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Testimony Before the FDA's Circulatory System Devices Panel on the Premarket Approval Application P100009 for the Abbott Vascular MitraClip Clip Delivery System
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I am Dr. Michael Carome, Deputy Director of Public Citizen's Health Research Group (HRG), testifying on behalf of myself and Dr. Sidney Wolfe, the HRG Director. We have no financial conflicts of interest.

We strongly oppose Food and Drug Administration's (FDA) approval of the MitraClip Clip Delivery System (MitraClip) for the percutaneous reduction of significant symptomatic mitral regurgitation (MR) (MR $\geq$ 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 MR. We oppose approval because:

(1) The device has known risks of serious harm;
(2) Abbott Vascular, the MitraClip sponsor, has failed to provide data from any prospective, well-designed, randomized controlled clinical trial (RCT) demonstrating that the device is at least as safe and effective as standard aggressive medical therapy for the intended patient population; and
(3) As a result of (1) and (2), there are insufficient data to provide a reasonable assurance that the device is effective for the proposed indication or that the benefits of using the device outweigh the risks.

Risks of the MitraClip

The MitraClip is a significant-risk device that can result in numerous serious adverse events, including:[1]

- Bleeding;
- Cardiac arrhythmias;
- Cardiac arrest;
- Cardiac perforation and tamponade;
- Endocarditis;
- MitraClip erosion, migration, and thrombosis;
- Mitral valve injury;
- Myocardial infarction;
- Early failure due to single leaflet device attachment;
- Need for emergency cardiac surgery;
- Stroke; and
- Death.

Insufficient Evidence of a Favorable Risk-Benefit Profile for the MitraClip

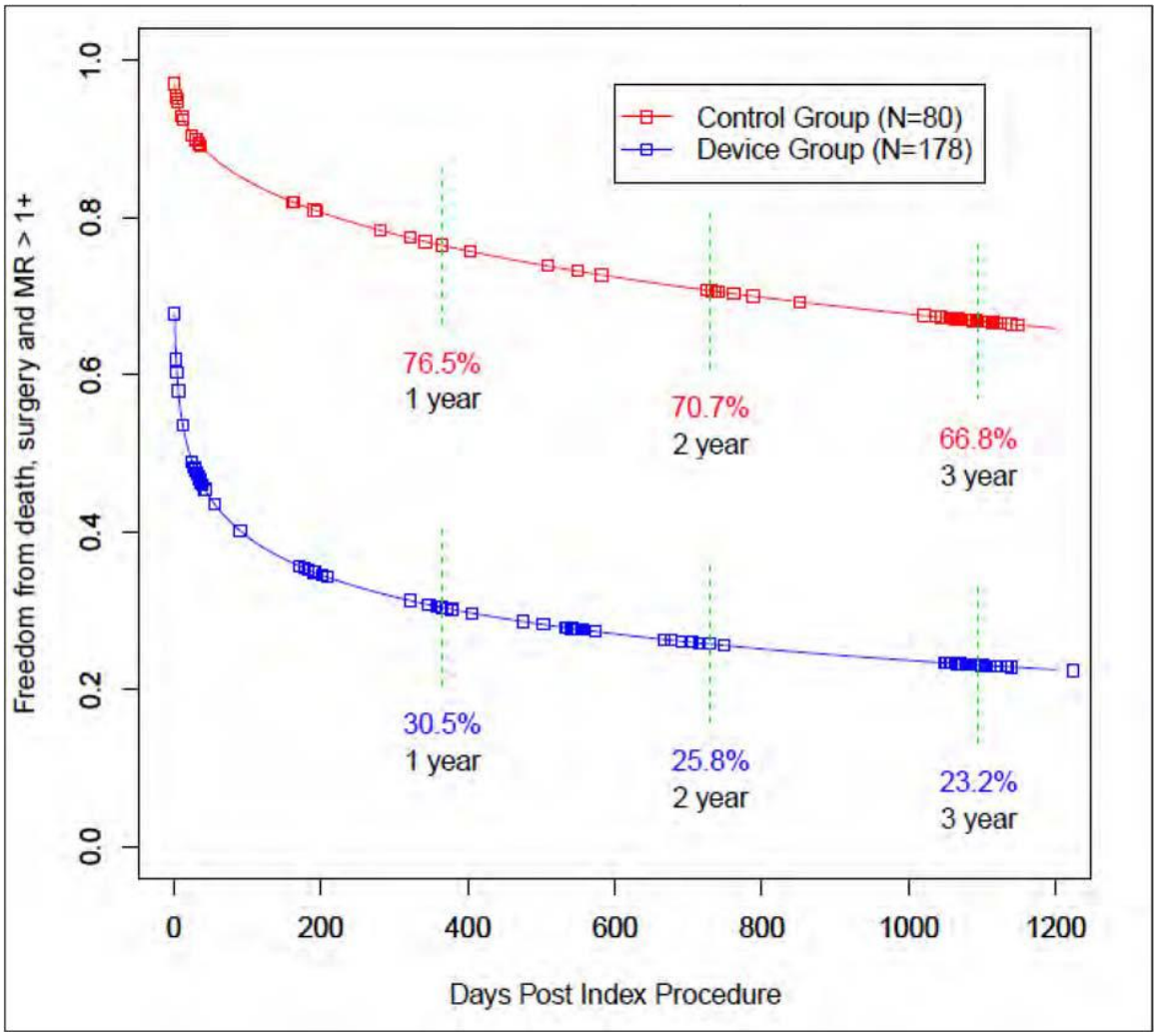
To justify approval in light of the device's significant risks, data must be provided from at least one well-designed RCT demonstrating that the risk-benefit profile of the MitraClip is at least as favorable as that of

[1] Abbott Vascular. MitraClip Clip Delivery System: Instructions for use. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM343688.pdf. Accessed March 19, 2013 (page 4).

medical therapy alone in the intended patient population. Such a study has not been conducted.

Based on results of the EVEREST II RCT, the only RCT presented evaluating the device, the sponsor originally proposed using the MitraClip for treating any patient with significant chronic MR. However, the FDA's analysis of this trial failed to demonstrate an appropriate risk-benefit profile for the device when compared to standard mitral valve surgery in a selected mitral valve patient population.[2] In particular, the FDA's analysis of the composite efficacy endpoint of freedom from death, surgery or re-operation, and MR > 1+ showed that the MitraClip performed significantly worse than traditional valve surgery (see figure below, excerpted from the FDA briefing document).[3]

Figure 4: EVEREST II RCT – Weibull Freedom from Death, Surgery (for Device group) or Re-operation (for the Control group) and MR > 1+



[2] The Food and Drug Administration. FDA executive summary prepared for the March 20, 2013 meeting of the Circulatory System Devices Panel: P100009 - Abbott Vascular MitraClip Clip Delivery System. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM343842.pdf. Accessed March 18, 2013 (page 9).
[3] *Ibid* (page 19).

Because the EVEREST II RCT data failed to support approval for the sponsor's original proposed indication, the sponsor performed additional *post-hoc* analyses on other patient groupings and changed the originally proposed indication to the one being considered today.[4] The FDA noted the following regarding the modified proposed indication:[5]

> The currently proposed indication for use was developed by Abbott Vascular after study results were known and analyzed by Abbott Vascular (*post-hoc*) and was advanced as an alternative after FDA communicated their concerns that the evidence available [from EVEREST II] to support a finding of safety and effectiveness of the device for the originally proposed indication …was insufficient. **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 re-configured to support an indication for use and population for use developed *post-hoc***. [bolded emphasis added]

Even a perfectly designed registry study with a prospective, well-matched, contemporaneous medical therapy comparator control group would not have been sufficient to support approval of the MitraClip for the proposed indication. And yet, as the FDA review points out, each of the retrospective evaluations of registry data presented by the sponsor were seriously flawed and fall well short of evidentiary standard needed for approval.

For example, the post-hoc analysis retrospectively comparing pooled data from 351 high-surgical-risk patients (from the EVEREST II High Risk Registry [HRR] and the REALISM high-risk [HR] cohort) to data on a cohort of medically treated, high-risk MR patients (extracted from the Duke database [Duke Cohort]) had numerous flaws highlighted by the FDA, including:

- Many patients in the "high-risk" MitraClip registry pool population were not "too high-risk for surgery" or inoperable, which are the designated target populations under the proposed indication.[6]
- There were clinically important differences between the HRR and REALISM HR patients, which undermines statistical validity of the pooled analysis.[7]
- Discontinuous enrollment of the HRR and REALISM HR patients may have been significantly impacted by selection-bias considerations over time, as operators gained more experience with patient selection.[8]
- The propensity scoring for matching the Duke Cohort patients to the MitraClip cohort was conducted without concealing mortality outcome data, which could have introduced bias.[9]
- There were significant differences in multiple relevant clinical characteristics (including age, gender, previous cardiac surgery, atrial fibrillation, diabetes, renal disease, and class III/IV symptoms, among others) between the integrated high-risk MitraClip cohort and the

[4] *Ibid* (page 6).
[5] *Ibid* (pages 6-7).
[6] *Ibid* (pages 28, 33, and 40).
[7] *Ibid* (pages 49-50).
[8] *Ibid* (pages 50-51).
[9] *Ibid* (page 59).

Duke Cohort. Attempts to create better-matched subsets for each cohort created patient groups that do not represent any well-defined population.[10]

Conclusions

- We agree with the FDA that the post-hoc analyses provided by the sponsor "do not constitute valid scientific evidence of safety and effectiveness for the MitraClip…for the proposed indication for use in an inoperable MR population."[11]
- The sponsor's proposed uncontrolled, single-arm registry post-approval study would be a grossly inadequate public health approach given the absence of data from an RCT demonstrating that the device is at least as safe and effective as standard aggressive medical therapy for the intended patient population**.**
- A pre-approval, well-designed RCT must be successfully completed before the FDA considers approving the MitraClip. The already-initiated U.S. COAPT trial may represent such an RCT.

[10] *Ibid* (pages 63-72).
[11] *Ibid* (page 83).