31%, $p<0.05$). Per the hemodynamic treatment strategy, patients in the Hemodynamic Arm were more likely to receive a vasodilating agent (angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, or calcium channel blocker) at the first visit after washout and also at any visit when their systemic vascular resistance index was high. Patients in the Hemodynamic Care Arm were also more likely to avoid beta blocker use or to have their beta blocker reduced in the presence of low or normal cardiac index. Patients in the Standard Arm were more likely to receive increases and decreases in medication dose, and were on a greater dose of thiazide diuretics. There were no differences in compliance with medications.
Conclusion: These study results indicate that antihypertensive therapy guided by TEB in uncontrolled hypertensive patients on one to three medications is more effective than standard care.

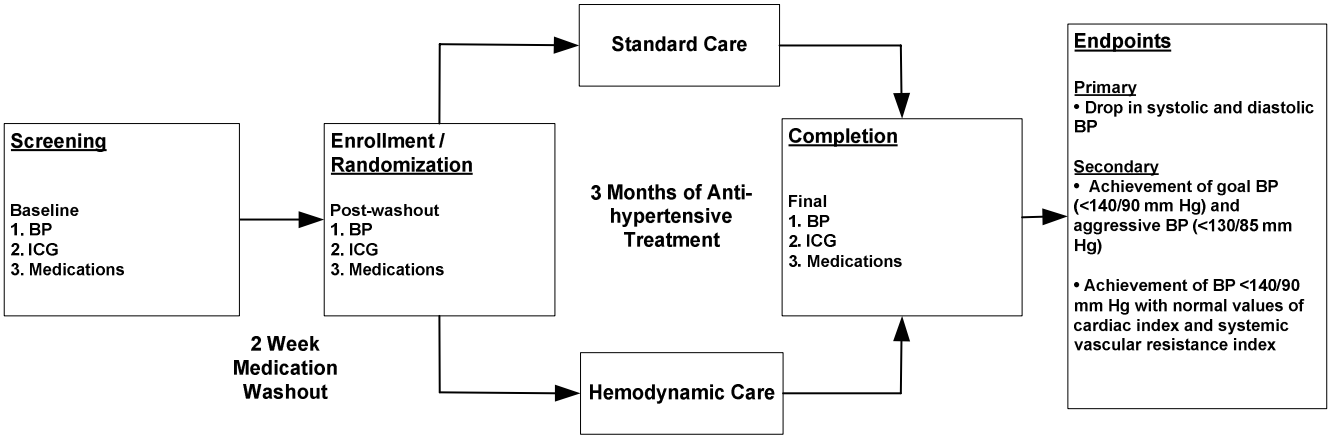

Figure 11. CONTROL Trial: Study Design

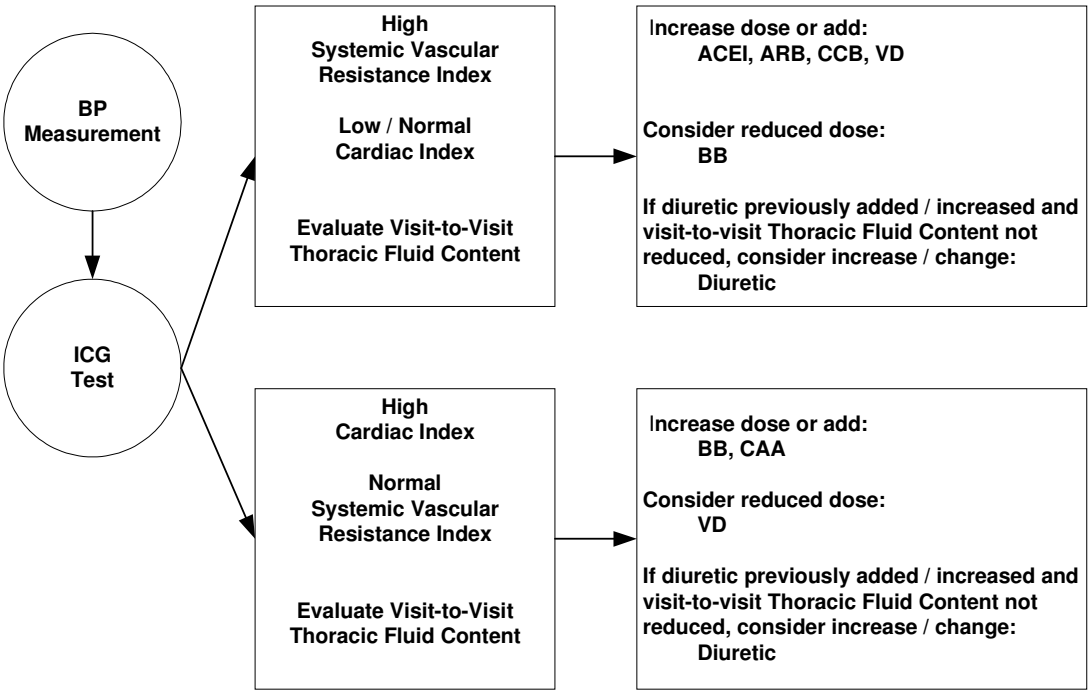

Figure 12. CONTROL Trial: Hemodynamic Treatment Strategy; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BB = beta blocker; CAA = central acting agent; CCB = calcium channel blocker; VD=vasodilator.

Table 7. CONTROL Trial: Patient Characteristics

Variable	Standard Care N=95	Hemodynamic Care N=69	P Value
Age (y)	54.5 ± 9.4	55.2 ± 9.2	ns
Body mass index (kg/m^2)	30.2 ± 6.3	30.8 ± 5.1	ns
Male	51 (53.4)	38 (55.1)	ns
Ethnicity			
White, non-Hispanic	75 (79.0)	53 (76.8)	ns
White, Hispanic	7 (7.4)	5 (7.3)	ns
Black	8 (8.4)	6 (8.7)	ns
Asian	3 (3.2)	3 (4.4)	ns
History			
Type II diabetes mellitus	4 (4.2)	3 (4.4)	ns
Ischemic heart disease	2 (2.1)	5 (7.3)	ns
Hyperlipidemia	14 (14.7)	12 (17.4)	ns
Baseline blood pressure and hemodynamics			
Systolic BP (mm Hg)	147 ± 9	148 ± 12	ns
Diastolic BP (mm Hg)	87 ± 10	89 ± 8	ns
Heart rate (bpm)	75 ± 12	74 ± 13	ns
Cardiac index (L/min/m^2)	2.8 ± 0.5	2.9 ± 0.6	ns
Systemic vascular resistance index (dyne sec m^2 cm^{-5})	2933 ± 576	2956 ± 605	ns
Thoracic fluid content (/kOhm)	28.6 ± 4.9	28.0 ± 4.8	ns
Isolated systolic hypertension at baseline	46 (48.4)	31 (44.9)	ns
Post-washout BP and hemodynamics			
Systolic BP (mm Hg)	156 ± 13	155 ± 13	ns
Diastolic BP (mm Hg)	92 ± 9	94 ± 9	ns
Heart rate (bpm)	79 ± 12	78 ± 14	ns
Cardiac index (L/min/m^2)	2.9 ± 0.5	2.9 ± 0.5	ns
Systemic vascular resistance index (dyne sec m^2 cm^{-5})	3083 ± 630	3122 ± 672	ns
Thoracic fluid content (/kOhm)	29.1 ± 5.0	28.4 ± 4.3	ns
Medications			
Total antihypertensive medications	1.7 ± 0.8	1.7 ± 0.7	ns

Categorical variables are expressed as N (%), continuous variables as mean ± SD; ns, not significant.

Table 8. CONTROL Trial: Final BP and Hemodynamic Values

Variable	Standard Care N=95	Hemodynamic Care N=69	P Value
Systolic BP (mm Hg)			
Final	136 ± 15	129 ± 14	<0.01
Δ Baseline to Final	-11 ± 18	-19 ± 17	<0.01
Δ Post-washout to Final	-19 ± 17	-25 ± 18	<0.05
Diastolic BP (mm Hg)			
Final	82 ± 10	76 ± 11	<0.01
Δ Baseline to Final	-5 ± 12	-12 ± 11	<0.001
Δ Post-washout to Final	-10 ± 11	-17 ± 12	<0.001
Heart rate (beats per minute)			
Final	77 ± 13	76 ± 11	ns
Δ Baseline to Final	1 ± 12	2 ± 13	ns
Δ Post-washout to Final	-2 ± 13	-2 ± 13	ns
Cardiac index (l/min/m^2)			
Final	2.9 ± 0.5	2.9 ± 0.5	ns
Δ Baseline to Final	0.1 ± 0.5	0.0 ± 0.5	ns
Δ Post-washout to Final	0.0 ± 0.5	0.0 ± 0.5	ns
Systemic vascular resistance index (dyne sec m^2 cm^{-5})			
Final	2714 ± 619	2523 ± 581	<0.05
Δ Baseline to Final	-219 ± 667	-433 ± 660	<0.05
Δ Post-washout to Final	-369 ± 642	-599 ± 738	<0.05
Thoracic fluid content (/kOhm)			
Final	27.8 ± 4.1	28.2 ± 4.9	ns
Δ Baseline to Final	-0.8 ± 3.6	0.1 ± 3.0	ns
Δ Post-washout to Final	-1.2 ± 3.3	-0.2 ± 2.7	<0.05

Variables are expressed as mean ± SD; ns, not significant.

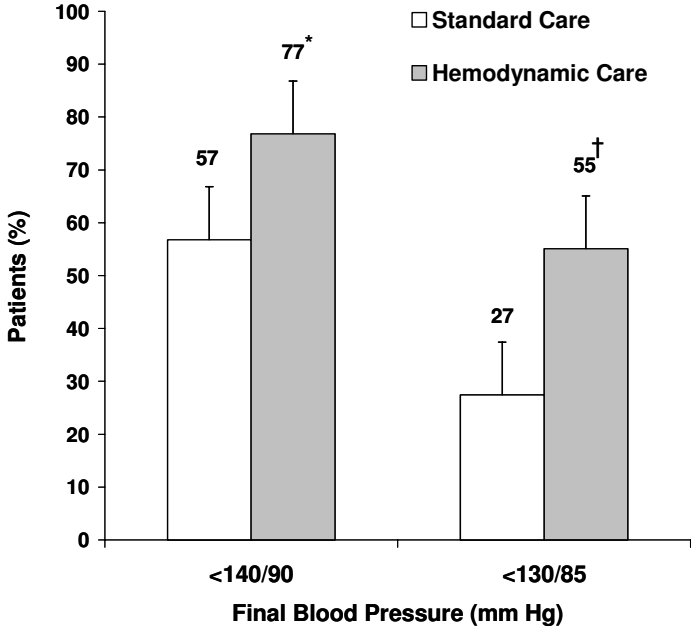

Figure 13. CONTROL Trial: Final Blood Pressure Control Rates; * = p<0.01 vs. Standard Care, † =p<0.0001 vs. Standard Care.

Table 9. CONTROL Trial: Final Antihypertensive Medications

Antihypertensive Medication	Standard Care N=95	Hemodynamic Care N=69	P Value
Number at final visit	2.0 ± 0.8	2.1 ± 0.9	ns
Alpha blocker	1 (1.0)	1 (1.4)	ns
Angiotensin converting enzyme inhibitor	51 (53.7)	34 (49.3)	ns
Angiotensin II receptor blocker	29 (30.5)	32 (46.4)	<0.05
Beta blocker	18 (19.0)	6 (8.7)	ns
Calcium channel blocker, dihydropyridine	36 (37.9)	28 (40.6)	ns
Calcium channel blocker, non-dihydropyridine	6 (6.3)	7 (10.1)	ns
Central acting agent	0 (0.0)	1 (1.4)	ns
Diuretic, thiazide	32 (33.7)	24 (34.8)	ns
Diuretic, loop	1 (1.1)	0 (0.0)	ns
Diuretic, potassium sparing	6 (6.3)	3 (4.3)	ns
Vasodilator	0 (0.0)	0 (0.0)	ns

Categorical variables are expressed as N (%), continuous variables as mean ± SD; ns, not significant.

Evidence Quality, Generalizability, and Magnitude of the Benefit

Evidence Quality

Study Design: The randomized controlled trial is universally accepted as the most rigorous form of study design to compare effectiveness of two methods. This is acknowledged by CMS officials and in the Medicare Coverage Advisory Committee (MCAC) "Recommendations for Evaluating Effectiveness".[73] However, the MCAC recommendations note that randomized trials are rarely performed with diagnostic tests:

> *"Although an effective diagnostic test can reduce the morbidity and mortality of disease by guiding clinical decisions, direct proof of effectiveness is usually unavailable. Few studies have directly measured the effects of a diagnostic or screening test on health outcomes (studies of occult blood testing for colon cancer represent one such exception). Typical studies that evaluate the effectiveness of diagnostic, screening, or monitoring tests focus either on technical characteristics (e.g., does a new radiographic test produce higher resolution images) or effects on accuracy (does it distinguish between patients with and without a disease better than another test)."*

Most existing diagnostic tests that CMS currently covers have not been evaluated in randomized controlled trials to determine whether they improve net health outcomes. For example, the 2002 NCD (CAG-00067N) for ambulatory blood pressure monitoring of suspected white-coat hypertension provided coverage despite the lack of any randomized controlled trial showing that ambulatory blood pressure monitoring improved health outcomes. In addition, CMS recently proposed coverage for Microvolt T-wave Alternans (CAG-00293N) for evaluation of patients at risk for sudden cardiac death. The proposed coverage for T-wave Alternans appears to be based on prognostic studies alone, with no randomized trials showing an improvement in health outcomes.

In contrast, both the Mayo Clinic and CONTROL Trials are randomized controlled trials evaluating the impact of TEB-guided therapy on health outcomes.

Endpoints: The endpoints used in both trials are well accepted. Reductions in blood pressure and increases in blood pressure control rates are accepted surrogate outcomes for morbidity and mortality, and represent improvements in health outcomes for the hypertensive patient.

Methods: Both trials utilized accepted methods to evaluate their study hypotheses in data collection, interventions, and data analyses.

Results: Both trials showed a clinically and statistically significant improvement in achievement of endpoints and an improvement in net health outcomes with TEB-guided treatment of hypertension. Both trials provide a mechanistic explanation of their study results in the form of hemodynamic and medication differences between groups.

Evidence Generalizability

The results from both the Mayo Clinic Trial and the CONTROL Trial are generalizable to the CMS population, based on the following factors:

Disease/Condition: Both trials evaluated the condition of interest, hypertension, which is common among CMS beneficiaries. Both studies evaluated patients with actively treated but uncontrolled hypertension. As previously noted, an estimated 44% of patients over the age of 60 years who are actively treated do not have controlled blood pressure.

Age: The Mayo Clinic Trial examined patients with an average age of 65 years. The CONTROL Trial examined patients with an average age of 55 years. In the CONTROL Trial, sub-group analysis and analysis of variance testing both indicated that age $\geq$55 years had no impact on treatment outcomes. It is accepted that the majority of clinical trials of chronic disease treatments enroll patients who are younger and more likely male and Causcasion than the normal clinical population.[74] However, this does not prevent the application of these study outcomes by CMS to an older populuation. For example, CMS made a positive coverage decision for implantable defibrillators (CAG-00157R3) based on multiple trial results that included a significant majority of subjects under the age of 65 years. In addition, the proposed coverage for Microvolt T-wave Alternans (CAG-00293N) is also based on studies in which the majority of subjects were under the age of 65 years.

Ethnicity: Non-whites make up approximately 18% of the CMS beneficiaries.[75] Ethnicity was not reported in the Mayo Clinic Trial. Non-whites comprised 24.3% of the subjects in the CONTROL Trial.

Comorbid conditions: Some CMS beneficiaries with hypertension have comorbidities and some do not have comorbidities. Because the Mayo Clinic Trial had already addressed a population with a high degree of comorbidities, the CONTROL Trial was not specifically designed to examine patients with comorbidities. The Mayo Clinic Trial demonstrated the utility of TEB in patients with a significant percentage of comorbid conditions, including half with hyperlipidemia, a third with diabetes, a fifth with coronary artery disease, and a sixth with left ventricular hypertrophy. The CONTROL Trial demonstrated the utility of TEB in a less morbid population.

Hypertension severity and type: CMS beneficiaries have a wide range of blood pressure levels and a significant percentage have isolated systolic hypertension.[76] The Mayo Clinic Trial examined patients with higher starting blood pressure, approximately 171/89 mm Hg. The CONTROL Trial examined patients with lower starting blood pressure, 156/93 mm Hg. The CONTROL Trial also included almost half of its patients with isolated systolic hypertension. Sub-group analysis demonstrated that superior outcomes with TEB-guided management were maintained in patients with isolated systolic hypertension.

Number of antihypertensive medications: CMS beneficiaries receive between one and six antihypertensive medications to lower their blood pressure. The Mayo Clinic Trial evaluated patients on two or more medications (refractory hypertension), with an average of 3.6

medications. The CONTROL Trial evaluated patients on one to three medications, with an average of 1.7 medications.

Type of antihypertensive medications: The antihypertensive medications prescribed in both trials are FDA-approved and commonly prescribed to CMS beneficiaries. Based on the results of other clinical trials, some believe that all patients with hypertension should receive a thiazide diuretic as first-line therapy. A large percentage of patients in the Mayo Clinic Trial received a thiazide diuretic. A smaller percentage of patients in the CONTROL Trial received a thiazide diuretic, which reflected real-world prescribing habits by generalists,[77] and the known physician preference for agents other than diuretics.[78] Nonetheless, when patients receiving a thiazide diuretic in the CONTROL Trial were examined as a sub-group, TEB-guided therapy maintained superiority over standard care, in spite of higher doses of diuretics in the standard care group.

Setting / physician specialization: CMS beneficiaries with hypertension are treated by both generalists and specialists in the outpatient setting. The Mayo Clinic Trial evaluated patients treated by hypertension specialists. The CONTROL Trial evaluated patients treated by generalists (internal medicine or family practice physicians). Both trials evaluated patients in an outpatient setting.

Magnitude of the Benefit

As CMS is aware, there is a strong need to improve blood pressure control in CMS beneficiaries. The lack of blood pressure control has enormous aforementioned clinical costs, as well as significant economic costs.[79] In the evaluation of uncontrolled hypertensive patients, TEB-guided management results in greater blood pressure reduction and improved blood pressure control. Improvement in blood pressure control is an accepted surrogate outcome for cardiovascular morbidity and mortality. Greater short-term blood pressure control will likely result in greater long-term blood pressure control, as short-term blood pressure advantages are largely sustained over the longer term in drug trials.[80] Long-term uncontrolled blood pressure is clearly linked to stroke, ischemic heart disease, and heart failure. According to the aforementioned meta-analysis by Lewington et al. of over one million patients, each 2 mm Hg systolic BP reduction over a ten-year period would result in 10% reduction in stroke mortality and 7% reduction in ischemic heart disease or other cardiovascular disease mortality. This may be why analyses of hypertension trials indicate that an antihypertensive agent is judged superior to placebo with as little as a 3 or 4 mm Hg benefit, or versus another antihypertensive agent when there is only 1 or 2 mm Hg additional blood pressure reduction.[81] In the Mayo Clinic and CONTROL Trials, TEB-guided management resulted in large advantages in blood pressure reduction compared to a standard care approach (4/4 mm Hg in the Mayo trial, 8/7 mm Hg in the CONTROL Trial). Therefore, TEB-guided therapy is likely to have significant benefit on the health of the Medicare population.

CMS Part D Implications

The advent of CMS Part D with payment for beneficiary medications provides an additional need for CMS to ensure that antihypertensive medications are being used as effectively as possible. TEB provides the ability to improve the clinical effectiveness of prescribed medications by more

objectively and effectively selecting medications based on the underlying hemodynamic abnormality. TEB also allows physicians to more objectively and efficiently determine whether the medications are having the desired hemodynamic effect. In the case of ineffectual medications, stronger dosing or alternate agents could be considered, which would likely result in more effective therapy. The approach with TEB is in contrast to the more typical "stepped therapy" approach in hypertension, which is a method based on trial and error.

Cost-effectiveness

One in every five dollars will be devoted to health care by 2015. CMS estimates that health spending will consistently outpace the growth in the gross domestic product over the next 10 years. While CMS does not formally evaluate costs in coverage analysis, cost considerations are increasingly important for health-care-policy-makers.[82] Cost-effectiveness evaluations quantify incremental costs versus incremental effectiveness of a new approach compared to a standard approach. A cost-effectiveness analysis of the CONTROL Trial has been performed but the manuscript has not yet been accepted for publication. The short-term cost-effectiveness of TEB Care was evaluated as the incremental cost per incremental mm Hg reduced. Short-term costs included office visits, TEB tests, and drugs. The long-term cost-effectiveness of TEB Care was evaluated as incremental cost per quality-adjusted life-year (QALY) gained and was modeled over a ten-year period with estimated cardiovascular event rates, reduction in risk with TEB testing, event-mortality rates, and short- and long-term costs. TEB Care resulted in a lower total cost per mm Hg reduced compared to Standard Care total cost per mm Hg reduced for both systolic BP ($31.39 vs. $40.21) and diastolic BP ($49.71 vs. $88.45). The short-term incremental cost of TEB testing was $19.28 per additional mm Hg reduced for systolic BP and $22.03 per additional mm Hg reduced for diastolic BP. The long-term cost-effectiveness of TEB Care was $6,137 per QALY gained ($301 per patient, 0.049 QALY gained). Sensitivity analysis with simultaneously low and high estimates for event rates, risk reduction, event mortality rates, and costs indicated that TEB could save lives and money ($206 per patient, 0.0947 QALYs gained) or cost up to $34,687 per QALY gained ($715 per patient, 0.0206 QALYs gained). The use of TEB testing in uncontrolled hypertensive subjects is cost-effective from both a short- and long-term perspective. More detailed methods and results are available to CMS upon request.

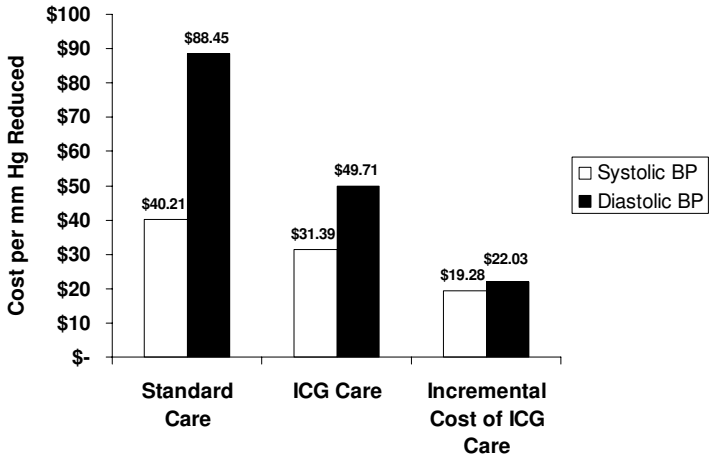

Figure 14. Incremental cost per mm Hg reduced for TEB Care vs. total cost per mm Hg reduced in Standard Care and TEB Care in the CONTROL Trial

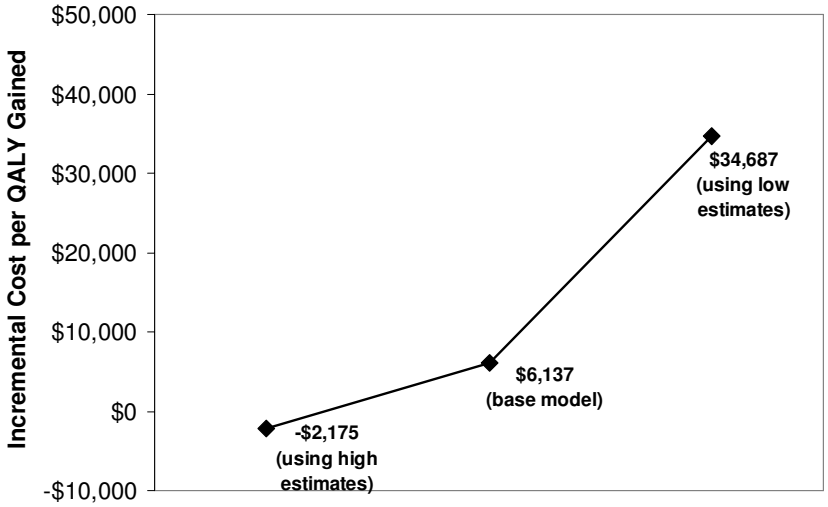

Figure 15. Incremental cost per QALY gained for TEB Care in the CONTROL Trial for base model estimate and simultaneously high and low estimates.

Response to Potential Questions on the Evidence

We expect that CMS will conduct a thorough evaluation of the evidence that will result in some questions. Below, we have attempted to answer some anticipated questions. If additional questions are raised during the reconsideration process, we are hopeful that we will be given the opportunity to answer these questions prior to the draft decision memorandum.

Questions Regarding Both the CONTROL and Mayo Clinic Trials

Question: Is a study duration of three months long enough to determine that TEB improved outcomes?

Yes. TEB-guided management definitively improved outcomes at three months, and as previously stated, shorter-term reductions in blood pressure have been maintained in longer-term pharmacologic trials. Both trials were designed with three-month terms because three months is a reasonable amount of time to evaluate whether a new method such as TEB improves blood pressure outcomes. Both the Mayo Clinic Trial and the CONTROL Trial showed significantly improved outcomes at three months. In the CONTROL Trial, the 57% control rate achieved in the standard care arm at three months compares very favorably to trials of longer terms. However, the 77% control rate achieved in the TEB-guided arm was substantially better.

Question: Does the use of a treatment algorithm/strategy in hemodynamic arms introduce a bias in the study results?

No. The goal of both studies was to evaluate whether TEB-guided care improved outcomes compared to standard care, which consisted of the best efforts to reduce blood pressure by specialists in the Mayo Clinic Trial and generalists in the CONTROL Trial. The use of this new hemodynamic information must be guided by some framework of understanding in the form of an algorithm or treatment strategy - otherwise it lacks any actionable influence. It is more relevant and generalizable to CMS beneficiaries to compare to standard care than anything else, as this is what CMS beneficiaries receive. Additionally, the use of an algorithm was not automated in the hemodynamic arms of the trials, but instead still relied on clinician determination of appropriate therapies. Therefore, the provision of the hemodynamic information is what made the difference in outcomes.

The issue of medication decision-making was given significant consideration during the CONTROL protocol development process. If investigators were required to use a hemodynamic treatment strategy (algorithm) without exception (100% of the time), it might both contradict sound clinical judgment in some cases and compromise the generalizability of the results to real–world decision-making, where physicians would not be required to use a rigid protocol or algorithm. We believe that the design of the trial ensured that TEB data along with a suggested treatment strategy could sufficiently influence the investigator's medication choices when added to everything else at their disposal. The result was an objective but practical approach that maintained the highest scientific rigor and real-world applicability.

Question: Could the medication differences that improved blood pressure control in both trials been accomplished without the use of TEB?

No. That is what both trials evaluated. Depending on the endpoint considered, the probability that the superior results obtained with TEB were due to chance alone ranged from less than 5 in 100 to less than 1 in 1,000. Clinicians not using TEB to guide therapy simply do not make the same mediation decisions as those clinicians who use TEB to help guide therapy. In the Mayo Clinic Trial, TEB use resulted in more aggressive diuretic dosing in patients already on multiple medications. In the CONTROL Trial, TEB resulted in greater use of angiotensin receptor blockers, and greater use of a vasodilating agent in the first visit and when systemic vascular resistance was high. Additionally, guidelines do not suggest blindly uptitrating diuretics or prescribing angiotensin receptor blockers. Therapy still needs to be adjusted for the particular patient. Indeed, that is what the study results prove - that TEB data changes physician behavior in a way that alters medication type and dose for the particular patient - and those medication decisions lead to improved outcomes.

Questions Regarding the CONTROL Trial

Question: Are there any differences between the CONTROL Trial definitions and the JNC definitions of hypertension or uncontrolled hypertension?

No, the definitions used in the CONTROL Trial were the same as those in JNC guidelines.

JNC 7 defines controlled goal blood pressure as <140/90 mm Hg and uncontrolled blood pressure as failure to reach goal blood pressure of <140/90 mm Hg (<130/80 mm Hg in those with diabetes or chronic kidney disease) with one or more medications. The CONTROL manuscript used the term "uncontrolled" as it is specifically used in JNC 7 and elsewhere to describe the blood pressure that is not at goal levels.

"Uncontrolled hypertension" (often also referred as complex hypertension) is a general term that does not specify a particular intensity or duration of treatment. In contrast, the terms "refractory" and "resistant" or "drug resistant" hypertension are terms that imply an intensity of treatment after which blood pressure is still not at goal. More specifically, "refractory hypertension" is defined as not at goal on two or more antihypertensive medications and "drug resistant hypertension" is defined as not at goal on three or more antihypertensive medications.

As JNC 7 defines hypertension as a mean systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg, based on blood pressure readings on each of two or more office visits, the inclusion criteria of CONTROL meet the JNC 7 definition of hypertension. The CONTROL criteria were systolic blood pressure of 140 - 179 mm Hg and/or diastolic blood pressure of 90 - 109 mm Hg, based on two or more properly measured blood pressure readings on each of two or more office visits (based on JNC 6 definition of Stage I or II hypertension, which were in place when the CONTROL Trial was initiated). Therefore, the patients must not have reached blood pressure <140/90 mm Hg in spite of lifestyle modifications and subsequent treatment with one, two, or three antihypertensive drugs.

Question: Why were setting and patients selected as they were for the CONTROL Trial compared to the Mayo Clinic Trial?

1. *Setting*

   When CMS reviewed the Mayo Clinic Trial, they questioned (both informally and in the formal decision memo) whether TEB-directed therapy would help nonspecialists achieve similar results in the treatment of hypertensive patients. Therefore, CONTROL evaluated the use of TEB by generalists.

2. *Hypertension classification and enrollment criteria*

   CONTROL was designed to address the additive value of TEB in an important hypertension population, patients who are not controlled after initial therapy with lifestyle modification and one or more medications. In the Mayo Clinic Trial, patients referred for specialist treatment of more severe blood pressure with significant comorbidities on two or more (average 3.6 at trial entry) antihypertensive drugs were evaluated. CONTROL was designed to expand and complement the results of the Mayo Clinic Trial and evaluate the effectiveness of TEB to assist in reducing blood pressure in a different, and more common, segment of the hypertensive population (one to three medications, average 1.7 at trial entry) in a different treatment setting (generalist). The CONTROL Trial patients represent the largest and best opportunity to improve blood pressure control rates in the CMS beneficiary population.

   Patients who were not on any antihypertensive drugs or who were already controlled (blood pressure <140/90 mm Hg) were not eligible for the CONTROL Trial. Prior to entry in CONTROL, participating physicians attempted therapy with lifestyle modification and one or more medications in accordance with standard clinical practice. If this standard care approach had failed, the treating physicians could enroll the patients in CONTROL, which then randomized patients to continued standard care or a TEB-guided arm.

3. *Duration of prior efforts to control blood pressure and duration of hypertension*

   JNC guidelines do not specify the length of time a patient has been treated in order to determine whether or not a patient is under control. This is because the clinical approach to reducing blood pressure is not different based upon the length of time the patient has had hypertension. By definition, patients entering the CONTROL Trial would have been enrolled and randomized only if they failed to achieve blood pressure control in spite of lifestyle modifications and receiving at least one antihypertensive drug for a period of at least two months. However, it is likely that many of these patients had hypertension for months or years prior to entering the trial. Patients were not excluded for long-standing uncontrolled hypertension; they were only required to have failed to achieve blood pressure control in spite of active antihypertensive treatment in a typical community-based practice setting.

Question: Were patients in the CONTROL Trial required to have tried and failed any specific antihypertensive therapies per JNC guidelines?

No one therapy was required to have been tried and failed, but all patients were required to have been treated with one or more antihypertensive therapies mentioned in JNC guidelines and failed to control blood pressure. The JNC 7 recommendations for treatment are not related to the diagnosis of hypertension. Physicians consider a multitude of factors in their treatment of hypertensive subjects, including national guidelines. Parenthetically, it is significant that despite JNC 7 and prior JNC recommendations for treatment, blood pressure control has not met national goals, with only an approximate 29%-31% control rate.

In contrast, the use of TEB has specifically and directly demonstrated an objective evaluation of the underlying hemodynamic abnormality and a targeted and tailored approach to prescribing initial antihypertensive drugs and titrating them to achieve blood pressure goals. All of the patients included in the CONTROL study prior to randomization had met the inclusion criterion by failing to reach normal blood pressure despite prior treatment efforts. No specific drug regimen was required to have been tried and failed before entering the CONTROL Trial. Treatment regimens and blood pressure levels varied from patient to patient, and it is well accepted that a large number of medications can be effective at reducing blood pressure.

The purpose of the CONTROL Trial was to determine, in patients with established but uncontrolled hypertension on one, two, or three medications, whether using TEB as part of a suggested treatment strategy would provide superior results when <u>added</u> to clinicians' customary approaches to hypertension treatment, which include the consideration of JNC guidelines.

Question: Were patients with comorbidities specifically excluded from the CONTROL Trial?

No. It is important to note that the presence or absence of comorbid conditions and the classification of hypertension as "uncontrolled" are not related. Patients with comorbid conditions were not excluded from the CONTROL Trial, but the study population does reflect the level of comorbidities expected in a community-based population of uncontrolled patients on one to three antihypertensive drugs. We purposely did not require comorbid conditions in CONTROL because the Mayo Clinic Trial demonstrated the effectiveness of TEB in resistant hypertension (uncontrolled on 2 or more meds) patients that expectedly had more comorbid conditions. Prior to the CONTROL Trial, it was unknown whether TEB was as effective in non-resistant hypertensive patients with fewer comorbid conditions as in resistant hypertensive patients with more comorbid conditions.

Question: Were the CONTROL Trial treatment goals and study endpoints consistent with JNC guidelines?

Yes, the CONTROL Trial primary endpoints of reductions in systolic and diastolic blood pressure are the goals of JNC-recommended treatment. The goal blood pressure of <140/90 mm

Hg is consistent with JNC target blood pressure. Because there is strong evidence (acknowledged in the JNC guidelines) that lower blood pressure results in lower risk, achievement of a more aggressive blood pressure of <130/85 mm Hg was also reported.

Question: Because the mean age of the subjects was approximately 10 years below the age of Medicare eligibility, are the study results generalizable to the Medicare population?

Yes, the study results are certainly applicable to the general Medicare population. Most clinical guidelines in cardiovascular medicine do not consider age to be a primary factor in diagnosis and treatment. Such is the case for JNC 7 for hypertension. Age is not a criterion in the diagnosis or classification of hypertension, nor in medication strategy or categorization of response to medications (i.e. whether the patient is "controlled" or "uncontrolled", "resistant" or "nonresistant"). JNC 7 specifically states:

> "*Treatment recommendations for older individuals with hypertension, including those who have isolated systolic hypertension, should follow the same principles outlined for the general care of hypertension*."

Moreover, in the previously referenced meta-analysis performed by Lewington et al., the authors state in their conclusion:

> *"Throughout middle and old age, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg."*

The Mayo Clinic Trial examined patients with an average age of 65 years. The CONTROL Trial examined patients with an average age of 55 years. For the reasons noted above, we did not exclude patients younger than 65 years of age in the trial.

Subgroup analysis of the CONTROL Trial indicated that TEB maintained superiority when evaluated in three key subgroups: those with isolated systolic hypertension, those age ≥55 years, and those receiving a thiazide diuretic. Additional evaluation of age-specific results was performed by a two-way analysis of variance for achievement of BP endpoints, in which treatment arm and dichotomized age (≥55 years) were included in the model. For reference, the age of the CONTROL Trial patients who were enrolled and completed the trial is shown in Table 10 below.

Table 10. Distribution of age in the CONTROL Trial

Age Category	Patients (N)	Subjects (%)
≥50	150	71%
≥55	81	51%
≥60	55	34%
≥65	24	15%

Question: How was the algorithm used in the CONTROL Trial derived, and how specifically were investigators told to use the TEB hemodynamic data?

The CONTROL algorithm was based on the algorithm used in the Mayo Clinic Trial to achieve superior blood pressure control in refractory hypertension.

Physician investigators prescribed medications consistent with published guidelines, their usual practice patterns, and patient clinical characteristics. In the Hemodynamic Arm, the treating physician was also encouraged to use a hemodynamic treatment strategy to guide therapeutic decisions about pharmacologic agents and dosing.

Per the suggested treatment strategy, investigators were advised to evaluate the TEB report specifically for high, normal, and low values for cardiac index (CI) and systemic vascular resistance index (SVRI) and to make medication changes accordingly. These types of recommendations based on hemodynamic parameters are essential in order to evaluate the incremental value of hemodynamically guided therapy using TEB. For patients in the Hemodynamic Arm, both the CI and SVRI values were displayed, along with a bar graph indicating the patient's values in relation to the normal range. Normal range for CI was defined as 2.5 to 4.2 L/min/m^2 and for SVRI as 1,680 to 2,580 dyne sec m^2 cm^{-5}. Therefore, cardiac index values >4.2 and SVRI values >2,580 were considered "high" by investigators, and a CI value between 2.5 and 4.2 and SVRI value between 1,680 and 2,580 were considered "normal". When values outside the normal range were present, the Hemodynamic Treatment Strategy suggested specific medication changes. For example, if SVRI was high, the investigator was encouraged to add a vasodilating agent or increase dose of a vasodilating agent (angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, calcium channel blocker, vasodilator). In contrast to the absolute values of CI and SVRI used to suggest treatments, thoracic fluid content (TFC) was evaluated in the context of prior values and in response to prescribed changes in diuretic from the prior visit (additions or increases in dose). Investigators were instructed that TFC decreases of 1.0 /kOhm or more should be considered a "reduced" TFC value. The 1.0 /kOhm threshold was based on the expected variability of TFC in stable outpatients undergoing no medication or known physiologic changes.

There were a total of five suggested treatment changes based on TEB measurements:

1. High SVRI: Increase angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, calcium channel blocker, vasodilator
2. Normal SVRI: Consider reduced dose of vasodilator
3. High CI: Add beta blocker or central acting agonist
4. Low/normal CI: Consider reduced dose of beta blocker
5. If diuretic was added or dose increased at previous visit, evaluate TFC measurement in comparison to the prior visit TFC measurement. If TFC not reduced (i.e. 1 /kOhm), consider adding another diuretic or increasing dose.

Question: How did TEB specifically improve outcomes through medication choices?

This is an important question - how did the use of TEB result in greater blood pressure reduction and better blood pressure control? While it is sometimes possible to intuit the *mechanism* by which a pharmacologic or diagnostic device improves outcomes, it is not the primary question asked in a randomized controlled trial. The identification of the mechanism by which TEB improves blood pressure control was also not the primary question that CONTROL sought to answer. The primary question was outcome-based and was whether the Hemodynamic Arm (subject to a guided treatment approach based on the diagnostic information provided by TEB) demonstrated greater blood pressure reduction and better blood pressure control than the matched Standard Arm.

After answering the primary question of improved blood pressure outcomes, it is natural to consider how the use of TEB was able to accomplish this. While there were many similarities between arms, there were also some important differences. Based on the five suggested treatment changes, it is clear that TEB affected #1 and #4 from above. However, the trial was only powered for the primary endpoint of blood pressure reduction and was not powered to find small disparities in medication use. Therefore, most medication differences did not reach statistical significance.

Mechanisms explaining why TEB improved blood pressure outcomes include:

1. Individualized Therapy Based on Underlying Hemodynamics

Patient treatment was *individualized* whereby drugs were selected based on the underlying hemodynamic abnormality associated with the increased blood pressure. The fundamental difference between the two Arms was that patient treatment in the Hemodynamic Arm was individualized and targeted at the hemodynamic abnormality associated with the elevated blood pressure. This approach led to greater reductions in SVRI in the Hemodynamic Arm, which allowed greater decreases in both systolic and diastolic blood pressure.

The treatment strategy in CONTROL led to two important differences in medications, based on the underlying hemodynamics. First, over the course of the study, patients in the Hemodynamic Arm were more likely to be prescribed an ACEI, ARB, or CCB when their SVRI was high, per the hemodynamic treatment strategy (78.3% vs. 67.1%, $p<0.05$). Second, patients in the Hemodynamic Arm were more likely to avoid a beta blocker or to have their beta blocker reduced in the presence of low or normal CI (85.4% vs. 77.0%, $p<0.05$), as the hemodynamic strategy suggested.

2. Minimization of "Trial-and-Error" Based on Fewer Dose Changes in the Hemodynamic Arm

In theory, a greater number of medication dose changes could result in greater blood pressure reduction, but only if such medication changes were appropriate. On the other hand, a greater

number of medication changes could result in less blood pressure reduction, if the medication changes were not chosen correctly or were not dosed as aggressively as they should have been.

TEB data provided physicians with objective, quantitative measurements that allowed them to more efficiently direct the patient's treatment (medication class and dose), determine whether their medication regimen was having the desired hemodynamic effect, and identify hemodynamic resistance to the pharmacologic effects of the chosen drugs and doses. Although there were no differences in medication class changes, there were a greater number of medication dose increases in the Standard vs. Hemodynamic Arm (3.6±1.3 vs. 3.0±1.2, $p<0.001$), as well as a greater number of dose decreases (2.7±1.3 vs. 1.7±1.0, $p<0.001$).

In CONTROL, the greater number of dose increases and decreases in the Standard Arm may indicate selection of the wrong drug or non-response of the patient. Alternatively, TEB may have facilitated choice of a more effective regimen.

Because blood pressure level alone provides no direct measure of the hemodynamic basis for the hypertension or the hemodynamic effects of medications, a stepped approach to the treatment of hypertension on one or two medications may lead to a greater number of changes than care guided by TEB. Patients in the Standard Arm were more likely to experience both increases and decreases in their medication doses, while medication class changes were not different between Arms. This result might have been expected, as treatment in the Standard Arm followed guidelines and usual practice patterns, in which a stepped approach to therapy contributes to a "trial-and-error" method of determining whether agents and doses are working.

3. Other Medication Similarities and Differences

When analyzing medications in general, there were both similarities and differences between the Arms, which are detailed below:

3a. Number of final medications

In theory, a greater number of medications could result in greater blood pressure reduction due to more intense pharmacologic effects.

> Similarities
> In the CONTROL Trial, there were no differences in the final number of medications *(2.1 in the Hemodynamic Arm and 2.0 in the Standard Arm).*
>
> Differences
> None

3b. Class of medications

In theory, different classes of medications could result in greater blood pressure reduction, if such medication types were more effective for the particular patients at reducing blood pressure. Conversely, selection of suboptimal medication classes may contribute to a poorer blood

pressure control, which may help explain the lower blood pressure control in the Standard Care Arm.

Similarities
Most medication classes were not different between Arms.

Differences
In the Hemodynamic Arm, ARB use was higher (46.4% vs. 30.5%, $p<0.05$), ACEI use was similar (49.3% vs. 53.7% $p>0.05$). In addition, the Hemodynamic Arm trended toward a lower percentage of patients on a beta blocker, although it was not significant ($p>0.05$).

3c. Final dose of medications

In theory, a greater dose of medications could result in greater blood pressure reduction due to more intense pharmacologic effects. However, if such doses were not effective, they may not contribute to more effective blood pressure reduction and might even contribute to less effective blood pressure reduction.

Similarities
Most medication doses were similar between Arms.

Differences
Medication doses were not different between Arms except that patients in the Standard Arm were on higher doses of thiazide diuretics (18.9±8.3 vs. 13.0±2.6 mg/day, $p<0.01$).

It is clear that the higher doses of thiazide diuretics did not result in greater blood pressure reduction for the Standard Care arm in the trial, either for the trial as a whole or when applied only to patients receiving a thiazide diuretic. When the study endpoints were analyzed only for patients on a thiazide diuretic in the final visit, patients in Hemodynamic Arm had greater decreases in systolic BP from baseline (26±19 vs. 8±17 mm Hg, $p<0.001$) and post-washout (36±17 vs. 21±20 mm Hg, $p<0.01$) and greater decreases in diastolic BP from baseline (16±11 vs. 3±14 mm Hg, $p<0.001$) and post-washout (20±12 vs. 11±13 mm Hg, $p<0.01$).

3d. Medication class changes

Similarities
Medication class changes in the Standard and Hemodynamic Arm were similar in both class initiation (1.0±0.9 vs. 1.1±0.9, $p>0.05$) and removal (0.8±0.8 vs. 0.7±0.8, $p>0.05$).

Differences
None

4. Summary

There were medication differences between the two Arms of the CONTROL Trial that support the concept of individualized therapy and provide important explanations for the more effective blood pressure control with TEB-guided therapy. In summary, the superior outcomes of the TEB-guided Arm are most likely due to the greater efficacy of *individualized therapy* resulting from objective data leading to more effective medication selection and dosing based on the underlying hemodynamic abnormalities causing the hypertension. Additionally, objective measurements of the hemodynamic actions of the medications *minimize the "trial-and-error" approach* to dosing medications. It is important to note that the manuscript recognizes that due to the large number of medications used in patients with hypertension, the trial was not powered to detect changes in specific medications. The CONTROL Trial was powered to evaluate in a statistically significant manner whether TEB improved blood pressure outcomes – which it did.

The primary medication differences in the Hemodynamic Arm (as compared to the Standard Arm) were:

- More likely to receive a vasodilating drug that reduced SVRI when SVRI was high (throughout the trial)
- More likely to avoid beta blocker use or have their beta blocker reduced in the presence of low or normal cardiac index
- Fewer dose increases and fewer dose decreases
- More likely to receive an angiotensin receptor blocker at the final visit
- Less likely to receive higher doses of thiazide diuretics

Question: Were patients treated by their own pre-study primary physician or were the study physicians new physicians who only treated them in the context of the study? Was hypertension treatment by non-study physicians specifically excluded by the protocol?

Patients were treated by their own pre-trial primary physician. Visits to other physicians and treatments by non-trial physicians were not specifically excluded during the protocol; however, they were queried during the trial and did not occur.

Appendix: Submitted Evidence for CMS to Evaluate

Primary Evidence

Taler SJ, et al. Resistant hypertension: Comparing hemodynamic management to specialist care. Hypertension. 2002;39:982-988.

Smith R, Levy P, Ferrario C. Efficacy of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels (CONTROL). Am J Hypertens. 2005. 18;(5 part 2):94A. (Note: The CONTROL manuscript has been accepted for publication in a peer-reviewed journal.)

Secondary Evidence

Diagnostic / Prognostic

Abdelhammed A, Smith R, Levy P, Smits G, Ferrario C. Noninvasive hemodynamic profiles in hypertensive subjects. Am J of Hypertens. 2005:2;51S-59S.

Galarza CR, Alfie J, Waisman GD, Mayorga LM, Camera LA, del Rio M, Vasvari F, Limansky R, Farias J, Tessler J, Camera MI: Diastolic Pressure Underestimates Age-Related Hemodynamic Impairment. Hypertens 1997;30:809-816.

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Therapeutic Monitoring

Toth PD, Demeter RJ, Woods, JR, Nyhuis AW, Judy WV: Comparison of the Effects of Pindolol and Atenolol on Hemodynamic Function in Systemic Hypertension. Am J Cardiol 1988;62:413-418.

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