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September 21, 2006

Madeline Ulrich, M.D., M.S.
Michael Lyman, RN, MPH
Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD

Dear Dr. Ulrich and Mr. Lyman:

The American College of Cardiology (ACC) is pleased to offer comments on CMS' proposed Medicare National Coverage Determination on electrical bioimpedance for cardiac output monitoring (CAG-00001R2). The ACC is a 34,000 member non-profit professional medical society and teaching institution whose mission is to advocate for quality cardiovascular care—through education, research promotion, development and application of standards and guidelines—and to influence health care policy. The College represents more than 90 percent of the cardiologists practicing in the United States.

Members of the ACC's Heart Failure and Transplant Committee and Prevention Committee have reviewed the proposed decision memorandum along with additional comments received from our membership concerning use of thoracic electrical bioimpedance (TEB) in the management of patients with hypertension. We had previously found that the evidence offered for the first reconsideration was not sufficient to support establishment of national Medicare coverage as requested for hypertensive patients on one or more anti-hypertensive drugs who are not at goal blood pressure. At this time, the ACC has not been presented with sufficient evidence to alter this opinion as expressed in our previous comments on this NCA. We therefore support CMS' proposed decision memorandum as written.

The ACC appreciates CMS' willingness to work with the physician community to develop appropriate Medicare coverage policies, and thanks you for this opportunity to comment. If you have any questions, or if we can be of any assistance, please contact Rebecca Kelly, Director of Regulatory Affairs by telephone at 301-493-2398 or by e-mail at rkelly@acc.org.

Sincerely,

Steven E. Nissen, M.D., F.A.C.C.
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September 22, 2006

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Centers for Medicare & Medicaid Services
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RE: Impedance cardiography (IC) for hypertension (CAG-00001R2)

Dear Drs. Phurrough, Jacques and Ulrich:

The International Society on Hypertension in Blacks (ISHIB) is pleased to provide comment on the decision memorandum on coverage of impedance cardiography (IC) for hypertension management. We have considered the data in the published literature from the Mayo Clinic hypertension clinic and from eleven primary care sites in the CONTROL trial. Though neither study was without flaws, we believe that both were executed in a rigorous enough fashion. Thus, we have confidence in the validity of the impressive final study results.

ISHIB is an organization that has long been on the forefront of seeking strategies that will either prevent hypertension and/or improve blood pressure control, especially in ethnic minorities. We view the approach of linking non-invasively determined vascular pathology to therapeutic selections as an important advance in truly individualizing hypertension therapy in a way that enhances blood pressure control. Hypertension is the number one reason that individuals attend ambulatory clinic visits and elevated blood pressure, per se, is linked to serious cardiovascular-renal consequences such as stroke, heart failure, and even myocardial infarction, cardiovascular conditions that disparately afflict African Americans.

Clinicians often use ethnicity rather that pathophysiology as a factor in selecting drug therapy. While the science of race as a selection factor is flawed, the science of the IC algorithm is robust. We therefore take the position that extending coverage nationally for impedance cardiography will ultimately lead to better patient care and fewer costly pressure-related clinical outcomes because of improved therapeutic decision-making and, we posit, less therapeutic inertia. Thus, we support extending coverage for impedance cardiography to high-risk (diabetes mellitus and/or chronic kidney disease according to JNC 7 definitions) on at least 2 antihypertensive medications and to all other hypertensive patients taking at least three antihypertensive drugs.

We anticipate that you will give our comments all due consideration. We appreciate the opportunity to speak on behalf a favorable advance in the management of hypertension.

Yours truly,

Kenneth Jamerson, MD
President

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September 22, 2006

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RE: Impedance cardiography (IC) for hypertension (CAG-00001R2)

Dear Drs. Phurrough, Jacques and Ulrich:

As a follow up to our meeting, I would like to provide a public comment regarding your proposed decision memorandum on coverage of impedance cardiography (IC) for hypertension. I am a specialist in clinical hypertension and Chief of the Division of Translational Research and Clinical Epidemiology at Wayne State University School of Medicine / Detroit Medical Center and have published approximately 135 articles on the subject of hypertension. I wrote an accompanying editorial for the manuscript titled "Value of Noninvasive Hemodynamics to Achieve Blood Pressure Control in Hypertensive Subjects" (Smith, RD et al. *Hypertension.* 2006;47:769-775), the primary evidence CMS is considering in its coverage analysis.

I believe the findings reported by Smith et al. were very encouraging. These investigators showed that consideration of hemodynamic parameters, as determined noninvasively by IC, in the treatment of hypertension in primary care practice settings improved systolic and diastolic BP reduction, rates of BP control, and normalization of selected hemodynamic parameters in drug-treated hypertensives with BP <140/90 mm Hg. Therefore, the study results indicate that antihypertensive therapy accompanied by IC measurements in uncontrolled hypertensive patients is more effective than standard care.

CMS has listed a variety of questions that are related to the mechanism by which IC improved BP control. While these questions are of scientific interest and may help tell us *why* IC improved BP control, they cannot tell us *whether* the provision of IC improves BP control. The results clearly demonstrate that provision of IC improves BP control. Without question, there is some linkage between abnormal hemodynamic parameters and elevated BP. For example, higher levels of SVRI can track higher levels of BP. In turn, when BP falls, systemic vascular resistance index (SVRI) also tends to fall if elevated at baseline. Additionally, in this study, investigators were able to show higher rates of BP control and simultaneous normalization of BP along with SVRI and cardiac index (CI) in participants randomized to the IC arm, relative to standard care. Accordingly, in the IC group, vasodilators (angiotensin receptor blockers, angiotensin converting enzyme inhibitors, and calcium antagonists) were used more often when SVRI was elevated than in the standard care group. Likewise, beta blockade was less often used

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study extend the observations of the Mayo Clinic trial (Taler et al.), showing that IC data accompanying physician antihypertensive therapeutic decisions improved BP control in resistant hypertensives in a hypertension specialty practice. I would also comment that the results of the Mayo Clinic trial showing incremental improvement of 4/3 mm Hg in BP control in the IC arm in the setting of a world class hypertension specialty clinic is a very impressive achievement.

There are considerable clinical implications of the Smith et al. study. By providing individual hemodynamic measurements over multiple visits, it was possible to improve BP control, as well as to more often normalize SVRI and CI. These favorable outcomes occurred even though the practitioners did not comply equally with all of the suggested therapeutic decisions in the study treatment algorithm. CMS cited in its proposed decision memorandum that the lack of adherence to the hemodynamic treatment strategy that I noted in my editorial was a criticism of the results. In doing so, CMS may have misunderstood the intent of my statement. I noted that it was likely that the magnitude of BP lowering in the IC group may have *underestimated* the maximum attainable BP lowering that could have been obtained if the treatment algorithm had been more closely followed.

The difference in BP (6/7 mm Hg lower in the IC group, post-washout to final; 8/7 mm Hg lower in the IC group, baseline to final), if sustained over the long term, would also lead to significantly lower rates of cardiovascular morbidity and mortality. Based on pharmaceutical trial methods and personal experience, I believe it is likely that the BP lowering would be sustained over the long term and may in fact have greater reductions in the long term than shown over the three month treatment duration of this trial. These data have considerable relevance to actual primary care clinical practice sites, because the data were derived from such practice locations. The concern about the portability of these findings into routine clinical practice is, therefore, minimal.

This study offers the practitioner a tool that provides validated, noninvasive measures that can vary even within an individual over time and that the availability of IC data, in conjunction with physician antihypertensive therapeutic choices, produce superior BP lowering than standard care. It is likely that IC, along with emerging molecular genetic markers and other complementary noninvasive hemodynamic measurements will be used in combination to optimize pharmacological BP lowering and target-organ protection while minimizing side effects and adverse events. It is very encouraging to see a new, valid technology that can be used to improve the likelihood of successful BP control. This, I believe, will be one of several advances in the coming years that will truly usher in the era of individualized hypertension management.

While scientific questions remain and are important to understand more about how IC measurements are best used in hypertension, they are not required to conclude that *the provision of IC measurements results in better BP control.* Based on the results of the two RCTs (Smith et al. CONTROL trial and Taler et al. Mayo Clinic trial), CMS currently proposed coverage is not consistent with evidence-based medicine. The evidence from these two RCTs does support coverage of IC for uncontrolled hypertensives on multiple drugs for some specified time period. Per CMS request during our September 18, 2006, meeting for a suggested reasonable policy, I believe there is sufficient evidence for the following improved coverage policy for IC in hypertensive patients:

Remove carrier discretion and provide national coverage of IC in high risk uncontrolled hypertensive patients on two antihypertensive drugs, with high risk patients defined as those with diabetes mellitus or those with microalbuminuria. Additionally, remove carrier discretion and provide national coverage of IC in non-high risk uncontrolled hypertensive patients on three antihypertensive drugs but not at goal BP.

A frequency limitation of a maximum of four tests/year for IC in the management of hypertensive patients. A reasonable interval between tests would be six weeks.

I appreciate the opportunity to provide further comments to you as well as your consideration of my thoughts.

Sincerely,

John Flack, MD, FACP, FAHA
Professor of Medicine and Physiology
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CardioDynamics
THE ICG COMPANY

September 23, 2006

Steve E. Phurrough, M.D., M.P.A.
Louis B. Jacques, M.D.
Madeline Ulrich, M.D., M.S.
Centers for Medicare & Medicaid Services
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Re: Administrative File, CAG No. 00001R2
Electrical Bioimpedance for Cardiac Output Monitoring

Dear Drs. Phurrough, Jacques, and Ulrich:

CardioDynamics appreciates the opportunity to submit written comments on the draft decision memorandum released on August 24, 2006 for electrical bioimpedance for cardiac output monitoring. We want to thank you for the time and attention that the Coverage and Analysis Group has devoted to the review of thoracic electrical bioimpedance (TEB) over the past several years. We have engaged CMS in another review of TEB because of the significant benefit we believe TEB testing would provide to Medicare beneficiaries with uncontrolled hypertension. We have carefully reviewed the draft decision memorandum and submit these comments as a supplement to our February 27, 2006 reconsideration request (CAG-00001R2) and to provide the agency with additional information to make your final decision on TEB coverage for Medicare beneficiaries with uncontrolled hypertension.

Summary

The proposed decision memorandum raises numerous important clinical points and questions. In our meeting with CMS on Monday, September 18, 2006, and in this comment letter, we have provided CMS with additional clinical information in response to these questions. The revised coverage request responds directly to issues raised by CMS and provides clear criteria and guidance on when TEB would be reasonable and necessary for Medicare beneficiaries with uncontrolled hypertension.

Major CMS Questions

The draft decision memorandum raised many questions and asked for answers. The CONTROL manuscript content was based on what the journal reviewers required, was limited by space constraints, and could not answer questions that were not yet asked. Therefore, in this comment letter, we seek to clarify the published data, report previously-available-but-unpublished data, and provide new analyses in response to CMS questions.

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The fundamental premise of the two available randomized controlled trials (RCTs), Mayo Clinic and CONTROL, was that physicians would treat hypertension better with TEB measurements than they would without TEB measurements. These two trials were conducted in accordance with the general methodological principles that CMS has previously outlined. Additionally, the CONTROL trial was designed in large part to address the previous methodological and reporting concerns that CMS noted with the Mayo Clinic trial. In both trials, patients were randomized and therefore assigned to each treatment arm without bias. The baseline characteristics in both arms of the studies were equivalent. Physicians received the same number of visits, and the only difference in the intervention arm of both trials was the provision of TEB data. The endpoints in the trials were measured similarly and with standard methods to prevent bias. Therefore, it can be concluded that the provision of TEB data to physicians resulted in improved BP control in these trials. While CMS has concluded that the evidence is not sufficient for the patient population we originally requested, we now ask you to consider the existing and new evidence in relation to a more narrowly defined population.

In the attached appendix, we have grouped our response to the CMS questions into the following eight categories:

1. Are more details on the study methods available, and were the study methods appropriate?
2. Did enrolled patients receive sufficient prior treatment to control BP?
3. Were improvements in TEB parameters associated with reduced BP?
4. Did the provision of TEB lead to adherence to the hemodynamic treatment strategy?
5. Did adherence to the hemodynamic treatment strategy lead to improved TEB parameters and BP?
6. Can improvement in BP control be attributed to the provision of TEB?
7. Is a three-month duration long enough to determine if TEB has clinical utility?
8. Is the evidence generalizable to the Medicare population and what would the expected benefit of using TEB be?

<u>Revised Coverage Request</u>

As discussed above, we respectfully request that CMS consider coverage of TEB for a more narrowly-defined subgroup of Medicare beneficiaries with uncontrolled hypertension. On February 27, 2006, CardioDynamics requested the following coverage language that was based on the inclusion criteria in both the Mayo Clinic and CONTROL trials:

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

During our September 18, 2006 meeting, some general language for revised coverage was presented. In response, CMS directed us to request more specific revised coverage language. Based on the CMS questions and concerns that we have noted, as well as the new evidence we have provided in response to the CMS questions and comments, we respectfully request removal of carrier discretion and provision of national coverage with the following revised coverage language:

TEB is covered for the following subgroup of patients with hypertension:

1. Hypertensive patients who are not at goal BP on three or more antihypertensive drugs.

2. High-risk hypertensive patients who are not at goal BP on two or more antihypertensive drugs. High-risk patients are defined by JNC guidelines and include patients with: a. Diabetes mellitus; b. Chronic kidney disease, defined as GFR <60ml/min or albuminuria (>300 mg/d or 200 mg albumin per gram of creatnine).

Conditions
Prior to receiving a TEB test for hypertension, the patient must have been diagnosed and treated for hypertension a period of at least six months.

Frequency Limitation
TEB testing for hypertension as a covered indication is limited to a maximum of four tests per patient in a 12 month period. If a patient has received a previous TEB test for hypertension, an additional TEB test for hypertension cannot be performed for at least 30 days.

Noncoverage
TEB for hypertension is not covered: a) as a screening test; b) for any patient already at goal BP; c) for any patient not at goal BP on only one antihypertensive drug.

We would like to work with CMS in the future to address the other questions that were raised in the proposed decision memorandum. All of CMS' points are interesting questions for future research.

We appreciate your consideration of this request. We look forward to working with you on the final decision memorandum to provide appropriate Medicare beneficiary access to TEB for the treatment of uncontrolled hypertension.

Sincerely,

Neil Treister, MD, FACC
Medical Director

Appendix: Response to CMS Questions with New Evidence

1. Are more details on the study methods available, and were the study methods appropriate?

1a. Patient selection

Patients were enrolled from eleven primary care physician offices. Patients were treated by their primary care physician for hypertension before being screened for participation in the CONTROL trial.

1b. Exclusion criteria for abnormal lab values

The specific values of the exclusion criteria for abnormal lab findings were as follows:

- Hematology: hemoglobin <10g/dL; WBC <2000/mL; platelets< 100,000/mL
- Blood chemistries: ALT and/or AST >2.5x upper limit of normal; creatinine >3.0mg/dL; potassium <3.3mEq/dL; Hemoglobin A1c > 10%

1c. Randomization

A total of 184 patients were randomized in a 3:2 ratio (107 standard arm, 77 hemodynamic arm). The greater number of patients in the standard arm offset the expected treatment heterogeneity (i.e. could choose any drug, for any reason) in the standard arm. Additionally, in the previous reconsideration process in 2001-2003, CMS offered informal comments that questioned whether the Mayo Clinic trial results in the specialist care arm truly reflected specialist care results, or whether they could be due to chance. The larger number of patients in the standard arm of CONTROL was also done to increase the confidence that the standard arm results would reflect primary care results and would not be due to chance. This meant that significantly more patients were enrolled than would have been required in trial with a 1:1 ratio. Randomization was stratified by site with block randomization through a central telephone service.

1d. Differences in treatment strategy vs. Mayo Clinic trial algorithm

The CONTROL trial used a *suggested* hemodynamic treatment strategy compared to a *required* algorithm in the Mayo Clinic trial. This meant that the physicians were encouraged but not required to use the TEB data. This approach simulated actual clinical application of TEB and removed a potential variable of a mandated approach, which was a previous CMS criticism of the Mayo Clinic trial.

The suggested medication choices based on hemodynamic data were very similar to the Mayo Clinic algorithm except for the use of thoracic fluid content (TFC) with diuretics. Because diuretics are suggested as first-line therapy in JNC guidelines, we did not want to suggest that TFC needed to be used to determine whether diuretics should be initiated. So instead, the CONTROL hemodynamic treatment strategy suggested using visit-to-visit TFC changes as indicator of diuretic effectiveness. This is in contrast to the Mayo Clinic's use of TFC as absolute indicator for intensification of diuretics. Since most of the patients in the Mayo Clinic trial were already on diuretics at baseline, it represented a different clinical scenario than the patients in CONTROL, many of whom were not on diuretics at baseline. In addition, the supine measurement of TFC was used to compare to orthostatic TFC measured in the Mayo Clinic trial.

While a single measurement of orthostatic TFC is associated with high intravascular volume, in the CONTROL trial, we felt that *changes* in supine TFC were a more appropriate measure to track volume *changes*.

1e. Use of hemodynamic treatment strategy

Each investigator treated patients in both arms. Physicians were required to view TEB data each visit in the hemodynamic arm. The high, normal, and low values were printed on each report. A normal cardiac index (CI) was defined as 2.5 to 4.2 $l/min/m^2$, so values below 2.5 were considered low and values above 4.2 were considered high. A normal systemic vascular resistance index (SVRI) was 1680 to 2580 dyne sec $m^2 cm^{-5}$, so values below 1680 were considered low and values above 2580 were considered high. Both the CI and SVRI values were displayed, along with a bar graph indicating the patient's values in relation to the normal range. If a "high" SVRI value of >2,580 was present, the bar graph displayed the value in the "high" range. Depending on the CI and SVRI values, the hemodynamic treatment strategy suggested four different medication changes. In contrast to the absolute values of CI and SVRI that were used to suggest treatments, the hemodynamic treatment strategy for thoracic fluid content (TFC) was based on TFC response to the administration of diuretic intensification. If TFC did not decrease 1.0 /kOhm in response to diuretic intensification, it was not considered to be "reduced" and further diuretic intensification was recommended.

1f. Early terminations

There were 20 patients who were enrolled but not included in analysis. These included 18 patients (11 standard, 7 hemodynamic) who had systolic BP <140 mm Hg and diastolic BP<90 mm Hg at screening (i.e. their BP was already controlled). This occurred because some investigators initially thought BP inclusion criteria applied to *post-washout visit* and not the *screening visit*. When this was discovered during routine study monitoring, the principal investigators decided that it was not appropriate to evaluate these patients with already-controlled BP because they represented a clinically different population than patients who did not have their BP under control. Therefore, all patients who were discovered to have not met the screening BP criteria were terminated from the study at the same time, regardless of how many visits they had completed. Two patients moved away (1 standard, 1 hemodynamic) during the study and did not complete the full follow-up period.

Table 1f. Screening visit values in patients who were excluded
Hemodynamic arm (N=8)

Patient #	**Screening systolic BP (mm Hg)**	**Screening diastolic BP (mm Hg)**
1002	133	84
1020	136	83
1023	129	73
1028	146	86
2044	121	72
2047	128	89
2070	134	75
3085	124	78

Standard arm (N=12)

Patient #	Screening systolic BP (mm Hg)	Screening diastolic BP (mm Hg)
1001	138	66
1014	127	78
1019	122	73
1033	135	80
2045	128	63
3087	124	63
3096	124	81
3103	107	68
3104	124	80
3109	126	84
4125	111	67
4138	148	76

Patients #4138 and #1028 had systolic BP>140 and therefore met BP entry criteria, but moved away during the study. Of the five scheduled visits in the trial, the 12 early termination patients in the standard arm completed an average of 3.4 visits and the 8 patients in the hemodynamic arm completed an average of 3.4 visits (p=ns).

1g. Results with early terminations included

The CONTROL trial results were not based on an intention-to-treat analysis. We note that the Mayo Clinic trial was also not an intention to treat analysis and CMS did not identify this as limitation in the 2004 decision. However, when the study results were reanalyzed including patients who were terminated early, the results were as follows:

Table 1f. Results with early terminations included

Change from screening to last visit	Standard arm (N=105)	Hemodynamic arm (N=77)	Hemodynamic arm advantage	P value
Systolic BP (mm Hg)	-9±4	-17±18	-8	<0.01
Diastolic BP (mm Hg)	-10±11	-4±12	-6	<0.001

The 8/6 mm Hg greater BP reduction with the early terminations included is essentially no different than the 8/7 mm Hg greater BP reduction with the early terminations not included, as was reported in the CONTROL trial manuscript.

2. Did enrolled patients receive sufficient prior treatment to control BP?

2a. Duration of hypertension

Time since original hypertension diagnosis was available for 162 of the 164 patients in the CONTROL trial. For all 162 patients, the average time since the patient's original hypertension diagnosis was 6.9±7.5 years (Standard arm 7.0±6.4 yrs, hemodynamic arm 6.7±6.4 yrs). The

distribution of time from hypertension diagnosis was as follows: <1 year, 23 (14%); 1 to 3 years, 38 (24%); >3 to 5 years, 25 (15%); >5 to 10 years, 40 (25%); >10 years, 36 (22%). A total of 86% of the patients enrolled in the trial had over one year since their original hypertension diagnosis.

2b. Prior treatment efforts

The patients in CONTROL were on an average of 1.7 antihypertensive medications at baseline. This treatment intensity is significantly greater than the baseline treatment intensity in many large pharmacologic trials. For example, it took three years for the average patient participating in ALLHAT to receive an average of 1.7 antihypertensive medications.[1] We believe this is strong evidence that the patients in CONTROL received greater-than-usual intensity of treatment prior to entry in the trial.

2c. Breakout of baseline medications

Calcium channel blockers (CCBs) and diuretics were not broken out into subclasses at baseline in the CONTROL manuscript.

Table 2c: Detailed CCB and diuretic use at baseline

	Standard Arm %	**Hemodynamic Arm %**	**P value for difference**
CCB, any type	33.7	39.1	Not significant
Dihydropyridine CCB	25.3	29.0	Not significant
Nondihydropyridine CCB	8.4	10.1	Not significant

	Standard Arm %	**Hemodynamic Arm %**	**P value**
Diuretic, any type	31.6	26.1	Not significant
Diuretic, thiazide	28.4	24.6	Not significant
Diuretic, potassium sparing	5.3	5.8	Not significant
Diuretic, loop	3.2	0.0	Not significant

Note: Some patients received more than one type of diuretic so the individual diuretic types do not add to the same number as "diuretic, any type"

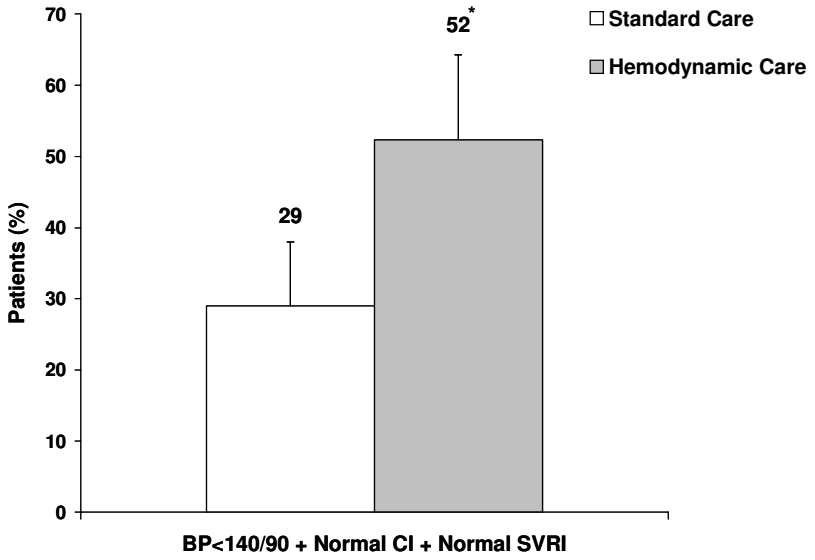
We also wish to clarify the method to report significant differences in medications in the CONTROL manuscript. Differences in medications were only evaluated *between* arms, not to whether differences occurred *within each arm* from the patient's baseline/screening BP values. Since both arms had similar medications at baseline, all medications were washed out, and both arms were expected to receive significant changes in treatment during the study, it was felt that changes in treatment within each arm from baseline levels would not aid in answering the question of whether the medications in the hemodynamic arm were different than the medication in the standard arm.

3. Were improvements in TEB parameters associated with reduced BP?

3a. Normalization of BP and hemodynamics

At the final visit, a total of 36/64 (52%) of patients in the hemodynamic care arm had a normalization of BP (<140/90 mm Hg) and normalization (within normal range) of cardiac index (CI) and systemic vascular resistance index (SVRI), while only 28/95 (29%) did so in the standard arm (p<0.01)

Figure 3a. Concurrent normalization of BP, CI, and SVRI at final visit (*=p<0.01)



3b. Prevalence of abnormal values

Both arms showed reductions in the prevalence of high SVRI from the post-washout to the final visit, but the hemodynamic arm had a significantly lower percentage of patients with high SVRI at the final visit.

Table 3b. Prevalence of abnormal values

	Standard arm	Hemodynamic arm
Visit 2 (post-washout)		
High CI (>4.2 l/min/m^2)	1%	0%
High SVRI (>2580 dyne sec m^2 cm^{-5})	74%	71%
Visit 5 (final visit)		
High CI (>4.2 l/min/m^2)	1%	0%
High SVRI (>2580 dyne sec m^2 cm^{-5})	56%*	35%* †

*= p<0.01 vs. visit 2 within each arm; † = p<0.01 for difference between arms

Based on the physiologic definitions of high CI configured on the TEB device for the CONTROL trial, very few patients were "hyperdynamic". However, if another definition of high CI were used, such as the average CI (3.0 l/min/m^2) of patients deemed "hyperkinetic" in a large study[2] of normotensives and hypertensives, there would be a significant percentage of

patients with "high-normal" CI. At the post-washout visit, 28% of the hemodynamic arm and 34% of the standard arm had a CI>3.0 l/min/m^2. This cut-off for high CI was obviously not evaluated in CONTROL, but may indicate a group of patients with "high-normal" CI who may respond better to CI-reducing treatment in clinical practice.

3c. Regression analysis

We performed regression analysis using analysis of variance (ANOVA) modeling with continuous measures for univariate association of changes in TEB parameters and BP. We pooled all changes in measurements from both arms because treatment arm assignment would not be expected to affect the association of changes in TEB parameters and changes in BP.

Figure 3c. Regression analysis of changes in systolic / diastolic BP to TEB parameters (N=656)

ΔSBP vs.	**F ratio**	**P value**	**Cause-Effect**
ΔCI	1.4	0.24	Not able to be evaluated
ΔSVRI	171.5	<0.001	100 unit drop = 1.3 mm Hg drop in SBP
ΔTFC	4.3	0.03	1 unit drop = 0.5 mm Hg drop in SBP

ΔDBP	**F ratio**	**P value**	**Cause-Effect**
ΔCI	0.9	0.35	Not able to be evaluated
ΔSVRI	150.1	<0.001	100 unit drop = 1.1 mm Hg drop in SBP
ΔTFC	3.6	0.06	1 unit drop = 0.3 mm Hg drop in SBP

The lack of significant association of CI to systolic or diastolic BP does not mean that decreases in CI would not lead to decreased BP. Decreases in CI did not occur as often in the trial due to the therapeutic choices selected in the trial. When only patients who experienced a large CI decrease ($\geq$0.3 l/min/m^2) were evaluated, 41/46 (89%) pts with CI reduction also had reduced systolic BP.

4. Did the provision of TEB lead to adherence to the hemodynamic treatment strategy?

Table 4. Differences in adherence to the suggested hemodynamic treatment strategies

Treatment Strategy	Statistical Difference in Adherence Between Arms?
If SVRI high, add or increase ACEI, ARB, CCB	Yes (78% vs. 67%, $p<0.05$)
If SVRI normal, consider reduce direct vasodilator (i.e. hydralazine)	No (direct vasodilators never used)
If CI high, add or increase BB	No (CI was rarely "high")
If CI low/normal, consider reduced BB	Yes (85% vs. 77%, $p<0.05$)
If diuretic previously prescribed & TFC not decreased, increase diuretic	No (when prescribed, diuretics usually reduced TFC)

There were no differences in 3 strategies, but these conditions were infrequent and do not limit the effectiveness of the strategy in the condition with the highest prevalence, high SVRI. The treatment differences in the presence of high SVRI are a likely primary cause of the lower SVRI and improved BP that was achieved in the hemodynamic arm.

5. Did adherence to the hemodynamic treatment strategy lead to improved TEB parameters and BP?

5a. Effectiveness of adherence to the high SVRI treatment strategy

Visits from both arms were pooled. Adherence was defined as when SVRI was high and ACEI, ARB, or CCB was increased or added. Nonadherence was defined as SVRI was high and ACEI, ARB, or CCB not increased or added. The subsequent effect in the next visit on SVRI, SBP, and DBP are reported.

Table 5a. Effectiveness of Adherence to High SVRI Treatment Strategy

Parameter Change in Next Visit	Did Not Adhere	Adhere
ΔSVRI (dyne sec m^2 cm^{-5})	-178	-434*
ΔSBP (mm Hg)	-5	-15*
ΔDBP (mm Hg)	-4	-9*

*$P<0.01$ for difference between adhere and not adhere

These results demonstrate the regardless of the arm adhering to the strategy, that adherence to the high SVRI treatment strategy results in greater reductions in SVRI, systolic BP, and diastolic BP.

5b. Effectiveness of adherence to the high SVRI treatment strategy by arm

Visits from both arms were examined separately. Adherence was defined as when SVRI was high and ACEI, ARB, or CCB was increased or added. Nonadherence was defined as SVRI was high and ACEI, ARB, or CCB not increased or added. The subsequent effect in the next visit on SVRI, SBP, and DBP are reported.

Table 5b. Effectiveness of Adherence High SVRI Treatment Strategy by Arm

	Hemodynamic arm		**Standard arm**	
Parameter Change in Next Visit	**Did Not Adhere**	**Adhere**	**Did Not Adhere**	**Adhere**
ΔSVRI (dyne sec m^2 cm^{-5})	-269	-430*	-129	-437***
ΔSBP (mm Hg)	-5	-15***	-5	-15***
ΔDBP (mm Hg)	-6	-10**	-4	-8**

*= P=0.17; **=p<0.05; ***=p<0.01 for difference between adhere / not adhere

These data indicate that adherence to high SVRI treatment was similarly effective in both arms.

5c. Effectiveness of four other hemodynamic treatment strategies

The other four hemodynamic treatment strategies did not show statistical differences (p<0.05) in effectiveness of systolic or diastolic BP lowering.

- Strategy: If CI low/normal, decrease BB intensity
  When this strategy was adhered to, CI was preserved (0.0 l/min/m^2 change) in the subsequent visit. When it was not adhered to, CI was reduced (-0.2 l/min/m^2) in the subsequent visit. This represented a statistically significant difference in the change in CI (p<0.05) when the strategy was adhered to, although it did not result in any significantly greater reductions in systolic or diastolic BP.
- Strategy: If SVRI normal, reduce direct vasodilators
  Direct vasodilators (ie hydralazine) never used and therefore could not be reduced in presence of normal SVRI
- Strategy: If cardiac index high, prescribe BB
  CI was almost never "high" as defined by device normal range, so there were no differences.
- Strategy: Increase diuretic if TFC not reduced after diuretic intensification
  Diuretics usually reduced TFC, so condition was infrequent

We do not believe that the lack of differences in these strategies minimizes the significant differences in the high SVRI strategy. While these strategies were prospectively defined, part of what the trial evaluated was the incidence of and adherence to the strategies.

5d. Changes in TFC and BP with diuretic intensification

While the treatment strategy using TFC with diuretics was not significantly different in effectiveness, we sought to determine whether changes in TFC without regard to the treatment strategy could be used to monitor diuretic effectiveness. We pooled visits from both arms and compared visits in which a diuretic was added or increased vs. visits when a diuretic was not added or increased for the effect on TFC, systolic BP, and diastolic BP in the subsequent visit.

Table 5d. Changes in TFC and BP with Diuretic Intensification

Parameter Change in Next Visit	**Diuretic Not Added or Increased**	**Diuretic Added or Increased**
ΔTFC (/kOhm)	-0.1	-1.0*
ΔSBP (mm Hg)	-5	-16**
ΔDBP (mm Hg)	-3	-9**

*=P<0.05, **=p<0.01 for difference between increased/added vs. not increased/added

These data support the notion that diuretic intensification decreases TFC, systolic BP, and diastolic BP more than non-diuretic intensification.

5e. Changes in CI and BP with beta blocker intensification

While the treatment strategy using CI with beta blockers was not significantly different in effectiveness, we sought to determine whether changes in CI without regard to the treatment strategy could be used to monitor beta blocker effectiveness. We pooled visits from both arms and compared visits in which a beta blocker was added or increased vs. visits when a beta blocker was not added or increased for the effect on CI, systolic BP, and diastolic BP in the subsequent visit.

Table 5e. Changes in CI and BP with Beta Blocker Intensification

Parameter Change in Next Visit	**BB Not Added or Increased**	**BB Added or Increased**
ΔCI (l/min/m2)	0.0	-0.2**
ΔSBP (mm Hg)	-7	-11*
ΔDBP (mm Hg)	-4	-9**

***= P=0.23, **=p<0.01 for difference between increased/added vs. not increased/added**

These data may support the notion that beta blocker intensification decreases CI, systolic BP, and diastolic BP more than non-beta blocker intensification.

6. Can the improvements in BP control be attributed to the provision of TEB?

According the Medicare Coverage Advisory Committee, evaluation of diagnostic tests in RCTs is rare.[3] Therefore, the availability of two RCTs using TEB in hypertension should allow a more confident determination of TEB's impact on net health outcomes than diagnostic tests that have not been evaluated in RCTs. The CONTROL trial results followed the general methodological principles that CMS has previously outlined, and the statistical results indicate that the various study endpoints have only a 5 in 100 to 1 in 10,000 probability of being due to chance (if there is truly no difference between treating uncontrolled hypertensive patients with and without TEB).

RCTs are not designed or powered to delineate mechanisms, and neither was the CONTROL trial. While mechanisms can be important to understand how an intervention improves an outcome, they are not required to determine whether an intervention improves an outcome. A variety of questions have been asked related to the mechanism by which the provision of TEB data resulted in improved BP control. Because RCTs are not powered to conclusively identify mechanisms, our mechanistic analyses offer possible but not definitive reasons for the differences in endpoints. In general, we believe that the positive BP outcomes that were achieved with TEB in the two RCTs occurred because TEB data and hemodynamic goals of treatment helped physicians identify and focus on the hemodynamic cause of high BP, which led them to treat patients differently, which led to improvements in BP control. In the Mayo Clinic trial in highly-resistant hypertensive population, a focus on thoracic volumes and systemic vascular resistance appears to have led to greater diuretic dosing and treatment with direct vasodilators. In the study by Smith et al. in a complex-but-less resistant population, a focus on high vascular resistance appears to have led to greater vasodilating agent intensification (ACE inhibitors, angiotensin receptor blockers, calcium channel blockers).

Regardless of the mechanism, the provision of TEB leads to improvement in BP control. Improvement in BP control is accepted as a significant health outcome for Medicare beneficiaries. Therefore, we believe the evidence demonstrates that TEB merits additional coverage to assist physicians in improving BP control.

7. Is a three-month duration long enough to determine if TEB has clinical utility?

Short-term BP response is acceptable for FDA approval of antihypertensive drugs. We also note that the Mayo Clinic trial was of three month duration, and CMS did not list this as limiting factor in its previous reconsideration decision. We believe that BP control at three months is a significant health outcome because immediate BP response is strongly associated with long-term BP control, and BP control at three months would likely prevent future office visits and drug changes. Importantly, the 77% BP control rate with TEB in CONTROL is superior to BP control rates achieved in pharmacologic trials of much longer duration, even though patients in CONTROL were not in control at baseline and were treated more intensely at baseline (1.7 medications) than in many pharmacologic trials. A high control rate is significant because it is likely to lead to fewer office visits and drug changes in an attempt to gain BP control.

8. Is the evidence generalizable to the Medicare population and what would the expected benefit of using TEB be?

8a. Generalizability - age

Results from cardiovascular trials of younger patients are applicable to elderly, and elderly often receive even more benefit. Additionally, JNC 7 does not consider age to be a primary factor in diagnosis and treatment: "*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.*"

The Mayo Clinic trial examined patients with an average age of 65 years and the CONTROL trial examined patients with an average age of 55 years. In CONTROL, subgroup analysis was performed in subjects with age ≥55 years and 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. Patients ≥55 years in the hemodynamic arm (n=33) had greater systolic BP reductions compared to the standard arm (n=51) from baseline (21±17 vs. 11±20 mm Hg, $p<0.05$) and trended greater from post-washout (26±20 vs. 21±19 mm Hg, $p>0.05$). Diastolic BP reductions were also greater in those ≥55 years in the hemodynamic arm from baseline (13±11 vs. 4±12 mm Hg, $p<0.001$) and post-washout (16±11 vs. 10±12 mm Hg, $p<0.05$). In patients ≥55 years, goal BP (<140/90 mm Hg) was achieved more frequently in the hemodynamic arm (76% vs. 53%, $p<0.05$), and the more aggressive BP (<130/85 mm Hg) was also achieved more often (58% vs. 27%, $p<0.01$). Analysis of variance also indicated that age ≥55 years had no effect on study endpoints ($p>0.05$).

8b. Generalizability - comorbidities

We believe that the provision of TEB has been shown to improve BP control in 2 RCTs across the spectrum of comorbidities. The Mayo Clinic trial examined patients with a high percentage of comorbidities, including a third with diabetes. 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 a high percentage of comorbidities but rather the level of comorbidities expected in a community-based population of uncontrolled patients receiving prior treatment for hypertension. Prior to the CONTROL trial, it was unknown whether TEB was as effective in patients with fewer comorbid conditions as it was in patients with more comorbid conditions.

8c. Magnitude of the benefit

Clinical inertia[4] is a major factor preventing the achievement of BP control. Even in randomized trials of long duration, many patients do not achieve BP control at the end of the study. For example, patients in ALLHAT achieved a 66% BP control rate after five years of treatment even though 27% of patients had controlled BP at baseline. That equates to a 39% absolute improvement in BP control after five years. In CONTROL, the hemodynamic arm was able to improve from a 0% BP control rate to 77% BP control rate after only three months.

As CMS is aware, there is a strong need to improve BP control in CMS beneficiaries. The lack of BP control has enormous clinical costs, as well as significant economic costs.[5] In a 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.[6] In the Mayo Clinic and CONTROL trials, TEB-guided management resulted in significant advantages in BP reduction compared to a standard care approach. Therefore, TEB-guided therapy is likely to have significant benefit on the health of the Medicare population.

We understand that CMS cannot formally consider cost-effectiveness as a factor of whether or not to cover TEB. However, we believe it is important background information. In a paper recently accepted for publication in the October/November 2006 timeframe,[7] the authors concluded that the use of TEB (referred to as impedance cardiography, ICG) in uncontrolled hypertension results in a cost-effective utilization of health care resources. An abstract summary of the paper is as follows:

To evaluate the short- and long-term cost-effectiveness of impedance cardiography (ICG) testing in uncontrolled hypertensives, we analyzed the CONTROL trial results that compared the BP lowering effects of Standard vs. ICG care. Short-term cost-effectiveness was evaluated as the incremental cost per incremental mm Hg reduced during the trial. Long-term cost-effectiveness was evaluated as incremental cost per quality-adjusted life-year (QALY) gained over ten years. ICG care short-term cost-effectiveness was $20 per incremental mm Hg reduced for systolic BP (vs. Standard care $36 per mm Hg reduced) and $23 per incremental mm Hg reduced for diastolic BP (vs. Standard care $79 per mm Hg reduced). In the long-term, ICG resulted in a $476 cost savings and 0.109 QALYs gained per patient (-$4,371 per QALY gained, sensitivity analysis -$8,764 to $13,163). The use of ICG testing to reduce BP in uncontrolled hypertensive patients is cost-effective from both a short- and long-term perspective.

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CardioDynamics
THE ICG COMPANY

September 23, 2006 [corrected October 9, 2006)

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Re: Administrative File, CAG No. 00001R2
Electrical Bioimpedance for Cardiac Output Monitoring

Dear Drs. Phurrough, Jacques, and Ulrich:

CardioDynamics appreciates the opportunity to submit written comments on the draft decision memorandum released on August 24, 2006 for electrical bioimpedance for cardiac output monitoring. We want to thank you for the time and attention that the Coverage and Analysis Group has devoted to the review of thoracic electrical bioimpedance (TEB) over the past several years. We have engaged CMS in another review of TEB because of the significant benefit we believe TEB testing would provide to Medicare beneficiaries with uncontrolled hypertension. We have carefully reviewed the draft decision memorandum and submit these comments as a supplement to our February 27, 2006 reconsideration request (CAG-00001R2) and to provide the agency with additional information to make your final decision on TEB coverage for Medicare beneficiaries with uncontrolled hypertension.

Summary

The proposed decision memorandum raises numerous important clinical points and questions. In our meeting with CMS on Monday, September 18, 2006, and in this comment letter, we have provided CMS with additional clinical information in response to these questions. The revised coverage request responds directly to issues raised by CMS and provides clear criteria and guidance on when TEB would be reasonable and necessary for Medicare beneficiaries with uncontrolled hypertension.

Major CMS Questions

The draft decision memorandum raised many questions and asked for answers. The CONTROL manuscript content was based on what the journal reviewers required, was limited by space constraints, and could not answer questions that were not yet asked. Therefore, in this comment letter, we seek to clarify the published data, report previously-available-but-unpublished data, and provide new analyses in response to CMS questions.

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The fundamental premise of the two available randomized controlled trials (RCTs), Mayo Clinic and CONTROL, was that physicians would treat hypertension better with TEB measurements than they would without TEB measurements. These two trials were conducted in accordance with the general methodological principles that CMS has previously outlined. Additionally, the CONTROL trial was designed in large part to address the previous methodological and reporting concerns that CMS noted with the Mayo Clinic trial. In both trials, patients were randomized and therefore assigned to each treatment arm without bias. The baseline characteristics in both arms of the studies were equivalent. Physicians received the same number of visits, and the only difference in the intervention arm of both trials was the provision of TEB data. The endpoints in the trials were measured similarly and with standard methods to prevent bias. Therefore, it can be concluded that the provision of TEB data to physicians resulted in improved BP control in these trials. While CMS has concluded that the evidence is not sufficient for the patient population we originally requested, we now ask you to consider the existing and new evidence in relation to a more narrowly defined population.

In the attached appendix, we have grouped our response to the CMS questions into the following eight categories:

1. Are more details on the study methods available, and were the study methods appropriate?
2. Did enrolled patients receive sufficient prior treatment to control BP?
3. Were improvements in TEB parameters associated with reduced BP?
4. Did the provision of TEB lead to adherence to the hemodynamic treatment strategy?
5. Did adherence to the hemodynamic treatment strategy lead to improved TEB parameters and BP?
6. Can improvement in BP control be attributed to the provision of TEB?
7. Is a three-month duration long enough to determine if TEB has clinical utility?
8. Is the evidence generalizable to the Medicare population and what would the expected benefit of using TEB be?

<u>Revised Coverage Request</u>

As discussed above, we respectfully request that CMS consider coverage of TEB for a more narrowly-defined subgroup of Medicare beneficiaries with uncontrolled hypertension. On February 27, 2006, CardioDynamics requested the following coverage language that was based on the inclusion criteria in both the Mayo Clinic and CONTROL trials:

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

During our September 18, 2006 meeting, some general language for revised coverage was presented. In response, CMS directed us to request more specific revised coverage language. Based on the CMS questions and concerns that we have noted, as well as the new evidence we have provided in response to the CMS questions and comments, we respectfully request removal of carrier discretion and provision of national coverage with the following revised coverage language:

TEB is covered for the following subgroup of patients with hypertension:

1. Hypertensive patients who are not at goal BP on three or more antihypertensive drugs.

2. High-risk hypertensive patients who are not at goal BP on two or more antihypertensive drugs. High-risk patients are defined by JNC guidelines and include patients with: a. Diabetes mellitus; b. Chronic kidney disease, defined as GFR <60ml/min or albuminuria (>300 mg/d or 200 mg albumin per gram of creatnine).

Conditions
Prior to receiving a TEB test for hypertension, the patient must have been diagnosed and treated for hypertension a period of at least six months.

Frequency Limitation
TEB testing for hypertension as a covered indication is limited to a maximum of four tests per patient in a 12 month period. If a patient has received a previous TEB test for hypertension, an additional TEB test for hypertension cannot be performed for at least 30 days.

Noncoverage
TEB for hypertension is not covered: a) as a screening test; b) for any patient already at goal BP; c) for any patient not at goal BP on only one antihypertensive drug.

We would like to work with CMS in the future to address the other questions that were raised in the proposed decision memorandum. All of CMS' points are interesting questions for future research.

We appreciate your consideration of this request. We look forward to working with you on the final decision memorandum to provide appropriate Medicare beneficiary access to TEB for the treatment of uncontrolled hypertension.

Sincerely,

Neil Treister, MD, FACC
Medical Director

Appendix: Response to CMS Questions with New Evidence

1. Are more details on the study methods available, and were the study methods appropriate?

1a. Patient selection

Patients were enrolled from eleven primary care physician offices. Patients were treated by their primary care physician for hypertension before being screened for participation in the CONTROL trial.

1b. Exclusion criteria for abnormal lab values

The specific values of the exclusion criteria for abnormal lab findings were as follows:

- Hematology: hemoglobin <10g/dL; WBC <2000/mL; platelets< 100,000/mL
- Blood chemistries: ALT and/or AST >2.5x upper limit of normal; creatinine >3.0mg/dL; potassium <3.3mEq/dL; Hemoglobin A1c > 10%

1c. Randomization

A total of 184 patients were randomized in a 3:2 ratio (107 standard arm, 77 hemodynamic arm). The greater number of patients in the standard arm offset the expected treatment heterogeneity (i.e. could choose any drug, for any reason) in the standard arm. Additionally, in the previous reconsideration process in 2001-2003, CMS offered informal comments that questioned whether the Mayo Clinic trial results in the specialist care arm truly reflected specialist care results, or whether they could be due to chance. The larger number of patients in the standard arm of CONTROL was also done to increase the confidence that the standard arm results would reflect primary care results and would not be due to chance. This meant that significantly more patients were enrolled than would have been required in trial with a 1:1 ratio. Randomization was stratified by site with block randomization through a central telephone service.

1d. Differences in treatment strategy vs. Mayo Clinic trial algorithm

The CONTROL trial used a *suggested* hemodynamic treatment strategy compared to a *required* algorithm in the Mayo Clinic trial. This meant that the physicians were encouraged but not required to use the TEB data. This approach simulated actual clinical application of TEB and removed a potential variable of a mandated approach, which was a previous CMS criticism of the Mayo Clinic trial.

The suggested medication choices based on hemodynamic data were very similar to the Mayo Clinic algorithm except for the use of thoracic fluid content (TFC) with diuretics. Because diuretics are suggested as first-line therapy in JNC guidelines, we did not want to suggest that TFC needed to be used to determine whether diuretics should be initiated. So instead, the CONTROL hemodynamic treatment strategy suggested using visit-to-visit TFC changes as indicator of diuretic effectiveness. This is in contrast to the Mayo Clinic's use of TFC as absolute indicator for intensification of diuretics. Since most of the patients in the Mayo Clinic trial were already on diuretics at baseline, it represented a different clinical scenario than the patients in CONTROL, many of whom were not on diuretics at baseline. In addition, the supine measurement of TFC was used to compare to orthostatic TFC measured in the Mayo Clinic trial.

While a single measurement of orthostatic TFC is associated with high intravascular volume, in the CONTROL trial, we felt that *changes* in supine TFC were a more appropriate measure to track volume *changes*.

1e. Use of hemodynamic treatment strategy

Each investigator treated patients in both arms. Physicians were required to view TEB data each visit in the hemodynamic arm. The high, normal, and low values were printed on each report. A normal cardiac index (CI) was defined as 2.5 to 4.2 $l/min/m^2$, so values below 2.5 were considered low and values above 4.2 were considered high. A normal systemic vascular resistance index (SVRI) was 1680 to 2580 dyne sec $m^2 cm^{-5}$, so values below 1680 were considered low and values above 2580 were considered high. Both the CI and SVRI values were displayed, along with a bar graph indicating the patient's values in relation to the normal range. If a "high" SVRI value of >2,580 was present, the bar graph displayed the value in the "high" range. Depending on the CI and SVRI values, the hemodynamic treatment strategy suggested four different medication changes. In contrast to the absolute values of CI and SVRI that were used to suggest treatments, the hemodynamic treatment strategy for thoracic fluid content (TFC) was based on TFC response to the administration of diuretic intensification. If TFC did not decrease 1.0 /kOhm in response to diuretic intensification, it was not considered to be "reduced" and further diuretic intensification was recommended.

1f. Early terminations

There were 20 patients who were enrolled but not included in analysis. These included 18 patients (11 standard, 7 hemodynamic) who had systolic BP <140 mm Hg and diastolic BP<90 mm Hg at screening (i.e. their BP was already controlled). This occurred because some investigators initially thought BP inclusion criteria applied to *post-washout visit* and not the *screening visit*. When this was discovered during routine study monitoring, the principal investigators decided that it was not appropriate to evaluate these patients with already-controlled BP because they represented a clinically different population than patients who did not have their BP under control. Therefore, all patients who were discovered to have not met the screening BP criteria were terminated from the study at the same time, regardless of how many visits they had completed. Two patients moved away (1 standard, 1 hemodynamic) during the study and did not complete the full follow-up period.

Table 1f. Screening visit values in patients who were excluded
Hemodynamic arm (N=8)

Patient #	**Screening systolic BP (mm Hg)**	**Screening diastolic BP (mm Hg)**
1002	133	84
1020	136	83
1023	129	73
1028	146	86
2044	121	72
2047	128	89
2070	134	75
3085	124	78

Standard arm (N=12)

Patient #	Screening systolic BP (mm Hg)	Screening diastolic BP (mm Hg)
1001	138	66
1014	127	78
1019	122	73
1033	135	80
2045	128	63
3087	124	63
3096	124	81
3103	107	68
3104	124	80
3109	126	84
4125	111	67
4138	148	76

Patients #4138 and #1028 had systolic BP>140 and therefore met BP entry criteria, but moved away during the study. Of the five scheduled visits in the trial, the 12 early termination patients in the standard arm completed an average of 3.4 visits and the 8 patients in the hemodynamic arm completed an average of 3.4 visits (p=ns).

1g. Results with early terminations included

The CONTROL trial results were not based on an intention-to-treat analysis. We note that the Mayo Clinic trial was also not an intention to treat analysis and CMS did not identify this as limitation in the 2004 decision. However, when the study results were reanalyzed including patients who were terminated early, the results were as follows:

Table 1g. Results with early terminations included

Change from screening to last visit	Standard arm (N=105)	Hemodynamic arm (N=77)	Hemodynamic arm advantage	P value
Systolic BP (mm Hg)	-9±4	-17±18	-8	<0.01
Diastolic BP (mm Hg)	-4±12	-10±11	-6	<0.001

The 8/6 mm Hg greater BP reduction with the early terminations included is essentially no different than the 8/7 mm Hg greater BP reduction with the early terminations not included, as was reported in the CONTROL trial manuscript.

2. Did enrolled patients receive sufficient prior treatment to control BP?

2a. Duration of hypertension

Time since original hypertension diagnosis was available for 162 of the 164 patients in the CONTROL trial. For all 162 patients, the average time since the patient's original hypertension diagnosis was 6.9±7.5 years (Standard arm 7.0±6.4 yrs, hemodynamic arm 6.7±6.4 yrs). The

distribution of time from hypertension diagnosis was as follows: <1 year, 23 (14%); 1 to 3 years, 38 (24%); >3 to 5 years, 25 (15%); >5 to 10 years, 40 (25%); >10 years, 36 (22%). A total of 86% of the patients enrolled in the trial had over one year since their original hypertension diagnosis.

2b. Prior treatment efforts

The patients in CONTROL were on an average of 1.7 antihypertensive medications at baseline. This treatment intensity is significantly greater than the baseline treatment intensity in many large pharmacologic trials. For example, it took three years for the average patient participating in ALLHAT to receive an average of 1.7 antihypertensive medications.[1] We believe this is strong evidence that the patients in CONTROL received greater-than-usual intensity of treatment prior to entry in the trial.

2c. Breakout of baseline medications

Calcium channel blockers (CCBs) and diuretics were not broken out into subclasses at baseline in the CONTROL manuscript.

Table 2c: Detailed CCB and diuretic use at baseline

	Standard Arm %	**Hemodynamic Arm %**	**P value for difference**
CCB, any type	33.7	39.1	Not significant
Dihydropyridine CCB	25.3	29.0	Not significant
Nondihydropyridine CCB	8.4	10.1	Not significant

	Standard Arm %	**Hemodynamic Arm %**	**P value**
Diuretic, any type	31.6	26.1	Not significant
Diuretic, thiazide	28.4	24.6	Not significant
Diuretic, potassium sparing	5.3	5.8	Not significant
Diuretic, loop	3.2	0.0	Not significant

Note: Some patients received more than one type of diuretic so the individual diuretic types do not add to the same number as "diuretic, any type"

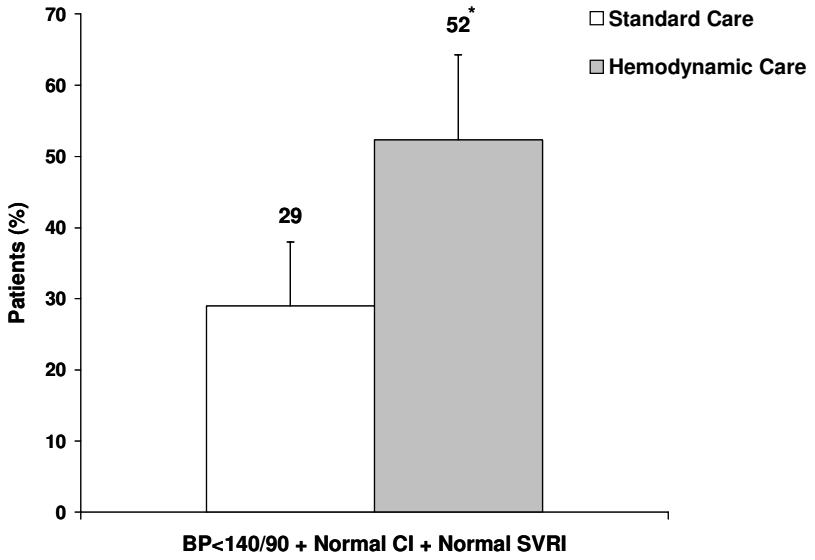
We also wish to clarify the method to report significant differences in medications in the CONTROL manuscript. Differences in medications were only evaluated *between* arms, not to whether differences occurred *within each arm* from the patient's baseline/screening BP values. Since both arms had similar medications at baseline, all medications were washed out, and both arms were expected to receive significant changes in treatment during the study, it was felt that changes in treatment within each arm from baseline levels would not aid in answering the question of whether the medications in the hemodynamic arm were different than the medication in the standard arm.

3. Were improvements in TEB parameters associated with reduced BP?

3a. Normalization of BP and hemodynamics

At the final visit, a total of 36/64 (52%) of patients in the hemodynamic care arm had a normalization of BP (<140/90 mm Hg) and normalization (within normal range) of cardiac index (CI) and systemic vascular resistance index (SVRI), while only 28/95 (29%) did so in the standard arm (p<0.01)

Figure 3a. Concurrent normalization of BP, CI, and SVRI at final visit (*=p<0.01)



3b. Prevalence of abnormal values

Both arms showed reductions in the prevalence of high SVRI from the post-washout to the final visit, but the hemodynamic arm had a significantly lower percentage of patients with high SVRI at the final visit.

Table 3b. Prevalence of abnormal values

	Standard arm	Hemodynamic arm
Visit 2 (post-washout)		
High CI (>4.2 l/min/m^2)	1%	0%
High SVRI (>2580 dyne sec m^2 cm^{-5})	74%	71%
Visit 5 (final visit)		
High CI (>4.2 l/min/m^2)	1%	0%
High SVRI (>2580 dyne sec m^2 cm^{-5})	56%*	35%* †

*= p<0.01 vs. visit 2 within each arm; † = p<0.01 for difference between arms

Based on the physiologic definitions of high CI configured on the TEB device for the CONTROL trial, very few patients were "hyperdynamic". However, if another definition of high CI were used, such as the average CI (3.0 l/min/m^2) of patients deemed "hyperkinetic" in a large study[2] of normotensives and hypertensives, there would be a significant percentage of

patients with "high-normal" CI. At the post-washout visit, 28% of the hemodynamic arm and 34% of the standard arm had a CI>3.0 l/min/m^2. This cut-off for high CI was obviously not evaluated in CONTROL, but may indicate a group of patients with "high-normal" CI who may respond better to CI-reducing treatment in clinical practice.

3c. Regression analysis

We performed regression analysis using analysis of variance (ANOVA) modeling with continuous measures for univariate association of changes in TEB parameters and BP. We pooled all changes in measurements from both arms because treatment arm assignment would not be expected to affect the association of changes in TEB parameters and changes in BP.

Figure 3c. Regression analysis of changes in systolic / diastolic BP to TEB parameters (N=656)

ΔSBP vs.	**F ratio**	**P value**	**Cause-Effect**
ΔCI	1.4	0.24	Not able to be evaluated
ΔSVRI	171.5	<0.001	100 unit drop = 1.3 mm Hg drop in SBP
ΔTFC	4.3	0.03	1 unit drop = 0.5 mm Hg drop in SBP

ΔDBP	**F ratio**	**P value**	**Cause-Effect**
ΔCI	0.9	0.35	Not able to be evaluated
ΔSVRI	150.1	<0.001	100 unit drop = 1.1 mm Hg drop in SBP
ΔTFC	3.6	0.06	1 unit drop = 0.3 mm Hg drop in SBP

The lack of significant association of CI to systolic or diastolic BP does not mean that decreases in CI would not lead to decreased BP. Decreases in CI did not occur as often in the trial due to the therapeutic choices selected in the trial. When only patients who experienced a large CI decrease ($\geq$0.3 l/min/m^2) were evaluated, 41/46 (89%) pts with CI reduction also had reduced systolic BP.

4. Did the provision of TEB lead to adherence to the hemodynamic treatment strategy?

Table 4. Differences in adherence to the suggested hemodynamic treatment strategies

Treatment Strategy	Statistical Difference in Adherence Between Arms?
If SVRI high, add or increase ACEI, ARB, CCB	Yes (78% vs. 67%, $p<0.05$)
If SVRI normal, consider reduce direct vasodilator (i.e. hydralazine)	No (direct vasodilators never used)
If CI high, add or increase BB	No (CI was rarely "high")
If CI low/normal, consider reduced BB	Yes (85% vs. 77%, $p<0.05$)
If diuretic previously prescribed & TFC not decreased, increase diuretic	No (when prescribed, diuretics usually reduced TFC)

There were no differences in 3 strategies, but these conditions were infrequent and do not limit the effectiveness of the strategy in the condition with the highest prevalence, high SVRI. The treatment differences in the presence of high SVRI are a likely primary cause of the lower SVRI and improved BP that was achieved in the hemodynamic arm.

5. Did adherence to the hemodynamic treatment strategy lead to improved TEB parameters and BP?

5a. Effectiveness of adherence to the high SVRI treatment strategy

Visits from both arms were pooled. Adherence was defined as when SVRI was high and ACEI, ARB, or CCB was increased or added. Nonadherence was defined as SVRI was high and ACEI, ARB, or CCB not increased or added. The subsequent effect in the next visit on SVRI, SBP, and DBP are reported.

Table 5a. Effectiveness of Adherence to High SVRI Treatment Strategy

Parameter Change in Next Visit	Did Not Adhere	Adhere
ΔSVRI (dyne sec m^2 cm^{-5})	-178	-434*
ΔSBP (mm Hg)	-5	-15*
ΔDBP (mm Hg)	-4	-9*

*$P<0.01$ for difference between adhere and not adhere

These results demonstrate the regardless of the arm adhering to the strategy, that adherence to the high SVRI treatment strategy results in greater reductions in SVRI, systolic BP, and diastolic BP.

5b. Effectiveness of adherence to the high SVRI treatment strategy by arm

Visits from both arms were examined separately. Adherence was defined as when SVRI was high and ACEI, ARB, or CCB was increased or added. Nonadherence was defined as SVRI was high and ACEI, ARB, or CCB not increased or added. The subsequent effect in the next visit on SVRI, SBP, and DBP are reported.

Table 5b. Effectiveness of Adherence High SVRI Treatment Strategy by Arm

	Hemodynamic arm		**Standard arm**	
Parameter Change in Next Visit	**Did Not Adhere**	**Adhere**	**Did Not Adhere**	**Adhere**
ΔSVRI (dyne sec m^2 cm^{-5})	-269	-430*	-129	-437***
ΔSBP (mm Hg)	-5	-15***	-5	-15***
ΔDBP (mm Hg)	-6	-10**	-4	-8**

*= P=0.17; **=p<0.05; ***=p<0.01 for difference between adhere / not adhere

These data indicate that adherence to high SVRI treatment was similarly effective in both arms.

5c. Effectiveness of four other hemodynamic treatment strategies

The other four hemodynamic treatment strategies did not show statistical differences (p<0.05) in effectiveness of systolic or diastolic BP lowering.

- Strategy: If CI low/normal, decrease BB intensity
  When this strategy was adhered to, CI was preserved (0.0 l/min/m^2 change) in the subsequent visit. When it was not adhered to, CI was reduced (-0.2 l/min/m^2) in the subsequent visit. This represented a statistically significant difference in the change in CI (p<0.05) when the strategy was adhered to, although it did not result in any significantly greater reductions in systolic or diastolic BP.
- Strategy: If SVRI normal, reduce direct vasodilators
  Direct vasodilators (ie hydralazine) never used and therefore could not be reduced in presence of normal SVRI
- Strategy: If cardiac index high, prescribe BB
  CI was almost never "high" as defined by device normal range, so there were no differences.
- Strategy: Increase diuretic if TFC not reduced after diuretic intensification
  Diuretics usually reduced TFC, so condition was infrequent

We do not believe that the lack of differences in these strategies minimizes the significant differences in the high SVRI strategy. While these strategies were prospectively defined, part of what the trial evaluated was the incidence of and adherence to the strategies.

5d. Changes in TFC and BP with diuretic intensification

While the treatment strategy using TFC with diuretics was not significantly different in effectiveness, we sought to determine whether changes in TFC without regard to the treatment strategy could be used to monitor diuretic effectiveness. We pooled visits from both arms and compared visits in which a diuretic was added or increased vs. visits when a diuretic was not added or increased for the effect on TFC, systolic BP, and diastolic BP in the subsequent visit.

Table 5d. Changes in TFC and BP with Diuretic Intensification

Parameter Change in Next Visit	**Diuretic Not Added or Increased**	**Diuretic Added or Increased**
ΔTFC (/kOhm)	-0.1	-1.0*
ΔSBP (mm Hg)	-5	-16**
ΔDBP (mm Hg)	-3	-9**

*=P<0.05, **=p<0.01 for difference between increased/added vs. not increased/added

These data support the notion that diuretic intensification decreases TFC, systolic BP, and diastolic BP more than non-diuretic intensification.

5e. Changes in CI and BP with beta blocker intensification

While the treatment strategy using CI with beta blockers was not significantly different in effectiveness, we sought to determine whether changes in CI without regard to the treatment strategy could be used to monitor beta blocker effectiveness. We pooled visits from both arms and compared visits in which a beta blocker was added or increased vs. visits when a beta blocker was not added or increased for the effect on CI, systolic BP, and diastolic BP in the subsequent visit.

Table 5e. Changes in CI and BP with Beta Blocker Intensification

Parameter Change in Next Visit	**BB Not Added or Increased**	**BB Added or Increased**
ΔCI (l/min/m2)	0.0	-0.2**
ΔSBP (mm Hg)	-7	-11*
ΔDBP (mm Hg)	-4	-9**

***= P=0.23, **=p<0.01 for difference between increased/added vs. not increased/added**

These data may support the notion that beta blocker intensification decreases CI, systolic BP, and diastolic BP more than non-beta blocker intensification.

6. Can the improvements in BP control be attributed to the provision of TEB?

According the Medicare Coverage Advisory Committee, evaluation of diagnostic tests in RCTs is rare.[3] Therefore, the availability of two RCTs using TEB in hypertension should allow a more confident determination of TEB's impact on net health outcomes than diagnostic tests that have not been evaluated in RCTs. The CONTROL trial results followed the general methodological principles that CMS has previously outlined, and the statistical results indicate that the various study endpoints have only a 5 in 100 to 1 in 10,000 probability of being due to chance (if there is truly no difference between treating uncontrolled hypertensive patients with and without TEB).

RCTs are not designed or powered to delineate mechanisms, and neither was the CONTROL trial. While mechanisms can be important to understand how an intervention improves an outcome, they are not required to determine whether an intervention improves an outcome. A variety of questions have been asked related to the mechanism by which the provision of TEB data resulted in improved BP control. Because RCTs are not powered to conclusively identify mechanisms, our mechanistic analyses offer possible but not definitive reasons for the differences in endpoints. In general, we believe that the positive BP outcomes that were achieved with TEB in the two RCTs occurred because TEB data and hemodynamic goals of treatment helped physicians identify and focus on the hemodynamic cause of high BP, which led them to treat patients differently, which led to improvements in BP control. In the Mayo Clinic trial in highly-resistant hypertensive population, a focus on thoracic volumes and systemic vascular resistance appears to have led to greater diuretic dosing and treatment with direct vasodilators. In the study by Smith et al. in a complex-but-less resistant population, a focus on high vascular resistance appears to have led to greater vasodilating agent intensification (ACE inhibitors, angiotensin receptor blockers, calcium channel blockers).

Regardless of the mechanism, the provision of TEB leads to improvement in BP control. Improvement in BP control is accepted as a significant health outcome for Medicare beneficiaries. Therefore, we believe the evidence demonstrates that TEB merits additional coverage to assist physicians in improving BP control.

7. Is a three-month duration long enough to determine if TEB has clinical utility?

Short-term BP response is acceptable for FDA approval of antihypertensive drugs. We also note that the Mayo Clinic trial was of three month duration, and CMS did not list this as limiting factor in its previous reconsideration decision. We believe that BP control at three months is a significant health outcome because immediate BP response is strongly associated with long-term BP control, and BP control at three months would likely prevent future office visits and drug changes. Importantly, the 77% BP control rate with TEB in CONTROL is superior to BP control rates achieved in pharmacologic trials of much longer duration, even though patients in CONTROL were not in control at baseline and were treated more intensely at baseline (1.7 medications) than in many pharmacologic trials. A high control rate is significant because it is likely to lead to fewer office visits and drug changes in an attempt to gain BP control.

8. Is the evidence generalizable to the Medicare population and what would the expected benefit of using TEB be?

8a. Generalizability - age

Results from cardiovascular trials of younger patients are applicable to elderly, and elderly often receive even more benefit. Additionally, JNC 7 does not consider age to be a primary factor in diagnosis and treatment: "*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.*"

The Mayo Clinic trial examined patients with an average age of 65 years and the CONTROL trial examined patients with an average age of 55 years. In CONTROL, subgroup analysis was performed in subjects with age ≥55 years and 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. Patients ≥55 years in the hemodynamic arm (n=33) had greater systolic BP reductions compared to the standard arm (n=51) from baseline (21±17 vs. 11±20 mm Hg, $p<0.05$) and trended greater from post-washout (26±20 vs. 21±19 mm Hg, $p>0.05$). Diastolic BP reductions were also greater in those ≥55 years in the hemodynamic arm from baseline (13±11 vs. 4±12 mm Hg, $p<0.001$) and post-washout (16±11 vs. 10±12 mm Hg, $p<0.05$). In patients ≥55 years, goal BP (<140/90 mm Hg) was achieved more frequently in the hemodynamic arm (76% vs. 53%, $p<0.05$), and the more aggressive BP (<130/85 mm Hg) was also achieved more often (58% vs. 27%, $p<0.01$). Analysis of variance also indicated that age ≥55 years had no effect on study endpoints ($p>0.05$).

8b. Generalizability - comorbidities

We believe that the provision of TEB has been shown to improve BP control in 2 RCTs across the spectrum of comorbidities. The Mayo Clinic trial examined patients with a high percentage of comorbidities, including a third with diabetes. 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 a high percentage of comorbidities but rather the level of comorbidities expected in a community-based population of uncontrolled patients receiving prior treatment for hypertension. Prior to the CONTROL trial, it was unknown whether TEB was as effective in patients with fewer comorbid conditions as it was in patients with more comorbid conditions.

8c. Magnitude of the benefit

Clinical inertia[4] is a major factor preventing the achievement of BP control. Even in randomized trials of long duration, many patients do not achieve BP control at the end of the study. For example, patients in ALLHAT achieved a 66% BP control rate after five years of treatment even though 27% of patients had controlled BP at baseline. That equates to a 39% absolute improvement in BP control after five years. In CONTROL, the hemodynamic arm was able to improve from a 0% BP control rate to 77% BP control rate after only three months.

As CMS is aware, there is a strong need to improve BP control in CMS beneficiaries. The lack of BP control has enormous clinical costs, as well as significant economic costs.[5] In a 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.[6] In the Mayo Clinic and CONTROL trials, TEB-guided management resulted in significant advantages in BP reduction compared to a standard care approach. Therefore, TEB-guided therapy is likely to have significant benefit on the health of the Medicare population.

We understand that CMS cannot formally consider cost-effectiveness as a factor of whether or not to cover TEB. However, we believe it is important background information. In a paper recently accepted for publication in the October/November 2006 timeframe,[7] the authors concluded that the use of TEB (referred to as impedance cardiography, ICG) in uncontrolled hypertension results in a cost-effective utilization of health care resources. An abstract summary of the paper is as follows:

To evaluate the short- and long-term cost-effectiveness of impedance cardiography (ICG) testing in uncontrolled hypertensives, we analyzed the CONTROL trial results that compared the BP lowering effects of Standard vs. ICG care. Short-term cost-effectiveness was evaluated as the incremental cost per incremental mm Hg reduced during the trial. Long-term cost-effectiveness was evaluated as incremental cost per quality-adjusted life-year (QALY) gained over ten years. ICG care short-term cost-effectiveness was $20 per incremental mm Hg reduced for systolic BP (vs. Standard care $36 per mm Hg reduced) and $23 per incremental mm Hg reduced for diastolic BP (vs. Standard care $79 per mm Hg reduced). In the long-term, ICG resulted in a $476 cost savings and 0.109 QALYs gained per patient (-$4,371 per QALY gained, sensitivity analysis -$8,764 to $13,163). The use of ICG testing to reduce BP in uncontrolled hypertensive patients is cost-effective from both a short- and long-term perspective.

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