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SUMMARY

Abbott's MitraClip is approved and used in Europe to treat mitral regurgitation, but the outlook at the FDA remains cloudy. The FDA's Circulatory System Devices Advisory Committee did not send the FDA a definitive message about approvability, voting 5-3 that the benefits outweigh the risks. The panel voted unanimously that it is safe, but split the other direction (4-5) on efficacy.

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FDA Advisory Committee Recommends Approval of Abbott Vascular's MitraClip

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The FDA's Circulatory System Devices Advisory Committee delivered a mixed verdict on Abbott Vascular's MitraClip Clip Delivery System (CDS), voting 5-3 that the benefits outweigh the risks, a margin the FDA generally considers neutral. Abbott is seeking approval for the reduction of mitral regurgitation in patients with significant symptomatic mitral regurgitation (MR ≥3+) who are at too high risk for open mitral valve surgery.

The issue wasn't safety. The panel voted unanimously (8-0) that MitraClip is safe. The concern was efficacy, and the panel was split on that, with 4 votes that it is effective and 5 that it isn't.

During a discussion of non-voting questions, the panel said:

- The two high-risk registries EVEREST-II HRR and REALISM HR shouldn't be pooled.
- The utility of the STS score as a comparator to MitraClip is problematic, but if it is used, it should be the repair score not the replacement score.
- STS score should only be part of the patient selection process for MitraClip.
- There was little enthusiasm for using the Duke database as a comparator for MitraClip. Panel members thought a randomized trial would be better.
- It was not opposed to the idea of using a retrospective subset analysis to support an indication for use, but there was concern that the data in the MitraClip retrospective analyses were not strong enough.
- It agreed with the FDA's conclusions that there are a lot of gaps in the MitraClip data, but that there probably is "something here of value," though it is "hard to put a finger on what it is that is beneficial for patients or which patients will benefit."
- The proposed indication for use probably only needs minor tweaking, adding references about medical therapy, anatomic appropriateness, appropriate decision-makers, and when the risk is too high. However, there should be a statement that the device should only be used in patients with at least a 1-year life expectancy.
- The panel did not find clear evidence of safety and efficacy, but, again, a "sense that there is something lurking there."
- The label needs a "little bit more flushing out."
- For a post-approval study, freedom from mitral valve surgery is not an acceptable primary endpoint. A functional endpoint was preferred.

Two panel members, including the acting chair, had to be granted waivers to participate in the panel. Jeffrey Borer, MD, temporary panel chair, a cardiovascular surgeon from State University of New York Downstate Medical Center, and president of the Heart Valve Society of America, was not involved with the MitraClip studies but is at an affiliated institution that participated in the studies. Panel member George Vetrovec, MD, an interventional cardiologist from Virginia Commonwealth University, has investments – valued between $25,000 and $50,000 – in Abbott Vascular and two competitors working on similar devices.

The 13-member panel had 10 voting members: 3 interventional cardiologists, 2 cardiac surgeons, 4 cardiothoracic surgeons, 1 cardiologist, and 3 non-voting members – a patient representative, a consumer representative, and an industry representative. However, one panel member left early without voting, and the panel chair only voted to break a tie.

FDA reviewers had a strong view on the device, strongly doubting its safety and effectiveness. They said that the currently enrolling COAPT and European trials are well designed and recommended that MitraClip continue to be used as an investigational device until those results are available, "Premarket approval is not appropriate at this time as major questions of safety and effectiveness, as well as the overall risk:benefit profile…remain unanswered." Even some panelists who supported approval noted that it should be a very limited approval. COAPT has not been underway long, so the results won't be available soon.

After the panel, in a ***CRTonline*** survey, 62.5% of respondents said MitraClip should not be approved in the U.S. until after the ongoing COAPT trial is completed, and 37.5% said it should be marketed now.

BACKGROUND

MitraClip was first manufactured by Evalve, which Abbott Vascular bought in September 2009. The FDA conditionally approved the EVEREST-II trial in November 2004. EVEREST-II was designed to evaluate the safety and effectiveness of the device vs. mitral valve surgery in the treatment of moderate-to-severe (3+) or severe (4+) chronic mitral regurgitation (MR). At the time, a single-arm registry was conditionally approved for high-risk, non-operative patients, but the FDA was concerned that the registry, without a successful rigorous pivotal trial, could not solely support premarket approval.

The REALISM continued access protocol (CAP) was approved in November 2008, and it used the same inclusion/exclusion criteria as EVEREST-II. So far, 545 patients have completed one year of follow-up in the study, and the CAP includes an extension of the High Risk Registry (HRR) called REALISM High Risk.

THE FDA PERSPECTIVE

Briefing Documents

FDA reviewers, in briefing documents for the panel, gave MitraClip a thumbs-down, saying that neither safety nor effectiveness was shown. They recommended against approval of the device. The FDA reviewers concluded:

- The EVEREST-II trial did not demonstrate an appropriate risk:benefit profile when compared to standard mitral valve surgery in a selected mitral valve patient population.
- For a variety of reasons, the EVEREST-II HRR single-arm registry data are not easily interpretable.
- EVEREST-II has fundamental study design and conduct problems, and acute procedural success was not achieved in 23% of MitraClip patients.
- Clinically meaningful safety was not demonstrated, and the safety profile of the device vs. optimal medical management is unknown.
- The definition of "inoperability" and "high risk" varied widely, and the FDA has much different ideas of those terms than the company.
- REALISM-HR is a continued access protocol cohort that was not intended to be used as a pivotal data set and is difficult to interpret.
- The integrated high surgical risk cohort, developed by pooling two registry datasets in a post hoc manner, has major design limitations and is basically not usable.
- The Duke Propensity Score Analysis was a retrospective, subset analysis with results that are difficult to interpret and where the matched cohorts do not represent any well-defined population.
- There were many other shortcomings regarding inclusion/exclusion criteria, lack of appropriate surgeon involvement in assessment of surgical risk, subjectivity, double-counting STS risk factors for determining high risk, and inappropriate use of STS scores for mitral valve replacement instead of repair.

The FDA reviewers said that the EVEREST-II results were problematic because they combined "all etiologies of mitral

regurgitation in this moderately sized study." They concluded, "It is difficult to interpret in the setting of a failed pivotal randomized trial."

The FDA told the company prior to the onset of the trial that the study should be powered separately for functional and degenerative etiologies. Additionally, the FDA said that while a major premise of the trial was that there was no downside and that patients could get an operation if the valve was unsuccessful, "It is unclear if acute injury occurred to the native valve from placement or attempt to place the device. In other cases, the valve was injured because of intense fibrosis, which affects the ability to remove the clips without injuring the underlying valve or chordae, thus preventing valve repair or making repair much more difficult. Therefore, it is difficult to determine whether the valve was injured during the MitraClip procedure or during the attempt to surgically remove the clips; the total rate of valve injury (including holes in one or both leaflets or torn chordae)…was 26% of [randomized patients] who went on to operation and 39% of roll-in patients. In addition, acute cardiac or great vessel injury from the procedure led to the need for emergency operations in three patients."

The FDA reviewers also suggested that some patients who should have been candidates for repair underwent surgery. In addition, acute procedural success was shown in only 77% of the MitraClip patients, showing the need for additional surgery after failure with the device.

The reviewers said the company came up with the proposed indication after doing a post hoc analysis of the EVEREST-II study, and it was proposed to the FDA *after* the FDA said it was concerned about the evidence of safety and effectiveness. The reviewers wrote, "FDA believes the evidence necessary for determination of safety and effectiveness sufficient for approval of a first-of-a-kind device should not be based on a retrospective evaluation of registry data reconfigured to support an indication for use and population for use developed post hoc… [There] is not enough evidence to show safety and efficacy for a first-of-a-kind device."

The FDA said it has been working with Abbott Vascular on a new trial and in February 2012 ***conditionally*** approved the COAPT trial to evaluate the device in the treatment of symptomatic (NYHA Class II, III, or IV) functional MR (≥3+) in patients with comorbidities that preclude surgery. FDA reviewers said the Agency believes this trial is "a reasonable pivotal trial and that the prospective analyses of it may support premarket approval of the device for patients at extremely high surgical risk."

High-Risk Registry (HRR)

FDA reviewers, in the briefing documents, said that the concerns about the HRR "are very significant…Using the HRR data alone, FDA is unable to determine that reasonable assurance of safety and effectiveness exists for MitraClip CDS for the proposed indication in the designated target population."

They said that the key to understanding the assessment of risk is the use of the STS risk calculator; the STS database is the world's largest cardiac surgical database. However, reliance on the STS mortality risk calculator for mitral valve replacement "results in several significant problems which affect the ability" to assess the data in a single-arm study. One problem is that a calculated STS score used for putting a patient into a high-risk cohort will be different if the cohort is mitral valve repair or mitral valve replacement.

The FDA reviewers concluded that the inclusion and exclusion criteria did not uniformly specify a clinically "high-risk" group, and they gave examples of patients included in the "high risk" for surgery group who did not belong there. They also mentioned the possibility of bias due to the highly experienced interventionalists at select institutions and said that the mortality comparison to the STS database was made to the predicted risk of mortality for mitral valve replacement instead of repair, saying, "Although this was the only calculation available to the sponsor at the time the majority of the patients were enrolled, it is an inappropriate comparator given the mitral valve anatomic inclusion/exclusion criteria which would predict a high (>90%) likelihood of repair in the overwhelming majority of patients in the hands of an appropriately experienced surgeon …For any set of STS risk factors, the predicted mortality for mitral valve replacement results in a calculated value of STS score approximately 1.5 to 2.5 times higher than that calculated for mitral valve repair, resulting in a gross overstatement of the true surgical risk. Misuse of an inflated STS score as a comparator cannot be justified even if no misuse was intended …FDA believes that the term 'high risk' merely reflects the relatively higher operative risk compared to the randomized trial group and reflects neither 'too high risk for surgery' nor 'inoperability'…It is difficult to accurately define the patients included in the HRR group as 'high risk,' and one cannot assume that these patients were inoperable."

REALISM-HR

FDA reviewers said that this continued access protocol study was not intended to be used as a pivotal dataset "and is difficult to interpret." However, the study has identical problems as the high-risk registry, and they said that it can't be used to adequately assess safety and efficacy.

Outside the U.S. (OUS) experience

FDA reviewers said that the European experience used a highly select group of patients with unknown selection processes and, therefore, gives little useful information.

Efficacy

FDA reviewers said that, using the company's definition of acute procedural success, the rate at discharge would be 85%. However, using its own definition, the rate would be 46%. They said it was "extremely difficult to assess whether device therapy resulted in any clinically meaningful improvement in patient outcomes."

The FDA said that the Agency:

- Repeatedly told Abbott Vascular that the high-risk registry would not stand alone for approval but could be used as addiitional data in support of approval based on the EVEREST-II data.
- Repeatedly told the company that the proposed analysis comparing safety to surgery and effectiveness to medical treatment was inappropriate because of bias in favor of the treatment group.
- Disagreed with the company on the makeup of its post hoc concurrent control group.

The FDA asked Abbott Vascular to provide 24-month follow-up data for the primary efficacy endpoint, using the FDA-recommended definition of freedom from death, reintervention, or surgery, and >1+ MR, "Mid-term follow-up showed worse results when more than mild (>1+) residual mitral regurgitation is seen on the post-repair echocardiogram, and water testing of the operative repair reveals residual mitral regurgitation (less than perfect)…The rehospitalization rate was higher in these patients with suboptimal reconstruction." The FDA reviewers said they believe that the appropriate population for efficacy analysis is the modified intent-to-treat population (mITT).

Safety

The FDA reviewers said, "After evaluation of each component of the composite, FDA does not believe that this percutaneous device has a superior safety profile over time to that of open operation in the population studied."

They wrote, "Using the surgeon's subjective estimate of predicted surgical risk to comparator…leads to the conclusion that the primary safety endpoint for the HRR registry was met. However, the opposite conclusion (Primary Safety Endpoint ***not*** met) would be reached using the mean of the objectively derived STS score of 14.2% for mitral valve replacement as the comparator…Using the more appropriate comparator for mitral valve repair would also have resulted in failure to meet the endpoint as well and would likely result in a mean STS score very close to the observed mortality rate for device use."

FDA Presentation to the Panel

Fernando Aguel, MSE, a biomedical engineer and lead reviewer in the FDA's Division of Cardiovascular Devices, Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH), described the MitraClip and its regulatory history and gave the FDA's summary highlights, including the conclusion that the EVEREST-II randomized trial did not show appropriate risk:benefit when compared to mitral valve surgery in a selected mitral valve population.

John Laschinger, MD, a cardiac surgeon and a medical reviewer in the FDA's Division of Cardiovascular Devices, CDRH, told the panel that the FDA's problems with the MitraClip include:

- Registries and post hoc data are hypothesis-generating only.
- Major unanswered questions include appropriate target population, safety and effectiveness, and risk:benefit profile.
- Premarket approval (PMA) is not recommended at this time because the data do not show reasonable assurance of safety and effectiveness and the numerous problems identified.
- Additional evidence for approval includes randomized trials COAPT and RESHAPE-HF.

MitraClip Components of Failure of Clinical Success (MR ≤1+) at 12 and 24 Months

Component of failure	12 months			24 months		
	MitraClip n=178	Control n=80	Difference	MitraClip n=178	Control n=80	Difference
Death	4.6%	6.8%	-2.2%	8.9%	11.4%	-2.6%
Mitral valve surgery for MV dysfunction after implant (device group) or reoperation of the MV for MV dysfunction (control)	21.1%	2.7%	18.4%	22.5%	4.3%	18.2%
MR >1+	49.7%	21.6%	28.1%	52.7%	17.1%	35.5%
Total	75.4%	31.1%	44.3%	84.0%	32.9%	51.2%

Giving the FDA's clinical overview, Dr. Laschinger discussed the seemingly endless problems with the trial hypotheses, definitions, and conduct. He told the panel that Abbott agreed that in the EVEREST-II randomized trial, MitraClip did not achieve clinical success of MR ≤1+ as completely as surgery, "It was determined that the benefit-to-risk profile of MitraClip did not warrant diverting surgical candidates away from the proven surgical therapy."

He said that the considerations included:

- The assumption by the company that clipable equals repairable.
- Heterogeneity
  - Symptomatic and asymptomatic patients and mixed etiologies.
  - Led to difficulties in data interpretation and protocol violations (exclusion criteria) in nearly 50% of patients.
- Definitions and analysis populations
  - The FDA and Abbott disagreed on definitions of acute procedural success, non-acute procedural success, and clinical success.
  - The FDA believes that MR 1+ at discharge is successful implantation, while sponsor called MR 2+ or less at discharge.
  - FDA's definition of clinical success is acute procedural success (resulting MR 1+ or less at discharge plus freedom from death, mitral valve reintervention, or surgery, and MR >1+ at 12 months; Abbott's definition is acute procedural success (MR 2+ or less at discharge) plus freedom from death, mitral valve reintervention, or surgery, and MR 2+ or more at 12 months.
- Safety driven by transfusion
- Effectiveness lacking (primary effectiveness endpoint = clinical success at 12 months). The FDA disagreed with the margin of reduced effectiveness (31%), with the analysis population chosen, and with the definitions used for clinical success and acute procedural success – MR reduction = residual MR and threshold of MR ≤2+ vs. MR ≤1+.

Dr. Laschinger said that using the FDA's preferred effectiveness endpoint and components of failure, the primary endpoint was not met, "So how did we end up here?" He described how the company revised the indications for use, then criticized the revisions and told the panel that the company then decided to use two registries, "None was designed to be used as a pivotal dataset…for use in a clinical trial…The registries were designed to complement the randomized study only…Device approval requires the same level of valid scientific evidence that would be required for any other device."

High-risk patients fall into one of two pathways: those with an STS score of 12% or greater, and those with an STS score of less than 12% but with disease-related comorbidities including functional mitral regurgitation, age >75, ejection fraction (EF) <40%, two or more prior surgeries, and three or more of select STS risk factors, including porcelain aorta, hepatic cirrhosis, etc.

Dr. Laschinger delineated problems with the use of STS scores for single-arm registries as the pivotal dataset. Problems included: inappropriate weighting of disease-related risk factors, different versions of risk calculator used for each registry, calculator for mitral valve replacement vs. mitral valve repair.

Dr. Laschinger explained that, at the time of EVEREST enrollment, calculated STS risk models were not available to the company. However, REALISM started enrollment using the latest version, using the calculator for mitral valve replacement, "Using the latest calculator version…both registries are comprised of two distinct and dissimilar samples…Close to 60% entered into the high-risk registry did not belong in the population of patients at too high risk for surgery."

He also explained the mortality differences between mitral valve repair and replacement, "These differences in STS scores and other anomalies make it impossible to identify a suitable target population…Over half can be considered inoperable… Most registry patients would likely be considered candidates at experienced centers." He said, "The use of the STS score as a primary safety comparator grossly overestimates the procedural risk."

Looking at procedural 30-day mortality in the high-risk registry, the STS score/MV replacement predicted 14.2%. However, the recalculated STS mean was 10.5%. He said, "The conclusion would be that the primary safety endpoint was not met." He basically said that the STS score should not be used as a primary safety comparator. Appropriate comparators are optimal medical therapy or another approved device.

As for mitral regurgitation severity at discharge, without knowing the quality of medical care of these patients and the inability to compare to patients well-treated by physicians, this is just for hypothesis generation and is unsuitable for evaluating effectiveness.

Dr. Laschinger said the REALISM high-risk registry is in trouble because it used the same STS scores for entry and for

comparators, "The sponsor's attempt to use data from EVEREST-II HRR and REALISM-HR is difficult to interpret [for many reasons, including] lack of comparators for safety and effectiveness."

The integrated high surgical risk cohort was made by pooling datasets, and Dr. Laschinger said, "The FDA does not believe the post hoc decision to pool datasets…does not enhance data …and only introduces confounders." Still lacking a comparator for effectiveness, the sponsor did more analyses of the data and concluded, "These analyses demonstrated mortality at one year in patients treated with MitraClip was comparable to the natural history of the disease." Dr. Laschinger told the panel that Abbott basically compared the same data to the same data over and over, but in no valid, scientific way.

Problems with pooling include:

- Post hoc analyses of pooled datasets retain all of the individual shortcomings of the individual datasets.
- Pooling does not enhance the utility and scientific value of uncontrolled single-arm registries with no comparators.
- Inappropriate pooling introduces additional confounders.
- 30-day procedural mortality (REALISM-HR cohort 4.0% vs. HRR cohort 7.7%).
- Clinical events committee (CEC)-adjudicated 30-day major adverse events.

Dr. Laschinger said that, excluding transfusions, the total 30-day major adverse event rate wasn't substantially different from the surgical risk cohort, "Close to 25% of patients have died at one year…Seven patients had surgery in the first year of this high-risk registry, and 13 patients total had surgery." He said that the same deficiencies exist to determine left ventricular function at baseline and 12 months.

The quality of life and NYHA function Class changes were also difficult to assess due to the lack of comparators and other problems. Regarding the effectiveness analysis, the integrated high surgical risk cohort, he said, "The device therapy…may have significant long-term implications."

Regarding the EVEREST-II trials, he concluded:

- It did not demonstrate an appropriate risk:benefit profile vs. standard mitral valve surgery in a selected patient population.
- EVEREST-II HRR and REALISM high-risk single-arm registry data were not designed to provide pivotal data sets and are not easily interpretable.
- Pooling fails to enhance the utility and scientific value of uncontrolled single-arm registry data with no comparators.
- Post hoc analyses of pooled datasets of the EVEREST HRR and REALISM-HR retain all of the individual shortcomings of the individual datasets.
- Pooling introduced additional confounders.

Statistical summary

Vandana Mukhi, PhD, a statistician in the FDA's Division of Biostatistics, Office of Surveillance and Biometrics, CDRH, gave the statistical summary. She said the pooling of the two datasets "was not adequately pre-specified…Also, there was a lack of adequate pre-specification in assembling a set of patients and conducting statistical analyses. Pre-post comparison with a control group also has problems because one cannot be sure that any pre-post differences are causally related to the intervention.

Dr. Mukhi said that the comparator drawn from the Duke database was not approved by the FDA but that the Duke Statistical Analysis Plans (SAP) were submitted in October 2012 with all of the other analysis results. She said there are many problems with the statistical analysis plans. For one thing, propensity score methodology should be implemented in the design phase in order to conceal outcome, all data should be available in order to build the model, and propensity score modeling must be conducted in order to achieve balance. Limitations of propensity score methodology are that it is not always possible to achieve balance; if adequate balance is not obtained, then the model fails. It also cannot be used to balance unobserved baseline covariates.

Dr. Mukhi said Duke may have included all important covariates in the propensity score model, adding confounding/bias. Some of the observed baseline covariates not included in the final logistic regression model that was used to derive propensity scores were: body mass index (BMI), history of smoking, hypertension, previous cardiac intervention, history of atrial fibrillation (AFib), STS score, left ventricular internal dimensions (LVIDs), and mitral regurgitation etiology. As far as matching, the makeup of matched subsets "is unknown and does not seem to represent any well-defined population."

She summarized:

- Integrated high-risk cohort (n=351) results were obtained by post hoc consolidating data from HRR and REALISM-HR and conducting statistical analysis.
- Duke Propensity Score Analysis was a retrospective subset analysis:
  - If propensity score model is influenced by outcomes data, then serious bias may be introduced.

- Confounding/bias due to baseline covariates not included in the model may not be reduced.

Duke propensity score analysis

Ileana Pina, MD, a cardiologist and heart transplant and heart failure specialist in the FDA's Division of Cardiovascular Devices, CDRH, called the Duke propensity score analysis "problematic" and said that it was:

- Difficult to interpret:
  - Duke database resulted in a problematic control.
  - Duke propensity score analysis results in two patient MitraClip subsets (matched and unmatched) which are difficult to understand and not well defined. The two groups are not comparable.
- Interesting to elicit an exploratory hypothesis rather than accept as confirmatory.
- There is no information as to how the patients were not operated on/defined as high risk.
- The matched cohorts do not represent any well-defined population.
  - Concerns with the creation of matching cohorts.
  - Difficult to interpret results.
  - Post hoc nature of the analyses.
  - Cohort not well defined because of different times of enrollment and no information as to why the Duke cohort did not have surgery.
  - Unmatched group is sicker and has higher mortality than the matched.

Dr. Pina concluded, "This analysis should be viewed with extreme caution and should be considered hypothesis-generating…Results are difficult to interpret, and the matched cohorts do not represent any well-defined population."

Post-approval study proposals

George Aggrey, MD, MPH, a medical officer in the FDA's Division of Epidemiology, Office of Surveillance and Biometrics, CDRH, discussed the company's post-approval study proposals. He said that concerns include:

- Long-term efficacy of MitraClip in patients with mitral regurgitation of different etiology or levels of surgical risk factors has not been established for the intended population.
- As a first-of-kind device, its performance should be assessed for rare/unexpected adverse events.
- Understanding of longer-term safety and effectiveness from implant to death or surgery (if considered) for the approved indication is necessary.
- Abbott's proposed surrogate endpoint, freedom from mitral valve surgery at 12 months, may not be appropriate.

THE ABBOTT VASCULAR PERSPECTIVE

Chuck Simonton, MD, chief medical officer and divisional vice president for Abbott Vascular, said there are 100,000 patients in the U.S. with significant mitral regurgitation who are at a high risk for surgery. He said 30% of those patients have anatomies suitable for treatment with the MitraClip and predicted that 2,000-3,000 patients a year would receive the device. He told the panel that the MitraClip meets a clear and important unmet need for patients with severe mitral regurgitation at too high risk for surgery and argued that the data support reasonable assurance of safety and effectiveness.

Dr. Simonton addressed the FDA's key findings, saying that:

- Clinical evidence meets FDA guidance for novel technology.
- The EVEREST-II High-Risk Registry meets guidelines.
- The benefits of the MitraClip outweigh the risks. He noted that some patients were willing to accept a higher risk in exchange for a small benefit, often with improvements in quality of life.
- The device has been used in 8,000 predominantly high-risk patients worldwide, with 900 enrolled in U.S. trials.

Addressing the FDA's concerns

Patrick McCarthy, MD, director of Bluhm Cardiovascular Institute and chief of cardiac surgery at Northwestern University School of Medicine, spoke on behalf of Abbott, telling the panel that some patients are too sick for conventional surgery. He described the "mitral regurgitation begets mitral regurgitation cycle," saying, "Patients eventually go into a downward spiral of heart failure symptoms. They have a poor quality of life and, untreated, mitral regurgitation progresses to an uncomfortable death…Breaking this cycle will improve hemodynamics, reverse modeling, and make these patients feel better. There is no medical therapy directed specifically at reducing mitral regurgitation…Many patients have serious comorbidities…We should also consider the impact to a patient's quality of life after a surgical procedure in these very sick patients."

Dr. McCarthy talked about the STS database, saying that "5.6% of STS database patients have an STS score of 12% or greater.

The surgical decision to replace the valve in high-risk patients is to avoid the potential for a failed repair and reoperation. In these patients, there are no differences in survival between repair and replacement."

He then addressed the FDA's argument that inclusion/exclusion criteria did not adequately define a high-risk patient population, saying that the use of risk factors not captured by STS risk score calculator is an accepted methodology. Dr. McCarthy argued that all 351 patients in the studies met protocol entry criteria for high surgical risk: 43% of patients had an STS score of ≥12%; 42% had an STS score <12% but with at least one of the protocol risk factors. He told the panel that he personally looked at all patients with a <12% STS score and concluded that 94% met high surgical risk criteria. He then described some of the patients with the lowest STS score.

Dr. McCarthy summarized: "I'm here because I have to turn down patients with severe conditions…There is no apparent adverse safety signal, and the median time to discharge was only two days, and 92% went home after a procedure, not to a nursing home. We cannot recover these patients so quickly after conventional surgery." He said:

- Mitral regurgitation is a debilitating disease, and surgery addresses only a portion of patients.
- Patients at too high risk for surgery have no other option for mitral regurgitation reduction.
- Lower-risk options for reducing mitral regurgitation are needed for patients at too high risk for surgery.

Efficacy

Paul Grayburn, MD, a cardiologist from Baylor Health Care System and a paid consultant to Abbott Vascular, told the panel that the MitraClip is effective:

- Left ventricular reverse remodeling hypothesis met.
- Significant acute reduction in mitral regurgitation.
- Improved hemodynamics.
- Durable mitral regurgitation reduction through one year.
- Significant improvements in NYHA class, SF-36, quality of life, and heart failure hospitalization rate.
- Benefits in high-risk patients are consistent with results in lower-risk patients.

There were 15 cases in which the devices were not implanted – 12 for technical reasons and three for procedural reasons, including cardiac tamponade (which he said was not related to device malfunction).

Dr. Grayburn said that the immediate hemodynamic effects after the procedure confirm the benefit of mitral regurgitation reduction. Four left ventricular sizes were measured at one year, and success was defined as a reduction in left ventricular size, "In left ventricular end diastolic…we see on average a reduction from 161 to 143 mls, or an 8 ml reduction in one year…The hypothesis for reverse remodeling was met…The definition for success…[for the trials] was agreed to be 2+ even though conventional surgery success is 1+. The change in left ventricular size from baseline…Reverse left ventricular remodeling is established as a major mechanism for patient recovery…Mitral regurgitation reduction to 2+ is beneficial in these high-risk patients…There is significant evidence of remodeling when 1+ is achieved. When 2+ is achieved, there was evidence for reverse remodeling for three of the measurements…Mitral regurgitation reduction to either 1+ or 2+ results in significant reductions of left ventricular size at one year consistent with the symptomatic relief experienced by these patients. This is striking."

The other major effectiveness endpoints measured change from baseline, and all had to show improvement:

- Freedom from death and MR >2+ at one year.
- Clinical measures of benefit in NYHA functional class, quality of life, and hospitalizations.

Dr. Grayburn said, "The MitraClip device successfully reduces mitral regurgitation severity to 1+ or 2+ in the majority of patients…Most patients treated with the MitraClip experience durable results."

He said 62.6% of patients achieved freedom from death and MR >2+ at one year, "Mitral regurgitation reduction breaks the cycle…[and] provides them with improved quality of life. Many patients are not looking to prolong life; they want to feel better."

He said that patients' quality of life scores improved at 30 days and one year, as did the NYHA class symptoms. The rate of hospitalization for heart failure one year after treatment dropped 48% in patients with mitral regurgitation grades 1+ and 2+, concluding, "The totality of the evidence provides reasonable assurance of the effectiveness of the MitraClip in this high-risk population."

Safety

Michael Mack, MD, a cardiovascular surgeon from Baylor Health Care System who works with Dr. Grayburn, was an investigator in the EVEREST trial. He argued that the safety of the MitraClip is better than conventional surgery. For the primary safety endpoint of 30-day mortality, Dr. Mack said the

predicted mortality risk was 18.2%, considerably higher than the observed 4.8% mortality risk, "There is clearly a safety advantage for the MitraClip over the mortality predicted if these patients had been treated with surgery."

As for the 17 deaths within the first 30 days in the high surgical risk cohort (n=351), five were related to stroke, myocardial infarction occurred in two patients, and vascular bleeding in two patients due to the pigtail catheter. There was one each of gastrointestinal bleeding, renal failure, and cardiac tamponade. The tamponade occurred during the transeptal puncture (not related to the device itself). Five died due to existing conditions. Three were device-related in cases where leaflet grasping was difficult and there was no mitral regur-gitation reduction.

Dr. Mack said the mortality rate was 4.8% at 30 days. There were nine strokes at 30 days, and renal failure and mild myocardial infarction occurred in several patients. He added: "The one-year stroke rate was 3.4% – not unexpected…Seven of the nine strokes were fatal, and two resolved. None was determined to be due to the device. The only variable which was significant was a prior history of stroke."

Dr. Mack said, "The main ICU stay was 1.5 days, and the mean hospital stay was two days. For patients in the STS registry, the norm was 16 days. 92% of patients receiving the MitraClip went home. Only 40% of surgical patients were discharged to home after surgery."

Safety Comparisons at 30 Days

Event	High surgical risk cohort n=351	STS score ≥12% MV surgery n=3,213
Death	4.8%	17.5%
Stroke	2.6%	4.5%
Renal failure	1.7%	13.9%
Non-elective CV surgery	0.3%	20.3%

Dr. Mack discussed the Duke Propensity Matched Comparator for mortality, saying that blinding was preserved during the matching and performed without consideration of mortality outcomes. The Duke score analysis showed no mortality increase from MitraClip and an analysis performed independ-ently by Duke University Medical Center showed that 211 of the 351 patients had one-year follow-up complete as of October 2011, with no evidence of increased mortality compared to the natural history of the disease.

He summarized: "The primary safety endpoint was met…and the 30-day mortality rate was significantly lower than pre-dicted mortality for surgical intervention…The safety events are low and acceptable for this population…Device-related complications were rare. It is impressive that these high-risk patients were discharged in three days compared to 16 days after mitral valve surgery. In addition, 92% of patients were discharged home…Finally, there is an acceptable risk of the procedure, with no adverse safety signal observed. Starting with the randomized trial and consistently demonstrated… MitraClip can reduce mitral regurgitation with safety that is [better] than surgery…Mortality with the MitraClip is lower than with surgery…The MitraClip procedure is reasonably safe and acceptable for high-risk patients and provides a meaningful clinical benefit when they have no other option for mitral regurgitation reduction."

Postmarketing proposal

Dr. Simonton described Abbott Vascular's post-approval com-mitments, which include comprehensive training of multi-disciplinary heart team and support personnel, participation in a mandatory transcatheter valve therapy (TVT) registry, and a post-approval study. Hospitals doing the procedure must perform at least 20 mitral surgeries a year and have the proper infrastructure. The postmarketing study would confirm safety and effectiveness of the MitraClip in a commercial use setting. It would be a prospective, single-arm, multicenter, 2,400-patient study.

Dr. Simonton also talked about the RESHAPE-HF and COAPT trials. COAPT, a North American trial, includes 420 high-risk heart failure patients with functional mitral regurgitation (FMR) randomized to medical management. The first data are expected in 2017. The RESHAPE-HF is a European trial of 800 FMR patients with severe heart failure that is expected to begin enrolling patients any day now.

Mitchell Krucoff, MD, an interventional cardiologist from Duke University Medical Center, speaking on behalf of Abbott Vascular, made a number of points, including:

- "This was not the original target population…There is no single clinical randomized trial for patients who have severe mitral regurgitation but no surgical option…The consensus [in EVEREST] was that surgery is better than MitraClip for patients with severe mitral regurgitation when surgery is an option. In fact, it was the conduct of the EVEREST trial that uncovered the population we are discussing today."
- "In patients with severe mitral regurgitation and no other options, the basis for reasonable assurance of safety and effectiveness is centered on all available data using this product in these patients. It does not include a pivotal randomized trial of these patients…It does not include any single dataset that stands alone…Rather, you have heard data from the registry and REALISM registry in conjunction

from clinical experience in Europe. You have heard safety studies…You have heard analyses of each dataset, pooled datasets, and you will hear even more analyses from the physician scientists at the FDA. Each of these analyses has significant limitations and is legitimately subject to statistically critique."

- "The reason we are here…is that every single analysis of every single dataset supports the same two things: the absence of any safety signal and the consistent reduction of mitral regurgitation and promotion of left ventricular remodeling sufficient to significantly improve outcomes in patients who have no other therapeutic options. While each analysis on its own has clear limitations, the remarkable consistencies…constitute valid scientific evidence that the use of the MitraClip in patients with severe mitral regurgitation and no other options, the likelihood of benefit far outweighs the likelihood of harm."
- "There is no effectiveness claim for mortality that is suggested or which could be supported…For all mortality models, the modeling procedures were completely delineating prior to the analysis…Mortality based on STS score calculators, on the Duke [scores]…all consistently support the absence of any detectable safety signals in these patients …At one year, the MitraClip reduces mitral regurgitation to 2+ or less in survivors in more than 80% of patients… We agree that 2+ MR is not a good result when there is a surgical option, but in patients at risk, patients with 2+ produces mechanistic improvement and clinical benefits."
- "That this is not the original target of the clinical study program doesn't erase the fact that this clinical program uncovered and has proceeded to systematically examine the MitraClip [in this population]…[which] constitutes an important area of unmet medical need in our country. Based on all analyses of all available data, the use of the MitraClip in these patients has a remarkable consistent safety profile. Based on use, the MitraClip provides remarkably consistent evidence of both mechanistic and clinical benefit. This probability of benefit substantially outweighs the probability of doing harm, and ultimately, informed patients with severe mitral regurgitation and no surgical option willingly accept the risk relative to the potential for benefit in using this device."
- "The panel's recommendation…will not be based on a randomized trial…nor a single analysis from any single pivotal dataset. Instead, it considers all analyses from all available datasets. The panel's recommendation will address the ability of heart teams at the bedside to work on behalf of symptomatic patients…who are at too high risk for surgery. In the absence of surgical option…the recommendation will advise that either we would add a percutaneous option to the bedside armamentarium (and study postmarketing) or whether we will make patients with no options wait for at least another five years for such an option to reach them in the U.S."

PANEL QUESTIONS FOR THE COMPANY AND THE FDA

Patient selection

Panel member Valluvan Jeevanandam, MD, a cardiothoracic surgeon from the University of Chicago, asked about patient selection – how many had STS risk factors and how many had things on top of that – said, "I know that we are picking on different data points to show the safety or effectiveness of this device, but the Duke matching was tested against high-risk patients not surgically treated, and at one year the mortality was non-significant with medical therapy vs. MitraClip. You can spin it two ways. It shows that MitraClip isn't worse, but it also shows that MitraClip isn't better at about a year." Abbott Vascular's Dr. Simonton said, "The purpose of the Duke comparator was not to show superiority…It was to show that the MitraClip was at least not showing a mortality hazard compared to the best matched patients we could find. We are not making claims that the therapy would have a strong trend or significant difference in mortality."

Dr. Jeevanandam asked Abbott Vascular's expert Dr. Mack about the non-elective cardiovascular surgery in the STS database of 0.3% – what kinds of procedures were they? Reoperations? Dr. Mack said they were not concomitant procedures; they were non-elective return to surgery within 30 days. The most common cause was return to the operating room for bleeding.

Learning curve

Dr. Vetrovec asked, "As the technology gets rolled out to general use, how many investigators were involved in the trials, how restrictive…and what was the learning curve?" Dr. Simonton responded, "There were 40 to 41 sites in high-risk and REALISM studies – usually one primary operator at each site plus echocardiographer and the surgeon. In Europe, in commercial use, the teams are very similar…On the learning curve, since the U.S. clinical trial program started in 2003… the procedure time has decreased by about 160 minutes. In EVEREST-I it was 280 minutes, and now it is 2.5 to 3 hours. The implant rate has gone from 90% to over 95%…One of the complications is a single-leaflet device attachment early on within 8% to 10%, and now it is 3%, and our international experience shows only 1.4% now…That gives us some idea about the learning curve over time."

Panel member Warren Laskey, MD, a cardiologist from the University of New Mexico School of Medicine, praised the company for its thorough presentation and then asked about NYHA Class IV and if that means heart failure. Abbott Vascular's Dr. Simonton said that he could break it down a little more later.

Heart failure

Bram Zuckerman, MD, director of the FDA's Division of Cardiovascular Devices, CDRH, asked how many patients had heart failure and asked Dr. Simonton to talk about Abbott's future plans, "It looks like the COAPT trial is designed to enroll a third of the functional mitral regurgitation patients because it is a heart failure trial. Who are the other patients, and how did you come to that one-third number?" Dr. Simonton replied, "One is looking at the patient population we enrolled in the entire cohort who had been hospitalized with heart failure the previous year…[and] also looking at the earlier sites who had enrolled…It is an estimate, of course… but that number is based on what we have seen in the number of patients who had heart failure hospitalizations within the first year of coming into the integrated high-risk cohort."

Panel member Craig Selzman, MD, a cardiothoracic surgeon from the University of Utah School of Medicine, asked about operability issues, "As we get our hands around the two pooled cohorts, how do you define an experienced heart valve surgeon? And did the surgeon actually see the patient?" Dr. McCarthy said that he would find out.

Robert Dubbs, a retired healthcare attorney and the panel's consumer representative, asked about death numbers subsequent to one year.

Post-device surgery patients

Panel member Gregory Dehmer, MD, an interventional cardiologist from Scott and White Healthcare and Texas A&M University College of Medicine, asked about three patients who had mitral valve surgery after having the device detached, "They all had surgery and did okay? Is that correct? Do you have their profiles? If you say they were very high-risk patients, they had a failed MitraClip procedure, they have surgery – it does question the whole screening process…You say they're not suitable for surgery, yet the MitraClip didn't work as well as you had hoped, and they had surgery and did okay. Any perspective on that? I am a little surprised they did okay." Abbott's Dr. Simonton said, "Seven had surgery after the procedure in the cohort of 351. Three had surgery within the first 30 days…They couldn't receive a clip at all. Four had surgery after 30 days; two were the single-leaflet detachment, and the others were worsening mitral regurgitation despite the MitraClip."

Dr. Dehmer also asked about how many days patients were in the hospital, "Have you ventured into doing any economic analysis?" Dr. Simonton replied, "We haven't done that."

Entry criteria

Dr. Borer asked about the entry criteria, "You said that they were identical in the HRR and the REALISM groups…But that seems to be almost true except for one thing. There was one in REALISM that wasn't listed for HRR, and that was any other comorbidity the surgeon felt was a big problem. How many people were eliminated from surgery in REALISM because of some comorbidity that wasn't listed there, and what were the comorbidities?"

Abbott's Dr. Simonton said it was the surgeon's judgment that said the patient wouldn't survive a year, but that was the only difference, that life expectancy would be one year. Dr. Borer said that Dr. Krucoff claimed that these were people for whom surgery was not an option, and yet surgery became an option when the MitraClip didn't work, "What happened between the time of the original assessment and reassessment? I'm not criticizing. I just want to know what happened to change the criteria for who was not so sick that surgery was not an option, and now it was an option."

- *Dr. Simonton:* "It was only seven patients, so 2% of the population."
- *Abbott expert Dr. McCarthy:* "Two percent of patients underwent surgery at one year…It's a compassionate decision. You have a patient not responding to the clip who still has symptoms, and you have a conversation with the doctor that surgery will be high risk. In the inoperable group, 6% of patients did have surgery."

Dr. Jeevanandam asked again for data on the patients who received MitraClip but then had surgery, "It reinforces the desire for the data. We would like to know how many patients were like Patient No. 1, older than 75 years old… It would be nice to have that type of information."

Duke study

Judith Currier, the panel's patient representative, may have thought she was helping Abbott by asking about the Duke study, but she actually did the opposite. She asked, "When we were talking about the Duke study…the purpose was to show that there was no difference in survival. The MitraClip did no harm. So, by choosing a sicker population, the result would be against what they are trying to prove. So, I don't see the

point…It would make the results tilt against that there was no difference in survival." The panel chair replied, "It would make the device look better, and that's what happened."

The panel chair then asked, "Exactly how was the trimming [of propensity score distributions] done so that we came up with unmatched populations?"

- *The FDA's Dr. Mukhi:* "Since the protocols were not pre-specified…I understand that they looked at the scores for the two sets of patients…and took a subset of the Duke cohort, calling it the trimmed cohort of 527 patients…And I would refer to the sponsor on how the trimming was done."
- *The FDA's Dr. Zuckerman:* "What the FDA is trying to say is that with the original 953 patients, we didn't get a good propensity score match…We then went to 527 [patients], and we tried to get a good balance and matching. We didn't. So, then we had to go to these actual matching algorithms called algorithm 1, 2, and 3, and what we are showing in algorithm 1, which is a rigorous algorithm for matching, is that a fair percentage of patients were just unmatchable. We now go to algorithm 2, and it is a little more relaxed, and again we get unmatchability; we can only match five more patients. Then we go to algorithm 3, and while they claim matching, it is a very reduced algorithm, and so the interpretation is very problematic. Ideally, we would have liked to see a good propensity score match with algorithm 1 instead of getting two separate cohorts. This is the big problem and is why Dr. Pina indicated that we don't think the Kaplan-Meier curves are really interpretable using this methodology. At the time the methodology was done, it is my understanding that…211 of the 351 patients had the full one-year results…The sponsor subsequently did the cohort with the full 351, but I must emphasize that…FDA has not seen that analysis…The methodology…is critical…The sponsor can show it…but you must understand the caveats."
- *The FDA's Dr. Aguel* corrected Dr. Zuckerman, saying that the sponsor had not done that analysis.
- *Marc Katz, MD, MPH, a cardiac surgeon from Richmond VA:* "This has been going on for eight years, and it seems as if the sponsor and the FDA are at odds even at something like the definition of success. The question is: Given that EVEREST-II didn't meet its endpoints, why were the registries continued?"
- *Dr. Aguel:* "At the time of the investigational device exemption (IDE) study approval, reasons for not approving a study are not study design questions such as an endpoint but rather safety questions. If FDA didn't have a safety question, then FDA would approve it…That's how we went on for this trial…The high-risk registry was enrolled while the randomized trial was enrolling, and once the randomized trial analysis and the PMA came into FDA – REALISM had been approved – through conversations with the sponsor, enrollment in the non-high-risk – the moderate-risk patients – was discontinued. However, the high-risk patients in REALISM-HR continued to enroll."
- *Dr. Katz:* "It seems that part of it is timing."
- *Dr. Zuckerman:* "The panel needs to understand that when IDE letters go out and the FDA has interactions with the sponsor, as noted with this PMA, while the FDA can certainly indicate significant concerns, and these are put in letters, previous to the passage of the FDA Safety and Innovation Act [FDASIA], the sponsors went ahead because they were willing to take the risk. It has become even more of our formal mechanism…that if there are not definite safety concerns, even if the FDA has concerns about overall risk:benefit, at the end of the day, overall effectiveness endpoints, if the sponsor is willing to take the risk, they can take that risk and come to a panel like this."
- *Panel chair:* "[On] the issue of the importance of 2+ MR, there wasn't a large database to evaluate that until around the mid-1990s, and even then it wasn't large…The Mayo Clinic published an important study…[but] that was relatively recent, and the company was already on its way… Those data are relatively recent in the birth of this development program, so it would have been hard for the FDA and the company to come to firm conclusions early."
- *Dr. Jeevanandam:* "In the trial and registries, was there a mandate that a cardiac surgeon had to evaluate these patients and turn them down? Was everyone turned down for cardiac surgery?"
- *The FDA's Dr. Laschinger:* "Our review of the patient data showed that 38% of patients were not seen by a surgeon pre-operatively."
- *Dr. Jeevanandam:* "Are there any data on medical therapy? It would be interesting to see if their medications changed dramatically or at all by a procedure."
- *Dr. Pina:* "These patients do extremely well in the trials; they are well taken care of. We have heard from the sponsor that the patients were medically treated. I haven't seen the drugs or types of drugs used…Certainly, the Duke folks…probably had a lot of these patients on ACE inhibitors, beta blockers, aldosterone blockers, etc."
- *Panel chair:* "They may have been medically treated, but unless they had functional mitral regurgitation, there is no evidence that that treatment does anything in terms of degenerative mitral regurgitation…That drug therapy is useful. They may have done it, they may not have done it, but we ought to know."

- *Dr. Pina:* "But the most common cause of mitral regurgitation is left ventricle…You take the drugs, and you can shrink the ventricle. Degenerative is a whole different course."
- *Dr. Jeevanandam:* "I'd like to see from the company some data on medical therapy."
- *Dr. Selzman:* "The word that hasn't been used yet so far is 'palliation.' I mean, this is palliative therapy…ultimately, for the patient…And the question for the FDA is how important is it in a palliative procedure to have 1+ MR at the end of the day. The question for the sponsor…is: If you do palliation therapy, quality of life is everything. So, when we have patients…if we can get them a few years, that's good, but if they are a few years on dialysis and in a wheelchair, that's not good. I'd like to know more about the numbers of patients in these graphs…It's limited…but that might be helpful."
- *Panel chair:* "We also need to consider what quality of life data mean in an unblinded, single-arm trial."

Medical management of patients

Abbott Vascular consultant Dr. Grayburn said the patients were very well medically managed, with not much change in medication at the end of 12 months, "Palliative care is a good way to describe this. Patients who have been turned down for surgery are…highly symptomatic. Their goal is to feel better. They are really miserable…If they have functional mitral regurgitation, they have had medical therapy, cardiac resynchronization therapy (CRT), they remain symptomatic."

Quality of life and missing data

The FDA's Dr. Zuckerman asked about improved quality of life and about what seemed to be missing data. Dr. Grayburn answered, "In the patient accountability chart, we started out with 351 patients; 80 died, and another 16 withdrew…So, we get down to 327 who had a one-year visit, and that includes the deaths…So, there were 225 who had echoes in a year. It is common…where echocardiography is part of the study, for 10% to 20% of the echoes to be unreadable. And of the 225, 203 had measures of left ventricular volumes: 10%. That is very acceptable for a clinical trial. I would dare say it's good."

Matt Reynolds, an electrophysiologist from Burlington MA, speaking for the company, said that a full accounting of quality-of-life data was provided, "There was about 10% quality-of-life data missing at baseline…Eighty patients, roughly, died during follow-up, so at one year they had no available data – 83 precisely – and 20% of the data were missing at 12 months."

Dr. Reynolds said, "We cannot exclude, in this trial design, the possibility of a placebo-like effect, which has been demonstrated with medical devices in the past…One is the magnitude of change, two is the durability, three is the correlation as the quality of life changes with objective evaluations of the disease's severity…The improvement in quality of life with MitraClip was similar to that seen with mitral valve in the surgical arm of EVEREST-II."

Abbott's Dr. Simonton said, "Those patients had to be present at all three visits. We have paired data for 191 patients for baseline and one year, and then you have about 20%-25% of patients for which quality-of-life data are missing."

STS scores <12%

As to the question about patients with an STS score <12 and how they were determined to be high risk, Abbott expert Dr. McCarthy said, "As a surgeon…I actually saw that there are a lot of patients…who are, in fact, very high risk." He said that, for the risk determination in patients with STS score <12% (n=200), other factors just weren't captured. Thirty-one patients had FMR with EF <40%, 18 were ≥75 years old with EF<40%, and four had both; 21 patients had one or more protocol risk factors, plus additional serious comorbidities including cancer, end-stage lung disease, end-stage renal disease, AIDS, and connective tissue disease. One hundred forty-eight patients had other high-risk factors, including porcelain aorta, etc.

Dr. McCarthy said, "There are a lot of patients on the fringe, and we don't capture them. For example, multiple sclerosis is not captured in the STS score," including severe atherosclerotic disease of the ascending aorta, severe liver disease, cirrhosis, or hostile chest. He summarized, "There are the protocol definitions, the ones greater than 12%, clearly high risk, and less than 12% were also a very high-risk group of patients…I actually looked at this group of patients. I was convinced that…I would not operate on them…These are outliers – very sick patients."

Dr. Jeevanandam asked to see the patients with STS score less than 12%, "If I look at that number, about 145 are probably operable, but there are probably another small subgroup that are inoperable. I wouldn't consider all those as truly what you and I would think of as inoperable."

- *Dr. McCarthy:* "There are ways going forward in a post-approval study that you can address that kind of issue, as what happened with PARTNER."
- *FDA's Dr. Zuckerman:* "I am unclear. What is your gestalt, from your surgical view, about what percentage was truly inoperable?"

- *Dr. Jeevanandam:* "I would say the 31 are not inoperable. I'd say that the 148 – those patent grafts I would not include – plus the greater than two chest surgeries – we often operated on them – so probably about 60% of that group are people that we may consider operating on, so about 40% are probably truly inoperable."

Basically, Dr. Jeevanandam said he thought that ~60% of what the company deemed to be inoperable probably were candidates for surgery.

Speaking for the company, Dr. Krucoff said that the Duke database has 30 years of data and that he selected the past decade only, "These patients who are not being operated on, with severe mitral regurgitation, the mortality rate is higher, but over the decade (2000s) from which the 900 patients were culled, is a time period where therapy has not changed particularly, at least in our institution."

As to the value in patient matching, he said, "It was not the intention of this series of matching to try to define or redefine the population of intended use." He said the final group was "perfectly matched," in direct contrast to what the FDA had told the panel. He also said the patients in the Duke database match were sicker than those in the trial, "We have the analysis of the complete 351 matched to the Duke database…The analysis is less than 48 hours old…The FDA has not reviewed the data."

The Kaplan-Meier one-year mortality estimate matched MitraClip and the Duke medical therapy cohort (n=351). This updated analysis used the identical programming and procedures that were defined before any outcomes data. Kaplan-Meier at 30 days was 4.9% for MitraClip vs. 7.5% for the Duke cohort and at one year was 22.8% for MitraClip vs. 30.2% for Duke.

Algorithm for covariates

The panel chair asked about what algorithm was used when it came to selecting covariates.

- *Abbott expert Dr. Krucoff:* "We started with the fundamental: How do you define sick patients with severe mitral regurgitation by echocardiograph who are not operated on? And we added STS score, and then ultimately we used propensity scores to look at the overall matchability of the patient cohorts against multiple factors which may affect outcomes. That is how you go from a wide net to a tighter model."
- *Panel chair:* "That would be helpful because there were some differences in the covariates."
- *Duke biostatistician:* "When we struggled with [matching], we looked at the data – all done without looking at the mortality outcome. The Duke patients were younger and had smaller ejection fraction, so those two continuous variables we picked to trim the data (NOTE: *Dr. Krucoff had just said that the Duke patients were sicker.*) We came up with 517 and then were close enough to overlap on the propensity matching, and then we did much more rigorous matching and came up with the 127 good matches, which all the covariates were insignificant."
- *Panel chair:* "This seems to be a palliative procedure. We want people to feel better; we don't necessarily think that they will live longer. If the propensity matching was done only for mortality, (what does that mean)?"
- *The FDA's Dr. Zuckerman:* "This is a critical question. Dr. Borer, when the FDA gets back up, I would like you to ask about propensity scoring and methodology again because there are some fundamental differences in technique and viewpoint which we won't be able to resolve today, but as a footnote to industry, the Agency would really ask sponsors who want to use propensity score analyses going forward to have extensive interaction with the Agency upfront because there is an art to doing this, and there are different viewpoints. It was only done for one variable, not the gamut of variables, which you would ideally like."
- *Abbott's Dr. Krucoff:* "As has been pointed out repeatedly, there are a lot of limitations to this type of ad hoc analysis. We thought this was a reasonable approach to looking for a safety signal. We did not think it was a reasonable approach to the answer about effectiveness. This was simply to look for any signs of a safety signal against the most contemporary and largest patient level available."
- *Panel member Dr. Laskey:* "You can only measure what you measure. What we have heard over the last hour are wonderful examples of…clinical judgment…[Dr. Krucoff] expanding or contracting the bounds. You can let in anything. You never know what you let in because you can't measure it, and that is part of the magic [Dr. Zuckerman] is alluding to. Maybe the statisticians can address that when we talk to them. It's a big deal…whether you look at all your variables or you start to throw stuff out."

Dr. Simonton said that at two years, in the integrated high surgical risk cohort of 351, the event-free rate is 62.7%, adding, "This was not a heart failure study."

- *Panel chair:* "From your prior knowledge, there was no reason for you to think that people would live longer than those without…while there was no comparator…Why would you have been considering them for mitral valve repair if they were too sick for surgery, if there was no particular reason for them to think they'd live longer, and if they didn't feel badly, and if they didn't have heart failure?"

- *Dr. Mack:* "The answer is that we wouldn't enroll them. This is mitral regurgitation causing symptoms which are due to heart failure."

Surgery in the year after the MitraClip

Seven patients went to surgery with an STS score of 10.6. The mean time was 68 days. Mean length of stay was 10 days. Five patients underwent replacement, and two underwent repair. Five discharged home after surgery, one died 84 days after, one went to rehabilitation, and one went to a skilled nursing facility. The question was raised: If they were truly inoperable, why did they have surgery? "In the PARTNER trial, these high-risk patients were deemed inoperable, in the CoreValve study they are extreme risk, and here they are called too high risk for surgery. Speaking as a surgeon, everybody is operable …But when we say someone is inoperable or extreme risk or too high risk for surgery, we weigh the risks vs. the benefits, and where the risks clearly outweigh the benefits, that's where we subjectively determine that the patient is inoperable or extreme risk…Clinically, we could do surgery and we can try to hit a home run here, but oftentimes we will strike out or end up with the ball caught in the field. With the MitraClip, I can probably hit a single or a double…I think you have a better risk of surviving."

As for the STS risk algorithm, he said, "This is like bracketology – or calculatorology. It is robust science…and the FDA has raised some concerns about what was used as the comparator here…The STS risk calculator was the current one used at the time when all patients entered into this. It is constantly updated based on more patients being added to the database and with changing demographics, time, operative results. The risk calculator used was the one current at the time the patient was entered. In the beginning, there was only one calculator, and it was the same for repair or replacement. We chose replacement because patients who fall in the high-risk group – 85% of them – if they went into surgery, got replacement instead of repair. However, if we don't accept those arguments and use the current calculator, we see that the predicted risk for repair would be 7.6% and observed mortality 4.8%, which is still a statistically significant difference."

Compassionate use patients

Abbott expert Dr. Mack said, "There were 33 patients in compassionate use. They didn't meet inclusion criteria for the REALISM registry – previous aortic valve replacement, left ventricular size too big, having an area other than A2P2 on the mitral valve that was the cause of the regurgitation (a P3 segment, for example). For them, the predicted risk of mortality was 23%. Many had previous heart surgery. Three percent was the observed 30-day mortality, and risk was 15%. Major adverse events: There was one death, no strokes, no renal failure, one myocardial infarction, and one non-elective surgery."

Panel member Norman Kato, MD, a cardiothoracic surgeon from Cardiac Care Medical Group in Los Angeles, asked about the compassionate use data, saying, "I'm getting really confused here…[If ejection fraction mean was 51.7% in the compassionate use patients] that means they are going to be operative."

- *Dr. Mack:* "The STS are due to patient comorbidities and not left ventricular function. You can see that 42% had moderate or severe renal disease, 57% have AFib history."
- *Dr. Kato:* "Where does the risk come in here?…Of course, they are going to have a good one-year survival rate."
- *Dr. Mack:* "These are weighted variables."
- *Dr. Kato:* "What is it in particular about this group that led the STS ranking to be that far off in terms of the predictive death rates?"
- *Dr. Mack:* "We can give examples."
- *Dr. Simonton:* "It is important to this group that these patients were excluded from REALISM. They didn't qualify. And in this group, two surgeons had to see the patient…The FDA approved each one of these cases individually."

Panel member Michael Ferguson, MD, an interventional cardiologist from Walter Reed National Military Medical Center, asked what percentage of the annual total number of patients truly are not surgical candidates and may be candidates for the MitraClip. Abbott's Dr. Grayburn said, "About 10 to 20 patients per month are allowed (with a humanitarian device exemption, HDE). Only about a third of patients actually have mitral valve anatomy you can actually use the clip on, and that's how we got to 30,000. In the first few years, we're in the 4,000 range, but the medically plausible group exceeds the number acceptable for an HDE."

Panel member Dr. Vetrovec asked about hospitalizations, "You lost 80 patients who died. Were they the major consumers of hospitalization the year before? Were the hospitalizations eliminated because of death?"

- *Abbott's director of clinical affairs and statistics:* "There is a higher rate of hospitalizations in patients who are dying, but looking at patients fully followed for a whole year, the effect of MitraClip was still there."
- *Panel chair:* "But isn't that surprising? Hospitalizations usually lead to risk of death. You are telling us that that isn't true in this population?"

Propensity scoring

The panel chair asked for the FDA view of propensity scoring. An FDA reviewer said, "The fact is that there is no well-defined criterion of what covariates should be included… Baseline covariates that are not included in the model may not be balanced, and that is what argues for including all covariates in the model [and that was not done here]. There were eight not included in the model. Second, regarding the matched cohort 1 [427 patients], I was using a rigorous matching criteria …Matches were not obtained for all 211 MitraClip patients, so the treatment group patients, if you don't find a match, it's kind of like you are throwing away the patients. That brings the question: What population is this? And that's why we said that the makeup of the matched cohort is unknown. Regarding matched cohort 3, matches were obtained for all 211 for MitraClip, but it was done using a relaxed matching criteria… And the sponsor presented results from 351 matching which used the same relaxed matching criteria said to generate the 211…To understand those results, we would first have to assess whether there was balance across the groups. We would need again to look at all observed baseline characteristics…for the 351 patients before we could even go on to look at the outcome analysis."

The FDA's Dr. Pina spoke about an earlier question, saying, "65% use of ACE inhibitors is very low, 76% beta blockade is equivalent to what we were doing in 1971, and calcium channel blockers are contraindicated for this population."

In another slam dunk for his team, the FDA's Dr. Laschinger said, "We don't think that having an STS score >12 has anything to do with the patients in this study." He pointed to a recent study written by a physician whose name had been invoked by the Abbott presenters.

In regard to unaccounted-for risk factors, he said, "Even if you add in two or more prior chest surgeries, that is still [a small percentage] of the total."

He said of a random sampling of 31 patients, functional mitral regurgitation and ejection fraction <40 were the only two risk factors checked off, "Specifically no patient…had previous cardiac surgery, no porcelain aortas, no stenosis. Of the patients picked out at random, all had normal creatinine, and three had EF >40%. And of those patients, five weren't even seen by a surgeon prior to being placed in the trial. Those are the kinds of problems we ran across…It was registry data, not pivotal data, and because of that, the problems are multiple."

Looking at risk factors, using the sponsor's own table, for cardiovascular risks and comorbidities, Dr. Laschinger said that actual values for the patients differed vastly."

- *The FDA's Dr. Zuckerman:* "This is why effectiveness is very difficult to interpret. We need these fine minds around the panel table to help us because we have no idea of what to make of it."
- *Panel member Dr. Selzman:* "I'm struggling, and I am upset at both the sponsor and the FDA. I'm upset at the FDA because you put a great document together that made a profound argument, then, because of the democratic process …the sponsors have done a nice job. And I'm upset with the sponsor because the data are unable to be interpreted… As I think about this…I might be wrong, but the way I put the numbers together, if we accept the Duke matched group – and I don't think 30 days is an adequate time for safety for a device that is in a human being – and look at the one-year data with the Duke group vs. the clip, the Duke group had a one-year death rate of ~28%, and the clip was ~22%. So, if we say in a year there is a 6% difference between the two groups, my question is: We need to find out if there is balance between safety and efficacy. The efficacy used by the sponsor is also troublesome. I don't have any patients who say, 'Boy, my end diastolic dimension is down 2 mm today, and I'm feeling great.' Given that's one of their primary endpoints, it's useless. What level of safety do we need to show? Since we don't have a numerator for efficacy, what do we need to do to allow this?…As clinicians, there is no question that we need something like this…but what is the FDA willing to do for that ratio? What ratio are you willing to accept? And, if so, do these folks have any chance at all of providing data?"
- *FDA's Dr. Pina:* "We are also thinking palliation, when patients come to us and say, 'I want to feel better'…In an unblinded trial, you have to be so persnickety for showing data that patients are feeling better and doing better. Quality of life is a pretty good tool. The SF-36 is a broad-based instrument that is not really heart failure-vetted. It hasn't been vetted well in the heart failure world. We have no correlates to say a six-minute walk – that would be a big help in this symptomatic group of patients. Even then, there is a lot of missing data, so I don't know how much of the quality of life is improved and how much of the NYHA class is improved. I have no objective knowledge to know if it works."
- *Dr. Selzman:* "If we say this is palliation, does the bar for efficacy change, perhaps? Clinically, it has to. This is the whole 2+ vs. 1+ [issue]. We have to focus in on what is the bare safety profile necessary to allow an increment of efficacy. So, my question is this 6% difference, which I made up. Is that acceptable safety?"
- *Dr. Zuckerman:* "You hit the thumb on the nail [sic], and it's why we need an independent advisory panel discussion…

Dr. Pina reminded you that we are not showing the comparison of the two Kaplan-Meier curves because we think the propensity score analysis has many flaws, and we don't know if it's -6% or 6%. Dr. Laschinger gave the FDA viewpoint that we have a comprehensive randomized trial. However, the panel may conclude something else. You are the experts. You are going to have to help us here – and the sponsor."

- *Panel chair:* "That 6% was a mortality differential, and we are talking about making people feel better. So, I'm not sure that 6% is evidence of benefit that may balance against whatever the risks may be."

PUBLIC SPEAKERS

There were 11 public speakers, including three patients, representatives from three professional societies, and a physician who flew in from Germany just for the meeting. One speaker, from Public Citizen, spoke against MitraClip approval, saying that the trial did not meet its endpoints and that safety and efficacy were not proved.

Augusto Pichard, MD, a cardiologist from Medstar Washington Hospital and speaking for the Society for Cardiovascular Angiography and Interventions (SCAI), told the panel, "MitraClip is a reasonable and safe option to surgery" for patients who are not surgical candidates. He stressed that it should be performed only in institutions with strong heart teams. He spoke in favor of the pooled data, saying that using the mitral regurgitation replacement model instead of repair was acceptable and that using the Duke database was appropriate.

STS/ACC joint presentation. John Carroll, MD, an interventional cardiologist from the University of Colorado who was representing the American College of Cardiology, was an investigator in the MitraClip trials. He said that one in 10 Americans age ≥75 has moderate-to-severe mitral regurgitation. He stressed the importance of echocardiography for patient selection. He also described the new STS/ACC Transcatheter Valve Therapy Registry.

Fred Edwards, MD, a cardiac surgeon from the University of Florida, described the STS/ACC TVT Registry, which tracks transcatheter aortic valve replacement (TAVR) procedures. He said he hopes the registry will include other implanted devices, with short- and long-term outcomes. The data will be linked with data from the Centers for Medicare and Medicaid Services (CMS). There are 201 participants in the U.S. registry. A few weeks ago, the registry got approval to test TAVR for unapproved uses. He said that, if approved, MitraClip would be included.

Michael Carome, MD, deputy director of Public Citizen's Health Research Group, said his group is against approval of the MitraClip because it has caused known harm and hasn't proved that it is as safe and effective as surgery. The risks are significant, including bleeding and cardiac arrhythmias. He said there was not at least one well-run randomized controlled trial, "Such a study has not been conducted." Even a perfectly designed registry study "would not have been sufficient…and yet…each of the retrospective evaluations of registry data was flawed."

Stephan von Bardeleben, MD, a senior cardiologist from Johannes Gutenberg University, who flew in from Germany that morning and was flying back that night, said the MitraClip has been used in 6,858 patients commercially in Europe. He said patients with recurrent hospitalizations have to have an option. An independent Germany registry of 1,400 patients will be closed in July 2013. He has done 120 procedures "with an excellent safety profile…There is a need for a randomized trial, but this is a novel and adjunct therapy which is important for the patients…and there is an important stress to the palliative approach in these patients." He added that the life expectancy should be above one year and said that echocardiography is critical to determining patient eligibility.

Randy Chitwood, MD, a cardiothoracic surgeon from East Carolina University in Greenville NC, who participated in the REALISM trial, said he has performed nearly 3,000 mitral valve operations, "There are stats, biostatistics, cohorts, and there are patients who are continuously short of breath because they don't have appropriate therapy. They are symptomatic patients…with prohibitive risk of mortality and morbidity that preclude an operation, but they are hoping for some safe option that will be available to them …They need another treatment option…I find myself counseling patients not to have mitral valve surgery. The risk of death is too high, [and the] possibility of becoming dialysis-dependent…Patients look at me and hope that I will wave a magic wand and rescue them from their ongoing misery…I know that if I operate, I will put them in peril of death or even worse: locked into chronic life support. Second, the MitraClip safely reduces mitral regurgitation…We know this…I think of my mother, who is 92 years old…She is fragile, real fragile, but active…No surgeon would operate on my mother…If she had symptomatic mitral regurgitation, I would happily opt for this procedure…I believe that this technique is safe."

Mark Gillinov, MD, a cardiothoracic surgeon from the Cleveland Clinic, said that each year his institution does thousands of heart operations, and 1,100 procedures are mitral valve operations, "So, I do 300 or more per year…patients who are too high risk for surgery is a common occurrence – very common. [Recently] I found an email from a heart surgeon at an Ivy League institution, and he asked if he could use mitral surgery in a patient he described…This surgeon judged him too high a risk for surgery. The patient is the father-in-law of the surgeon emailing me. My initial judgment is: too high risk. His quality of life is terrible, and it is his severe mitral regurgitation that is robbing him of his life. What if I could offer a therapy that could reduce his mitral regurgitation from 4+ to 1-2+? Would it be good enough? In my clinical judgment, the answer is emphatically yes…We would make this person substantially better, and it would give him back his life."

Steven Bolling, MD, a cardiac surgeon from the University of Michigan, who has published more than 300 articles on mitral valves, said the majority of patients are best served by surgery; however, if there were a group of extreme high-risk patients who might be best served by MitraClip, that would be useful. He said he has not been involved in the trials but may be a COAPT investigator. He said, "There is a large population of these extreme high-risk patients…There is probably no such thing as a totally inoperable patient. It becomes a difference of could vs. should, and that is not based on an STS score." He said he believes the MitraClip is safe and asked if there is a sweet spot in that high-risk population, "While reduction in mitral regurgitation is not a patient-oriented goal, left ventricular remodeling could be considered a true marker of outcome…Reduction of mitral regurgitation …leads to ventricular remodeling…Some substantive reduction in mitral regurgitation may be good enough for these extreme high-risk patients…I urge you to consider approval."

Robert Keeley, MD, a semi-retired thoracic surgeon from Jefferson Surgical Clinic in Roanoke VA, is 92 and got his MitraClip four years ago. He said that, before the surgery, "Between you and me, I thought my goose was cooked."

He and his wife have 15 children (!!!), 31 grandchildren, and six great-grandchildren. He received two clips and went home the next day. He had more energy and could exercise. The difference was striking, "I believe the MitraClip has a role in the treatment of mitral regurgitation. It is an outstanding technology. It is easy on the patients. The results are almost immediate." He got a round of applause from the folks in the room.

Ina Roblas, a MitraClip patient from Texas, said she received her MitraClip almost four years ago, "I am living proof that this procedure is a success." After her heart attack, she was so weak that she couldn't work or even dress herself. A patient of Dr. Grayburn, she said that at her checkups she can still do her "rock and roll dance moves from the old days."

Irwin Flax, an 86-year-old MitraClip patient from Nevada, received his MitraClip nearly three years ago. He said, "I am a scrawny, tough kid from the Bronx, and I am a veteran of WWII." He has had three heart attacks and three bypass surgeries, a pacemaker, and multiple stents. When his valve started deteriorating, his doctors said that the risk was too high for surgery, "For the very first time in my life, I lost hope."

After his MitraClip implantation, he was home the next day and was soon able to get back to his usual activities, "I turn 87 next month, and an adjustment to my pacemaker has allowed my battery to last 14 more years, and I expect to replace the battery when I am 100 years old."

PANEL CONSIDERATION OF FDA DISCUSSION QUESTIONS

The FDA wrote, "Abbott Vascular has performed analyses on the 'Intended High Surgical Risk Cohort,' (n=351) which is created by pooling EVEREST-II HRR and the REALISM HR cohort, for which one-year follow-up exists. A poolability analysis shows that statistically significant differences in several parameters exist between the two original cohorts. A similar poolability analysis was performed on the MitraClip Propensity Score Matching Cohort (n=211)."

QUESTION 1. Discuss. Please comment on the appropriateness of pooling these two apparently different cohorts.

The panel chair summarized: "The panel generally believes that these really can't be pooled."

Panel member comments included:

- *Dr. Jeevanandam, a cardiothoracic surgeon:* "It was problematic …They were different enough patients…that I think it's a tough one. I don't think it's appropriate to pool them."
- *Patient rep:* "The two looked quite similar."
- *Consumer rep:* "It's useful in terms of giving us some indication, but it is not definitive and not something to rely on."

- *Dr. Laskey, a cardiologist:* "Technically, I don't want to be an egghead, but the use of pooling is inappropriate – they're just combined. There is no treatment effect here because there is no control or comparative group. But getting past that, since there is so much subjectivity in the judgment of what is high risk and who is operable and who is not, I am beginning to doubt my own sanity as to whether my clinical judgment is appropriate either…I'm hesitant to say that they are combinable."
- *Dr. Dehmer, an interventional cardiologist:* "It was a reasonable effort, but it was not appropriate."
- *Dr. Katz, a cardiac surgeon:* "There are clearly difficulties with this, and it goes to the whole position we're put in: trying to fit a square peg into a round hole…The study came up with one question, and now we are trying to answer another question."
- *Dr. Ferguson, an interventional cardiologist:* "It's pretty difficult to combine them."
- *Dr. Selzman, a cardiothoracic surgeon:* "If your right shoe goes into horse poop, and your left shoe goes into dog poop, it's still poop."
- *Dr. Vetrovec, an interventional cardiologist:* "It's risky to pool them…The data are somewhat different for each group. On the other hand…Dr. Laskey made an important point, and that is the subjectivity of the decision-making in much of this may supersede some of the issues about the STS database… No, you can't pool them."
- *Dr. Kato, a cardiothoracic surgeon:* "No, you can't pool the data. This should have been a PARTNER-type mitral – as brought up by another colleague."
- *Gary Lofland, MD, a cardiothoracic surgeon from the University of Missouri-Kansas City:* "I don't have difficulty in pooling the datasets to reach statistical power…They worked for me."

QUESTION 2a. Discuss. Comment on the limitations of using the STS score for mitral valve replacement as a comparator in the analyses presented.

The panel chair summarized: "There are real concerns about using the STS score, period, as a comparator, but if you are going to do it, it is not clear why replacement vs. repair would be used as the comparator."

Panel member comments included:

- *Dr. Lofland, cardiothoracic surgeon:* "The STS registry has its limitations, but they used the comparator of mitral valve replacement because that would have been a sicker group of patients, so I thought it was appropriate."
- *Dr. Kato, cardiothoracic surgeon:* "Since the score is changing, it is difficult to use it as a comparator…Then again, the STS score honestly, and from a practical perspective, doesn't really capture the true risk involved. Rarely do I rely upon it for my own decision-making, so I'm not sure of the value of the score here."
- *Patient rep:* "I was glad to hear from others that STS didn't have much to do with anything."
- *Dr. Vetrovec, interventional cardiologist:* "I think it is more about matching the patients to what they are going to need rather than just focusing on the valve."
- *Dr. Jeevanandam, cardiothoracic surgeon:* "There are two concepts: One is using the STS score to select the patient, and the other is using the STS database as your control arm and comparator, so as a comparator, when you have numbers that are varying, I think that it is not the appropriate comparator. The other issue in terms of valve repair vs. replacement: They are different populations…These are repairable valves in this population. And I don't think it's a true comparator because the numbers are changing."
- *Dr. Selzman, cardiothoracic surgeon:* "The question is not the validity of using the score; it's whether that should be the comparator at all. If we stay with the palliative concept, it is not an adequate comparator – conventional medical therapy is."
- *Dr. Ferguson, interventional cardiologist:* "They used the STS indicator available at the time…It does seem from what the FDA presented that using mitral valve repair would be more appropriate in these patients."
- *Dr. Laskey, cardiologist:* "Picking up on Dr. Ferguson, I would agree, but when you read that paper, it gives you pause. There is very little repair in this country, despite what we are seeing in this room with experts. I have trouble with comparator being a predictive probability – I don't like that idea. And the instrument itself is changing – specificity, etc. – and you have to do the same exercise every time you stabilize, and that hasn't been done here either. Those are all limitations of using the STS score."
- *Dr. Dehmer, interventional cardiologist:* "Adding to Dr. Laskey, it's the use of the STS score, period. It is one of the best predictors out there in terms of surgery, but the only reason is that you know what the outcome of the operation eventually ends up to be. You enter 27 risk factors, and you know what happens to the patient afterwards in terms of survival. MitraClip is a game-changing technology…and you have no

data on the people who were inoperable before the MitraClip."

- *Dr. Katz, cardiac surgeon:* "I am a big fan of the STS score when it is used appropriately, and I'm not sure this is its appropriate use."

QUESTION 2b. Discuss. Comment on the use of the STS score for mitral valve replacement rather than the STS score for mitral valve repair for selection of high surgical risk and inoperable patients into this and future trials for the MitraClip CDS.

The panel chair summarized: "There is a trend to use the STS score as a criteria, supplemented by characteristics not characterized by the STS score. There is a healthy subset which thinks the STS score would be an okay place to start."

Panel member comments included:

- *Dr. Dehmer, interventional cardiologist:* "Going forward, it would be reasonable to know what the STS score would be on patients proposed for either therapy. I am not troubled by the use of other variabilities, for example frailty or the eyeball test."
- *Dr. Katz, cardiac surgeon:* "This is a totally appropriate use of the STS score. As for replacement vs. repair, that was difficult since the scoring changed in mid-data collection here, and I could probably argue that one both ways. In general, I'd lean toward saying it is okay to use it…I would use repair going forward [with future studies] because the MitraClip is an analog for surgical repair. If this were a transcatheter mitral valve replacement, then it would be appropriate to use replacement."
- *Dr. Ferguson, interventional cardiologist:* "I think that you could use both. About 80% could be used for repair. You could incorporate it into the STS score…There may be patients who are candidates for the clip who would not be candidates for repair. You wouldn't have to exclude patients just because they weren't repairable."
- *Panel chair, cardiovascular surgeon:* "It's not that 80% could be repaired and 20% replaced; all of the patients were deemed clipable."
- *Dr. Selzman, cardiothoracic surgeon:* "It is important for us to recognize the way the mitral valve replacement outcomes were developed, including patients who had completely separate disease…I would use the repair score…It is important not to mix the two concepts of high surgical risk and inoperable. The STS can be used to assess risk, but it's probably not going to be what assesses inoperability. Having those two statements are really very different points."
- *FDA's Dr. Zuckerman:* "Would you agree that one might consider in a prospective trial the STS mitral valve repair score as one selection variable?"
- *Dr. Selzman:* "Correct, using the clipable equals repairable."
- *Dr. Laskey, cardiologist:* "If everybody is eligible for repair, why would you put it in there as a predictor? But, anyway, I think the exercise should be done: evaluation for selection for high surgical risk, [with] repair as the comparator. But if we are starting out with a population in which everyone is going to be repaired, I'm not sure that the language is needed."
- *Dr. Kato, cardiothoracic surgeon:* "I would use the selection criteria for repair, and if a person has less than 12%, then they could add radiation, mediastinitis, because those aren't captured in the STS risk analysis…There are some things that make a chest hostile that aren't incorporated in the STS."

The Duke cohort was used as a comparator in the integrated high surgical risk cohort. A propensity score matching analysis (Duke Analysis) was performed to compare the two groups for mortality alone.

QUESTION 3. Discuss. Comment on the limitations of using the Duke database as a comparator for mortality and whether any other valid comparators may exist for comparing other effectiveness measures.

The panel chair summarized: "You heard a sort of tepid response for using the Duke database for the uses for which it was used, but going forward a randomized trial would be better than doing this."

Panel member comments included:

- *Dr. Lofland, cardiothoracic surgeon:* "I think it was appropriate."
- *Dr. Kato, cardiothoracic surgeon:* "I can't tell just using a known database as a comparator for a new trial of a new device. I was impressed by one of the comments by a surgeon from the Cleveland Clinic. He said they get 500 patients a year whom they turn down for surgery…It seems as if there are a number of patients going to one center, and 500 turned down. That's more than the other non-operated-on control groups in any of the comparators that have been used…So, I would say no."

- *Dr. Vetrovec, interventional cardiologist:* "It was reasonable. There was no perfect comparator…I'm not too uncomfortable with that. This was basically just to provide safety… and that was a reasonable way to do it."
- *Panel chair:* "What about the fact that there were a number of characteristics that just couldn't be matched?"
- *Dr. Vetrovec:* "That's the risk that always happens with a new device, and you don't have a baseline for it…In some ways the patients were skewed…because they took people with radiation, cancer…The population was skewed in a peculiar way. So, it's hard to find a comparator, and, yes, there were differences, but I'm not sure that would have made the valve do worse."
- *Consumer rep:* "It was interesting but not a predictor."
- *Dr. Jeevanandam, cardiothoracic surgeon:* "This was as good as they could do for this study…You can't propensity-match for the hostile chest. Going forward, a proper study would be to compare this to medical treatment. We should look at the PARTNER B trial, and then you would have your medical control."
- *Dr. Laskey, cardiologist:* "It is entirely reasonable to use the Duke database. It is rich and complete. But I was under the impression that there are other large centers out there…I'd like to see this exercise replicated in another environment …Other than that, I have a whole bunch of questions about propensity scores for this purpose, and when and how and why did you do it? It is a whole art, and we haven't heard even the half of it. I am very concerned. There are other ways to look at this issue of confounding when you don't have randomization – and I don't know why that wasn't done – that are sometimes better than propensity scores, and I have a big problem with that in this case."
- *Dr. Dehmer, interventional cardiologist:* "The Duke database is well-known and is a rich database…It sounds like there is no agreement amongst our statisticians about how best to do this propensity scoring. All that needs to be settled and agreed upon before doing this all over again."
- *Dr. Katz, cardiac surgeon:* "In the absence of a random control comparator, it's as good as it gets."
- *Panel chair:* "It was just done for mortality as the outcome. They were looking for harm. And, in general, we are talking about quality of life…Does that enter into your thinking?"
- *Dr. Laskey:* "A more elegantly designed study could have looked at a variety of other parameters, but given that this was a registry, there were severe limitations on the data available."

Abbott Vascular has performed several retrospective subset analyses on the MitraClip clinical data to support the indication for use: The MitraClip clip delivery system is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥3+) in patients who have been determined by a cardiac surgeon to be too high risk for open mitral valve surgery and in whom existing comorbidities would not preclude the expected benefit from correction of the mitral regurgitation.

QUESTION 4. Discuss data analysis. Comment on the use of retrospective subset analyses to support this indication for use and whether these analyses constitute valid scientific evidence of safety and effectiveness for first-of-a-kind device and first-of-a-kind indication, as is the case with the MitraClip CDS.

The panel chair summarized: "No one is irrevocably opposed to restrospective analyses. The concern is the way these data were defined and the lack of a reasonable control. This is not a total negative, but there is concern about the strength of the data."

Panel member comments included:

- *Dr. Kato, cardiothoracic surgeon:* "Retrospective analyses are not supposed to be used for this kind of indication, and I would hope that it would not be done in the future."
- *Dr. Lofland, cardiothoracic surgeon:* "I worked for years with the congenital heart function association, and we did all of our papers retrospectively…I don't have any difficulty with this. It is a well-established precedent in the literature."
- *Burke Barrett, vice president of regulatory and clinical affairs at CardioFocus and the panel's industry rep:* "This is a central question of the deliberations today, and from a purely regulatory point of view, just because a device and indication are first of a kind doesn't mean that a randomized trial is absolutely required."
- *FDA's Dr. Zuckerman:* "Certainly, I would like the panel to recognize that Mr. Barrett is correct…Valid scientific evidence does not necessarily have to be a randomized trial. About 50% of our trials are randomized. However, when we go back to the regulations and CFR860.7, what I think the sponsor and Mr. Barrett missed on their first delineation of valid scientific evidence is that, in addition to the panoply of trial designs, valid scientific evidence does have to allow one to…fairly and responsibly be concluded…that there is reasonable assurance of the safety and effectiveness of a device…and I think the reason why this question is worded as such is this isn't the tenth-of-a-kind device, where it is often the case where we would not use a randomized trial. This is the first of a kind, where there are many questions

out there, and we'd like to know what type of scientific evidence is appropriate."

- *Patient rep:* "I would like to see real hard data…The sponsor should look at what really matters, and that is whether you are feeling better."
- *Dr. Jeevanandam, cardiothoracic surgeon:* "This is a tough one. There are probably circumstances where retrospective analyses could work, but here there were data from two separate registries, and there wasn't a very good comparator. That is what I had more problems with, and I wish the data were more homogenous and coherent."
- *Dr. Laskey, cardiologist:* "The question is worded in such a way that if you are on the panel, you have to agree with it. There is probably some room to disagree, but the way we got here – the sponsor got up at bat twice and didn't hit anything, and there was a third time at bat, and there was a 'Well, let's go somewhere else,' with a new hypothesis and new endpoint. Now we are here, and we arrived at this patient population, which was not prospectively defined up front on Day One. And that's the problem with assembly of a cohort. You don't know how they got in the cohort, and yet they're here…Who is the patient group? We still can't define it, and the propensity score only confused things even more…I don't like to do that. It is not the high road… Arriving at this group the way the sponsor and investigator did – this is not the way you want to design a clinical trial and get a meaningful endpoint."
- *Dr. Dehmer, interventional cardiologist:* "The sponsor started out in EVEREST…[and] did not meet efficacy…and then came to the logical conclusion that their device would be more appropriate for high risk…They continued to refine their hypothesis and which patients it would be best in, and all that is very logical and understandable and the same thing any of us might do, but now we have a conglomeration of data…It is provocative, it is hypothesis-generating, and I am very sympathetic to what they are doing, from hearing the patients whose lives have been greatly benefited and hearing surgeons saying they need this device, so I am a bit torn, but do the retrospective analyses hold enough water? No, they don't."
- *Dr. Vetrovec, interventional cardiologist:* "I am biased in the direction [of randomized trials]. No one is claiming this is better than surgery in acceptable patients. All that is being claimed is that in patients who are really not good surgical candidates – and it seems to be a surgeon making that decision – we are looking at more generalized databases and starting to make clinical decisions based on that. So, we may be at a transition point, and this is a unique circumstance that isn't trying to say that it's better than anything except for patients who have no other alternative."
- *Dr. Selzman, cardiothoracic surgeon:* "There is precedent…I think part of our duty is to try to fill this gap for this group of patients…to support this indication. I have trouble with some of the wording of the indication, but I do feel comfortable with using retrospective data."
- *Dr. Ferguson, interventional cardiologist:* "It may be appropriate to lower the bar, especially for some patients. When you lower the bar, how low will it go is the question."
- *Dr. Katz, cardiac surgeon:* "For a first-of-a-kind device in a first-of-a-kind indication, you need a randomized trial. They did one, but they were a little too optimistic in the indication. It showed the safety, and the efficacy is what we are trying to draw out. In this unusual circumstance, it might be reasonable to use the retrospective study."

QUESTION 5. Discuss FDA conclusions. Please comment on the validity of the FDA's five conclusions.

1. The EVEREST-II randomized trial did not demonstrate an appropriate risk:benefit profile when compared to standard mitral valve surgery in a selected mitral valve patient population.
2. For a variety of reasons, the EVEREST-II HRR single-arm registry data are not easily interpretable.
3. REALISM-HR is a continued access protocol cohort that was not intended to be used as a pivotal data set and is difficult to interpret.
4. The integrated high surgical risk cohort, developed by pooling two registry data sets in a post hoc manner, has major design limitations.
5. The Duke propensity score analysis was a retrospective, subset analysis with results that are difficult to interpret and where the matched cohorts do not represent any well-defined population.

The panel chair summarized: "Everybody agrees with all five points, but there is a nagging sense that somehow there might be something here of value. There probably is, but it's just that the population, use of the comparators, etc., makes it very hard to put a finger on what it is that is beneficial for patients or which patients will benefit. 'Something is here somewhere' is the nagging sense."

Panel member comments included:

- *Dr. Katz, cardiac surgeon:* "I generally agree with most of the conclusions. Number one (EVEREST) was a little harsh."

- *Dr. Selzman, cardiothoracic surgeon:* "I agree, but I urge the FDA to think about the patients who are hidden in there."
- *FDA's Dr. Zuckerman:* "The FDA is quite concerned with patient care…but as people have noted, there are certain bars for data interpretation…Would you agree with [the FDA]…as to why the current data are difficult to interpret, or do you see things differently?"
- *Dr. Selzman:* "I was convinced that the STS risk score was going to be higher, and I plugged it in…That can't be captured in what we are talking about right now. I can't argue with [the FDA]…The data are the data, and I wish it didn't have so many holes in it. But in regard to this question, I feel as if we are on the stand and we have to say, 'Yes, yes, yes…I agree with every single one of the points 1-5,' and many from the company agreed as well."
- *Dr. Kato, cardiothoracic surgeon:* "I agree with each of the five major findings…We all have patients who could benefit by this. The problem is that in the absence of defining who that population is, the use of this device is problematic. Even [for] the Europeans, it is only a Class IIb recommendation with C-level evidence. Even our colleague from Germany stated point-blank that there are no randomized trials, and that is of serious concern to me in fulfilling my responsibility to patients in the U.S…On my watch, I will try to ensure safety and efficacy."
- *Dr. Lofland* agreed with Dr. Selzman.
- *Dr. Jeevanandam, cardiothoracic surgeon:* "I agree that there are one or two patients in there who would benefit, and we have to tease them out, but this trial hasn't done it."
- *Dr. Laskey, cardiologist:* "These are fine investigators, but it doesn't get us out of the problem of who it's best for and how you go about deciding that."

QUESTION 6. Discuss the indication for use. Provide any suggested major changes to the indications for use that better describe patient population and/or intended use (reduction of MR 3+ or more).

The proposed indication is: for the percutaneous reduction of significant symptomatic mitral regurgitation MR 3+ or greater in patients who have been determined by a cardiac surgeon to be too high risk for open mitral valve surgery and in whom existing comorbidities would not preclude the expected benefit from correction of the mitral regurgitation.

The panel chair summarized: "The committee is generally not unhappy with the indication for use as it's written but suggested some tweaking to include a statement about medical therapy, which doesn't necessarily mean medical therapy for mitral valve disease…perhaps with some statement about anatomic appropriateness of the valve for this kind of therapy, and perhaps with some statement about who is making the decision about whether the risk is too high for surgery. And the expected benefit from correction of mitral regurgitation should include a statement that the expectation [is] that the patient, absent any other problem, would live for at least a year."

Panel member comments included:

- *Dr. Kato, cardiothoracic surgeon:* "I would add 3+ despite medical therapy…and I would change too high risk to "excessive risk" and expected benefit to be life expectancy of at least one year…Medications would have to be used first."
- *Dr. Vetrovec, interventional cardiologist:* "I'm happy with it the way it is."
- *Dr. Selzman, cardiothoracic surgeon:* "In patients who have been determined by – I wouldn't put cardiac surgeon – I'd say experienced mitral valve surgeon. I am not part of our TAVR program, but I have counseled patients and all of a sudden have found that patients are in the valve-in-valve program in the TAVR program."
- *Dr. Ferguson, interventional cardiologist:* "I would include other members of the heart failure team – heart failure cardiologist – and a valve surgeon."
- *Dr. Katz, cardiac surgeon:* "I agree with the statement as is with the addition of optimum medical therapy."
- *Dr. Dehmer, interventional cardiologist:* "Take out cardiac surgeon and make it the heart team."
- *Dr. Jeevanandam, cardiothoracic surgeon:* "We need to optimize medical therapy – that has to be in there – and also I'd leave the cardiac surgeon in there. I wouldn't make it a team though."

QUESTION 7. Discuss risk:benefit. Comment on whether you believe the totality of the data presented and discussed demonstrates a reasonable assurance of safety and effectiveness for the MitraClip CDS in the intended population.

The panel chair summarized: "The panel does not find clear evidence of safety and efficacy. However, there is a clear sense that there is something lurking there."

Panel member comments included:

- *Dr. Laskey, cardiologist:* "It does not in totality demonstrate benefit vs. risk."

- *Dr. Jeevanandam, cardiothoracic surgeon:* "The benefits don't outweigh the risks."
- *Dr. Dehmer, interventional cardiologist:* "Safety, yes, effectiveness, the data are very muddled. I'd throw back effectiveness in which patient population and under which circumstances, so I would say effectiveness unknown. I believe the device does bring about changes in left ventricular size that should be favorable, but as someone commented earlier, patients don't come in saying, 'My left ventricle size is 4 mm smaller. I feel a lot better today.' It is a surrogate endpoint, and it is effective for that, but I don't know what that means. The functional heart class is much more valid, and there is some suggestion that it improves function…I believe there is a signal that it is effective in these high-risk patients, but again it's confusing to me because the populations we've seen are very mixed."
- *Panel chair:* "It is safety for intended use…There are safety issues which would be acceptable if there were effectiveness …People are having a hard time grappling with the effectiveness part. And there isn't effectiveness, there isn't safety, unless the safety is absolutely 100%.
- *FDA's Dr. Zuckerman:* "That fits well with the FDA definition of safety. Without knowing effectiveness, there is no knowing safety."
- *Dr. Katz, cardiac surgeon:* "I've seen nothing that makes me question the safety of the device…There was one perforation; the number of deaths perhaps was as expected. The effectiveness is really the big question, and that's because of the conglomeration of different types of data…This whole session is incredibly frustrating, and in many ways, whether it is the bullheadedness of the sponsor not willing to change the trial and whether the FDA didn't bend too far. This has been going on for eight years…and it would seem that maybe the system is broken in some way…We have trials lagging so long, maybe there needs to be a requirement for better understanding and better communication…Are patients who might benefit going to have to wait five years?"
- *Panel chair:* "What data do we have that it's being used in Europe with efficacy? I don't know of those. It's being used, that's for sure, and people with mitral regurgitation…have their mitral regurgitation go away, but what data are you thinking about?"
- *Dr. Katz:* "We're just expected to make decisions without any information."
- *Dr. Selzman, cardiothoracic surgeon:* "I don't believe that holding the sponsors to mitral regurgitation of more than 3+ is [unreasonable] when we are talking about palliation… holding efficacy to mitral regurgitation is what a surgeon is held to, but maybe that's not what this therapy needs to be held to. So, 'the totality of the data is lacking' is my answer."
- *FDA's Dr. Zuckerman:* "In general, the cardiac surgical comments have been very helpful. You recognize that there may be a role for percutaneous therapy, but in fairness to the sponsor…you said there were only 40 patients in follow-up NYHA classification. There are actually 234, and perhaps that is the most persuasive evidence of effectiveness, but is that enough to clear the water?"
- *Dr. Selzman:* "My comment stands."
- *Dr. Vetrovec, interventional cardiologist:* "This is a safe device for the patient population. In terms of efficacy, I think things like the volume analysis are at best hypothesis-generating, and there isn't evidence that the device does something helpful for patients. But it's hard to see that a difference of 82% to 17% isn't something more than just bias, so I'm convinced that these patients are better…So, my answer is yes."
- *Dr. Kato, cardiothoracic surgeon:* "I would say no. The data are blurry at best. I was disappointed that despite the fact that the device has been used in Europe, no data was presented on the outside the U.S. [OUS experience]. Even our European colleagues, [had] a chance to present some data, [but there were] no data. All we have is a Class IIb recommendation…and that really isn't a strong recommendation. Most people I speak to who use evidence-based guidelines say, 'Well, IIb is short of a III.' In that case, the device, as it stands right now, given the dataset, does not reach the threshold of safety and efficacy."
- *Dr. Lofland, cardiothoracic surgeon:* "Yes."

QUESTION 8. Discuss labeling. Comment on the appropriateness of the study data included in the labeling, and discuss whether there are any analyses or data not provided that would be important to provide to the user in the labeling.

The panel chair summarized: "It needs a little bit more flushing out."

The FDA's Dr. Zuckerman replied, "We've got time."

No one had any comments (*NOTE: Maybe no one really read them.*)

Dr. Zuckerman pointed out that there were no contraindications in the label.

- *Dr. Vetrovec, interventional cardiologist:* "The full label, I can think of a lot of contraindications – patients with the anatomy for this clip – and they should be determined to be non-surgical candidates by however it is defined. And patients who have less than a year of life, etc."
- *Dr. Zuckerman:* "But for specific contraindications, for which there are none right now, you would feel comfortable if they did that specific procedure? It has to be an egregious thing to be a contraindication."
- *Dr. Vetrovec:* "It is a high-risk, unknown population. As long as that has been well defined, that provides some safety if you are thinking about lawsuit issues."
- *Panel chair:* "I think this deserves some more thought, although we aren't going to get to it today. That will need more discussion."

QUESTION 9a. Discuss the post-approval study. Discuss the appropriateness of the proposed post-approval study in the following area: The sponsor proposes to demonstrate long-term effectiveness by evaluating freedom from mitral valve surgery at 24 months in patients with moderate-to-severe or severe mitral valve regurgitation who are deemed too high risk to undergo surgery.

The panel chair summarized: "There is no enthusiasm at all for freedom from mitral valve surgery as a primary endpoint, but some other endpoints used in heart failure trials as well as the addition of some functional endpoints such as treadmill time, six-minute walk…might be reasonable in a post-approval study."

QUESTION 9b. Discuss endpoint. Discuss the appropriateness of using freedom from mitral valve surgery as a primary effectiveness endpoint in the intended patient population.

Panel member comments included:

- *Dr. Dehmer, interventional cardiologist:* "I would probably have freedom as a secondary endpoint and some clinical variables like SF-36, Seattle HF score, or other variables as the primary endpoint. Answering the questions, 'Does the patient feel better?' and 'Can they do more of their daily activities?'"
- *Dr. Jeevanandam, cardiothoracic surgeon:* "Freedom from mitral valve surgery is not an appropriate endpoint. A six-minute walk or some assessment of improvement would be appropriate. I would go for a functional assessment."
- *Panel chair:* "I would agree that freedom from mitral valve surgery isn't a good endpoint, but what about freedom from indications for mitral valve surgery – might that work?"

QUESTION 9c. Discuss alternative endpoints. Discuss possible alternative primary effectiveness endpoints, such as a composite of death and heart failure hospitalization.

Panel member comments included:

- *Dr. Kato, cardiothoracic surgeon:* "I would hope that the endpoints would not be composites. That muddies the endpoints. Sure, quality of life, functional assessment. Sure, they have to be around."
- *Panel chair:* "None of the data suggest that there is improvement in length of life. Maybe there is in a big, well-designed study. But data do suggest that there ***may*** be a reduction in hospitalizations. How about that as an endpoint? (*Dr. Zuckerman nodded affirmatively.*) "That is common in heart failure drug trials." (*Others nodded yes.*)
- *Dr. Kato:* "I would agree with that. As opposed to aortic stenosis, where if you fix the stenosis you do live longer, here we don't know…Let's say there was a significant survival benefit. Well, that would really tip the scales. You have to be open to that concept, but we don't have the data."
- *Dr. Vetrovec, interventional cardiologist:* "Functional improvement would be my biggest one. I wasn't totally convinced about the lessening of hospitalization. You could technically say that the sickest people died off, and that is why you had less hospitalization."
- *Dr. Selzman, cardiothoracic surgeon:* "This is a palliative therapy, and…you'd have to have a composite, like a cardiac pulmonary stress test…You have an idea of what they can do, and that might be the most quantitative way of looking at that."
- *Dr. Ferguson, interventional cardiologist:* "Using this in combination with hospitalization and death would not be unreasonable."

PANEL CONSIDERATION OF FDA VOTING QUESTIONS

In his closing remarks, Abbott expert Dr. Mack said there is a National Institutes of Health (NIH) trial comparing mitral valve repair and replacement, "There is a very robust postmarket infrastructure in place should the panel recommend approval …including mandatory participation in the TCT registry… Having surgeon gatekeepers assures that the appropriate patient population will be treated with this device." He reminded the panel that more than 6,000 devices have been implanted in Europe, and he warned them that it will be five years for some patients if the device is not recommended for approval.

Dr. Laskey left before the votes were taken.

QUESTION 1. Is there reasonable assurance that the MitraClip is *safe* for the indicated patient population?

VOTE: 8 Yes, unanimous

QUESTION 2. Is there reasonable assurance that the MitraClip is *effective*?

VOTE: 4 Yes, 5 No

There was a tie until the panel chair broke it with a No vote.

The Yes votes were 2 interventional cardiologists (Dr. Dehmer and Dr. Vetrovec), cardiac surgeon Dr. Katz, and cardiothoracic surgeon Dr. Lofland. The No votes were the panel chair Dr. Borer, a cardiovascular surgeon; 3 cardiothoracic surgeons (Dr. Jeevanandam, Dr. Kato, and Dr. Selzman); and Dr. Ferguson, an interventional cardiologist.

Panel members explained their votes:

- *Dr. Kato, cardiothoracic surgeon:* "I'd like to see a randomized trial. There are enough patients who would satisfy the criteria for a randomized trial quickly. I am concerned that we need to maintain at least some bar of scientific validity here to…give some additional assurance that it is scientifically based [so] that I can believe that these data are true."
- *Dr. Selzman, cardiothoracic surgeon:* "I question all the data for efficacy, but my overall opinion is that the safety profile is so low that when it comes to No. 3, an apparent benefit is a favorable ratio."
- *Dr. Ferguson, interventional cardiologist:* "I'd really like this device, but the company did not do a good job of identifying the patients and clearly defining that the patients were not surgical candidates."
- *Dr. Jeevanandam, cardiothoracic surgeon:* "There are patients who would benefit from this device, and we should make sure that this goes into a really small group of people who are truly inoperable, and that's why I voted no."
- *Panel chair, cardiovascular surgeon:* "I was concerned. I had a great deal of difficulty interpreting the registry data for all the reasons listed in the preamble to Question 5. At the end of the day, it was very difficult for me to say who could benefit from this. This is a potentially useful device, but I didn't know who, and that was my concern, and that is why I voted no."

QUESTION 3. Do the benefits outweigh the risks?

VOTE: 5 Yes, 3 No

The Yes votes were interventional cardiologists Dr. Dehmer and Dr. Vetrovec; cardiac surgeon Dr. Katz; and cardiothoracic surgeons Dr. Lofland and Dr. Selzman. The No votes were cardiothoracic surgeons Dr. Jeevanandam and Dr. Kato, and interventional cardiologist Dr. Ferguson.

Panel member comments after the vote included:

- *Dr. Lofland, cardiothoracic surgeon:* "I had no problem with this question."
- *Dr. Vetrovec, interventional cardiologist:* "I was convinced that it was more than happenstance. It seemed to be real, and the overall risks seemed reasonable for this very selective, limited population."
- *Dr. Selzman, cardiothoracic surgeon:* "I said yes with trepidation. There were some great stories…It is easy to be swayed by great stories…but they are true…Neat things happen. I hope that when it comes down to the labeling, the discussions come up with next phases of things – that it stays true. Truly inoperable patients is what I worry about. I worry that the sponsor said it will do a post-approval study in 2,400 patients, and I worry about patient creep that can get to 2,400 a little quicker."
- *Dr. Katz, cardiac surgeon:* "The patient in the wheelchair was the one that I referred, and she did remarkably well. I also thought the NYHA data was impressive. I have a hard time telling patients that we have to wait five years…In no way was this an elegant study. It was really poor in a lot of ways, but weighing the alternatives was the deciding factor."
- *Dr. Dehmer, interventional cardiologist:* "This is not my very first panel, but I don't have as much experience as many of the others here…Usually, when I finish, I am mentally somewhat exhausted…I will continue to think about this

panel because it has been incredibly challenging. Both the sponsor and the FDA are to be commended…The data the sponsor presented had as many holes as Swiss cheese, and the FDA did a fantastic job finding every one of them. Nevertheless, I was probably going to vote differently until I heard definitions of what constituted valid scientific data again, and it is not restricted to randomized trials. There are other data that are acceptable, and the totality of the data that we see…swayed me to feel like this is a device that has value for a selected group of patients. The challenge moving forward is for the Agency and sponsor to heavily re-engage themselves and find a solution that would, in a limited way, allow this device to be available to a select group of patients."