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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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CIRCULATORY SYSTEM DEVICES PANEL

MEETING

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MONDAY,  
SEPTEMBER 10,

+ + + + +

The panel met at 9:00 a.m. in Salon of the Gaithersburg Marriott Washingtonian Center, 9751 Washingtonian Boulevard, Gaithersburg, Maryland, Dr. Cynthia Tracy, Chairperson, presiding.

PRESENT:

- |                             |                         |
|-----------------------------|-------------------------|
| CYNTHIA M. TRACY, M.D.      | Chair                   |
| SALIM AZIZ, M.D.            | Member                  |
| MICHAEL D. CRITTENDEN, M.D. | Temporary Voting Member |
| ROBERT DACEY                | Consumer Representative |
| RICHARD A. HOPKINS          | Temporary Voting Member |
| WARREN K. LASKEY, M.D.      | Member                  |
| NANCY L. MCDANIEL, M.D.     | Temporary Voting Member |
| MICHAEL MORTON              | Industry Representative |
| DAVID J. SKORTON, M.D.      | Temporary Voting Member |
| CHRISTOPHER J. WHITE, M.D.  | Temporary Voting Member |
| ROBERTA G. WILLIAMS, M.D.   | Temporary Voting Member |
| JANET T. WITTES, Ph.D.      | Member                  |
| KENNETH-G. ZAHKA, Ph.D.     | Temporary Voting Member |
| MEGAN MOYNAHAN              | Executive Secretary     |

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P-R-O-C-&E-D-I-N-G-S

9:04 a.m.

DR. TRACY:: Good morning. I'd like to call to order this meeting of the Circulatory System Device Panel. The topic is discussion of premarket application for AGA Medical Amplatzer Septal Occluder and Delivery System.

MS. MOYNAHAN: I would like to read the conflict of interest statement for this morning, or today rather. The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of any impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interest reported by the committee participants. The conflict of interest statutes prohibits special government employees from participating in matters that could affect their or their employer's financial interest.

However, the agency has determined that participation of certain members and consultants the

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1 need for whose services outweighs the potential  
2 conflict of interest involved is in the best interest  
3 of the government.

4 Therefore, a waiver has been granted for Dr.  
5 David Skorton for his interest in a firm that could  
6 potentially be affected by the panel's  
7 recommendations. Copies of this waiver may be  
8 obtained from the agency's Freedom of Information  
9 Office, Room 12A-15 of the Parklawn Building.

10 In the event that the discussions involve  
11 any other products or firms not already on the agenda  
12 in which an FDA participant has a financial interest,  
13 the participant should excuse him or herself from such  
14 involvement and the exclusion will be noted for the  
15 record.

16 With respect to all other participants we  
17 ask in the interest of fairness that all persons  
18 making statements or presentations disclose any  
19 current or previous financial involvement with any  
20 firm whose products they wish to comment upon.

21 DR. TRACY: Can I ask the panel members to  
22 introduce themselves.

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1 MR. MORTON: I'm Michael Morton. I'm the  
2 Industry Representative. I'm employed by W. L. Gore.

3 DR. WHITE: My name is Christopher White.  
4 I'm a cardiologist from Ochsner Clinic in New Orleans.

5 DR. WILLIAMS: Roberta Williams, pediatric  
6 cardiologist and Chairman of Pediatrics, University of  
7 Southern California.

8 DR. SKORTON: I'm David Skorton. I'm a  
9 cardiologist. I'm the Vice President for Research for  
10 the University of Iowa. I want to say for the record  
11 that the waiver that was granted, my conflict is  
12 institutional, not a personal financial conflict.

13 DR. ZAHKA: I'm Kenneth Zahka. I'm a  
14 pediatric cardiologist at Rainbow Babies and  
15 Children's Hospital in Cleveland in Case Western  
16 Reserve University.

17 DR. HOPKINS: Richard Hopkins. I'm a  
18 pediatric and adult cardiac surgeon, Chief of  
19 Cardiothoracic Surgery at Brown University.

20 DR. AZIZ: Salim Aziz. I'm an adult cardiac  
21 surgeon in Denver, Colorado, University of Colorado.

22 DR. TRACY : I'm Cindy Tracy. I'm from

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1 Georgetown University Hospital, lecture physiologist.

2 MS. MOYNAHAN: My name is Megan Moynahan.  
3 I'm the Executive Secretary of the Circulatory System  
4 Devices Panel.

5 DR. LASKEY: Warren Laskey, interventional  
6 cardiologist from the University of Maryland.

7 DR. McDANIEL: Nancy McDaniel, pediatric  
8 cardiologist, University of Virginia.

9 DR. CRITTENDEN: Mike Crittenden, Cardiac  
10 Surgery, Harvard University, West Roxbury, VA.

11 MR. DACEY: I'm Robert Dacey, Consumer  
12 Representative from Boulder County, Colorado.

13 MR. DILLARD: Jim Dillard. I'm the Director  
14 of the Division of Cardiovascular and Respiratory  
15 Devices, Anesthesiology. They are also at the Food  
16 and Drug Administration.

17 DR. TRACY: I will at this point open the  
18 open public hearing. Oh, I'm sorry. I jumped one  
19 step on the script, Megan.

20 MS. MOYNAHAN: This is the appointment to  
21 temporary voting status for today. Pursuant to the  
22 authority granted under the Medical Devices Advisory

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1 Committee Charter dated October 27, 1990, and as  
2 amended August 18, 1999, I appoint the following  
3 individuals as voting members of the Circulatory  
4 System Devices Panel for this meeting on September 10,  
5 2001.

6 Michael Crittenden, Nancy McDaniel,  
7 Christopher White, Richard Hopkins, David Skorton,  
8 Roberta Williams, and Kenneth Zahka.

9 For the record, these people are special  
10 government employees and are consultants to this panel  
11 and to the Medical Devices Advisory Committee. They  
12 have undergone the customary conflict of interest  
13 review and have reviewed the material to be considered  
14 at this meeting.

15 DR. TRACY: Thanks. Okay, now we'll open  
16 the open public hearing. At this point there were no  
17 specific requests from the public to speak but is  
18 there anybody here present who would like to make a  
19 statement?

20 MS. MOYNAHAN: I have a couple of -- if  
21 there's no one from the public who **wants** to speak, I  
22 received a couple of letters. Actually, I received

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1 eight letters in support of the Septal Occluders that  
2 are being discussed today. I don't really have time  
3 to read all the letters into the record but what I  
4 would like to do is summarize one of them.

5 The eight letters were actually on behalf of  
6 the same patient who received a Septal device last  
7 year and she writes in her letter that she had a  
8 procedure done and was discharged the very next day.  
9 Since that time there has been a big improvement in  
10 her endurance and energy and she's has no adverse  
11 effects at all.

12 "These devices not only repaired my defect,  
13 saved me the trauma of open-heart surgery along with  
14 a lengthy recuperation but also enabled me to return  
15 to work within just a few days.

16 I'm contributing my views in the hope it  
17 will have a positive effective on the vote for  
18 approval for these devices so they will become  
19 available to all those cardiac patients out there who  
20 are in need." The other seven letters were in support  
21 in a similar fashion.

22 If there are no other comments, then we'll

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1 close the open public hearing and move on to the  
2 sponsor's presentation.

3 DR. TRACY: Before you start, I would just  
4 like to remind you to introduce yourselves and state  
5 any conflict of interest.

6 MR. GOUGEON: Members of the panel, members  
7 of the FDA, ladies and gentlemen, good morning. My  
8 name is Franck Gougeon. I'm the Executive Vice  
9 President of AGA Medical Corporation who is the  
10 sponsor of this study. I am also one of the founding  
11 officers.

12 It is my pleasure to read out the  
13 presentation of the transcatheter closure of secundum  
14 atrial septal defect using the Amplatzer Septal  
15 Occluder.

16 We have brought with us three cardiologists  
17 who conducted a clinical trial. They include Dr.  
18 Ziyad Hijazi of the University of Chicago Children's  
19 Hospital in Chicago, Dr. John Cheatham of the Nemours  
20 Cardiac Center in Orlando, and Dr. John Moore of St.  
21 Christopher's Hospital for Children in Philadelphia.  
22 They will present the study clinical results and be

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1 available for your questions.

2 In addition, there are a number of people  
3 here who provide a cross-function representation  
4 involved in the clinical trial or the development of  
5 the Amplatzer system.

6 Among them Mr. Ken Lock who managed the  
7 study will act as the moderator for questions raised  
8 by the panel.

9 Following my brief introduction, Dr. John  
10 Cheatham will provide a study for background evade  
11 detorsion. Dr. Hijazi will provide a summary of the  
12 study. Dr. Moore will cover the fenestrated Fontan  
13 arm of the study. Finally, Dr. Hijazi will conclude  
14 with a summary of revised performance in both  
15 indications.

16 We are seeking approval for two indications  
17 today. The first covers the transcatheter closure  
18 atrial septal defect in secundumposition. The second  
19 concerned the closure fenestrations post-Fontan  
20 operation. And Amplatzer Septal Occluders in sizes  
21 ranges from 4 to 38 mm needed to cover both  
22 indications.

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1 AGA Medical is a sponsor of this study.  
2 This is a privately held operation located in  
7 Minneapolis, Minnesota. The company was founded in  
4 1995 and currently employs 55 full-time employees.

5 The facility consist of 35,000 square feet  
6 most of which is dedicated to manufacturing. The last  
7 stages of application are done in 10,000 cleaning  
8 rooms. Sterilization is assured by a local  
9 contractor.

10 The Amplatzer Septal Occluder is  
11 manufactured onsite. The device is a self-expanding,  
12 self-centering, double-disc device made from 4,000 to  
13 8,000 nitinol wires.

14 The two discs are linked together by short-  
15 connecting waist corresponding to the thickness of the  
16 atrial septal. Sizes range from 4 to 48 mm. These  
17 dimensions are based on the center portion of the  
18 occluder as the device is designed to stunt the  
19 defect.

20 Polyester patches are sown in both disc and  
21 the waist to induce some urgency. In addition, the  
22 left atrial disc is slightly angled toward the other

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1 disc to provide firm and secure contact between the  
2 device and the muscular atrial septum rim. We believe  
3 this is an important feature to ensure proper  
4 endothelialization of the implant.

5 For introduction, the prosthesis is attached  
6 to a stainless steel delivery cable using a microscrew  
7 and pulled into a loader. It is then pushed through  
8 a six to 12 French introducer sheath and placed across  
9 the atrial septal defect.

10 It relies exclusively on the super elastic  
11 properties of the nickel-titanium alloy, a part  
12 existing in the tip of the introducer sheath. The  
13 left-atrial disc immediately resumes its original  
14 shape. The sheath is pulled back to take advantage of  
15 the self-center capability of the connecting waist.  
16 The implant is pulled gently against the EFD and the  
17 right-atrial disc is released to a sandwich effect.

18 The Amplatzer Septal Occluder study was  
19 initiated in May of 1997 as a randomized clinical  
20 trial comparing the results of the device with those  
21 in open-heart surgery which currently is a gold  
22 standard in the United States for repair of atrial

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1 septal defects. We refer to this as a Phase IIA of  
2 the clinical trial.

3 However, due to a high fallout rate in the  
4 surgical arm of the study, the surgical device panel  
5 organized by AGA was held in October 1997 at which  
6 time a non randomized prospective clinical trial  
7 comparing the device with surgery was deemed clear.

8 It was also decided that the device patients  
9 already enrolled in a trial under the randomized study  
10 where a known appropriate to comparison between the  
11 two groups.

12 An investigation plan was modified  
13 accordingly and the study resumed in March 1998. We  
14 refer to this as Phase IIB of that clinical trial  
15 which is the basis for the analysis being presented  
16 today. This phase is highlighted in yellow on this  
17 slide.

18 Further modification to the investigational  
19 plan, the authorization October 1998 for device  
20 centers to capture the prospectively surgical patient  
21 as well as device patients and because of slow  
22 enrollment in surgical cohort the authorization in

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1 January 1999 to capture data retrospectively on  
2 patients who underwent surgical repair.

3 Furthermore, an extension was granted to AGA  
4 Medical to continue enrolling patients in the device  
5 group was a number of surgical patients needed for the  
6 PMA analysis could be reached.

7 The study was completed in May of 2000 with  
8 a total of 459 device patients and a surgical cohort  
9 of 155 patients. Although only 110 patients in each  
10 group are needed for the analysis, the FDA requested  
11 that all device patients be included for comparison  
12 between the two groups. We will, therefore, report  
13 today on this entire pool of patients.

14 Finally, I would like to add that from June  
15 2000 to May 2001 an additional 465 patients had been  
16 treated with this device and the continued access  
17 protocol D96-1. Although we are not reporting on this  
18 additional pool of patients today, AGA Medical is not  
19 aware of any issues that risk the safety and efficacy  
20 of the Amplatzer Septal Occluder.

21 With that, I would like to introduce Dr.  
22 John Cheatham who will give you an overview of the

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1 history of ASD closure.

2 DR. CHEATHAM: Thank you. I'm Dr. John  
3 Cheatham, Director of Cardiac Catheterizations and  
4 Interventions at the Nemours Cardiac Center located in  
5 Arnold Palmer Hospital, Children's Heart Institute in  
6 Orlando, Florida. I'm one of the principal  
7 investigators. I have no financial interest in AGA  
8 Medical. My travel expenses are being reimbursed by  
9 the company.

10 The first clinical question that comes to  
11 mind is why close an atrial septal defect. Most  
12 patients with a hemodynamically significant ASD are  
13 asymptomatic during the first decade of life. However,  
14 by 20 years of age, 50 percent will complain of  
15 exertional dyspnea from chronic right intricular  
16 volume overload and virtually all, or 90 percent, will  
17 have symptoms by 60 years.

18 If uncorrected until after 50 years of age,  
19 a 75 percent mortality can be expected. Another  
20 complication of unrepaired atrial septal 'defect is  
21 high rate of atrial flutter and fibrillation with  
22 increasing age. However, if correction of the defect

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1 at an appropriate age occurs, then congestive heart  
2 failure, pulmonary hypertension, thromboembolic  
3 events, and atrial arrhythmias may be avoided.

4 Since the development of cardiopulmonary  
5 bypass circuit in the 1950s, surgical repair of atrial  
6 septal defect has been possible and is considered the  
7 gold standard of therapy. However, this invasive  
8 treatment requires a median sternotomy orthoracotomy,  
9 exposure to cardiopulmonary bypass, aortic cross-clamp  
10 with resulting myocardial ischemia and a right  
11 atriotomy.

12 It also requires a blood transfusion during  
13 or after repair of the defect or, at the very least,  
14 results in delusional anemia. The repair usually  
15 involves either primary suture or patch closure.  
16 Surgery is typically performed after two to three  
17 years of age, but in selected individuals may be  
18 required at an earlier age.

19 Open-heart surgical correction of ASD  
20 usually requires three to five days of hospitalization  
21 with a convalescent period of four to six weeks where  
22 school and/or work days may be missed.

1           There are several possible advances of  
2 percutaneous transcatheter closure of atrial septal  
3 defect compared to conventional surgical repair. Pain  
4 and discomfort may be minimized while an incisional  
5 scar is eliminated.       There's no exposure to  
6 cardiopulmonary bypass and the procedure is unlikely  
7 to require blood or blood product transfusion or  
8 result in delusional anemia.

9           There should be an expected reduction in  
10 hospital stay and rapid return to normal activities  
11 including school and work.       Finally, this less  
12 invasive procedure may result in cost savings.

13           The history of percutaneous transcatheter  
14 closure of atrial septal defect actually began over 25  
15 years ago with King and Mills' first description of  
16 success.       However, it was a decade later before FDA  
17 sponsored clinical trials were initiated in the United  
18 States.

19           Over the ensuing 15 years various device  
20 designs, materials, and delivery techniques were  
21 tested.       However, there were problems associated with  
22 some of the early devices.       Initially the delivery

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1 sheath was as large as 24 French but later was reduced  
2 to 11 to 14 French, hardly small by today's standards.

3 Some of the designs required hooks to secure  
4 the device or were configured as a square umbrella  
5 which lead to difficult delivery and/or implant.  
6 There was a high residual shunt rate associated with  
7 some devices which has been linked to poor self-  
8 centering capabilities.

9 Structural flaws resulting in a high  
10 percentage of metal frame fatigue fractures or  
11 "unbuttoning" of the device also occurred. Finally,  
12 virtually all of the early ASD devices were extremely  
13 difficult, if not impossible, to reposition and/or to  
14 retrieve during implantation.

1s When defining the characteristics of an  
16 ideal device for transcatheter closure of ASD, there  
17 are several important features. First, a device and  
18 delivery system must be user friendly with simply  
19 mechanics. The delivery system should be small in  
20 order to treat infants and young children without  
21 causing vascular compromise. There must be an  
22 effective and high rate of complete closure of the

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1 defect which requires self-centering properties.

2 The occluder should be able to close most  
3 atrial septal defects regardless of defect size. The  
4 device must be extremely easy to reposition and/or to  
5 retrieve to ensure safety and efficacy.

6 In the rare occurrence of device  
7 embolization, preservation of flow and cardiac  
8 function must be maintained. The device should be  
9 durable while endothelialization occurs and there  
10 should be a lack of ongoing morbidity during follow-  
11 up.

12 Finally, the device should be economical.  
13 The Amplatzer Septal Occluder and delivery system meet  
14 these criteria set forth in the ideal device.

15 If it's possible, could we dim the lights.  
16 I think this is going to be a short movie. This short  
17 movie was filmed during a live-case demonstration  
18 during one of the recent PIC symposium. The patient  
19 and the family has given their permission for this  
20 demonstration to the panel today as well as use of  
21 their names.

22 Amplatzer Septal Occluder and the delivery

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1 system will be demonstrated. This is an animation of  
2 the percutaneous entry into the femoral vein where the  
3 sheath is passed into the infera vena cava through the  
4 right atrium and the atrial septal defect into the  
5 left atrium.

6 The left atrial disc is deplored on the left  
7 side of the atria septum and the entire system brought  
8 back toward the atrial septal defect with the middle  
9 waist stenting the ASD and the right atrial disc  
10 redeployed. The device is then released with the  
11 sheath removal.

12 Over a period of time complete  
13 endothelialization occurs. It's very important that  
14 the positioned echocardiographer and the operator  
15 complete the review of the transesophageal  
16 echocardiogram prior to beginning the procedure.

17 This is an example of a multi-plane  
18 transesophageal echocardiogram on a patient with a  
19 large isolated secundum ASD demonstrating the septal  
20 rims as well as the isolated defect.

21 It's very important to identify all of these  
22 structures at the time of preimplant. Ordagonal views

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1 demonstrate an ASD size of 28 to 23 mm in this  
2 particular patient.

3 The AP camera is angled in an LAO cranial  
4 position in order to profile the atrial septum leaving  
5 plenty of room for the anesthesiologist and the  
6 echocardiographer to perform their duties during the  
7 procedure.

8 The operator will typically perform a  
9 hemodynamic study initially along with angiography to  
10 demonstrate the atrial septal defect. In this  
11 particular instance, a right pulmonary vein injection  
12 will demonstrate the secundum ASD.

13 After the angiogram has been performed, an  
14 in-hole catheter is then delivered across the atrial  
15 septal defect into the left upper pulmonary vein where  
16 an exchange guidewire is placed. Over the exchange  
17 guidewire a sizing balloon is then placed and  
18 positioned across the atrial septal defect.

19 It's at this point that we determine that  
20 the balloon' stretch diameter of the defect. The  
21 balloon is inflated until there is no further flow  
22 across the defect and the diameter of the balloon on

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1 transesophageal echocardiogram, as well as on the  
2 corresponding fluoroscopic image here are measured.

3 At this point the appropriate size Amplatzer  
4 Septal Occluder is chosen with the middle waist equal  
5 to or slighter greater than the balloon stretch  
6 diameter. The device is then loaded on the delivery  
7 cable using the microscrew technique and then the  
8 entire loading system is submerged under saline in  
9 order to avoid any introduction of air into the  
10 loading sheath.

11 The short loading sheath is then attached to  
12 the long delivery sheath using a lure lock mechanism  
13 and the delivery cable advanced. This is the sheath  
14 in the left atrium near the left atrial appendage.

15 One can see under transesophageal  
16 echocardiographic guidance the deployment of left  
17 atrial disc in this particular patient. One can even  
18 see the polyester patch material as well.

19 Thecorrespondingangiographicappearanceor  
20 fluoroscopic appearance demonstrates the left atrial  
21 deployment of the disc, the middle waist being  
22 expanded and the entire system brought into the ASD to

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1       stent the ASD with the right atrial disc formed. This  
2       is the same process on the transesophageal  
3       echocardiogram with release of the device.

4               One can see the left atrial disc, the right  
5       atrial disc, and the middle waist at appropriate  
6       position.       At this time Doppler flow is also  
7       interrogated demonstrating proper function of both AV  
8       valves as well as small flow in the device material  
9       itself.

10              A right atrial angiogram is performed and in  
11       levo phase typically one may see a little bit of smoke  
12       material going through the device while the patient is  
13       fully heparinized.

14              The patient is typically either moved to a  
15       separate holding room or, actually more commonly,  
16       extubated in the cath lab.       With 30 minutes to 60  
17       minutes is fully awake and taking PL fluids and will  
18       be discharged usually approximately 24 hours later.

19              This is a follow-up transesophageal  
20       echocardiogram on this particular patient six months  
21       later.       One can see there is complete closure of the  
22       defect.       In addition, there is normal flow through

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1 mitral and tricuspid valve.

2 It's also important to demonstrate at this  
3 point in time some of the memory characteristics of  
4 nitinol. That is, after six months you can see the  
5 lower profile pre-implant configuration resumed.

6 Next I would like to introduce my colleague,  
7 Dr. Ziyad Hijazi, to discuss the study data.

8 DR. HIJAZI: Good morning. My name is Ziyad  
9 Hijazi. I am Professor of Pediatrics and Medicine at  
10 the University of Chicago and Chief of Section of  
11 Pediatric Cardiology. I have no financial interest in  
12 AGA Medical. My trip here is being sponsored by AGA  
13 Medical.

14 My task over the next 15 minutes or so is to  
15 share with you the results of catheter closure for  
16 secundum ASD using the Amplatzer Septal Occluder and  
17 comparing those results with open-heart surgery.

18 Let me give you a little detail about the  
19 study organization. We had an independent  
20 statistician to analyze the data of the trial. We had  
21 an independent echocardiography core lab consisting of  
22 two experienced pediatric cardiac echocardiographers

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1 to evaluate the results. We had an independent data  
2 safety monitoring board to review all complications  
3 and adverse events.

4 Before we proceed, it is important for me to  
5 go over certain definitions that are important in this  
6 trial. Intent to treat is defined as patient who  
7 consented, however a device was not introduced into  
8 the patient. Technical success is defined as  
9 successful deployment of the device.

10 Procedural success is technical success with  
11 no significant residual shunt. Significant residual  
12 shunt is being defined as any residual shunt measuring  
13 in diameter more than 2 mm as measured by color  
14 Doppler echocardiography.

15 Primary efficacy success is defined as  
16 technical success with no significant residual shunt  
17 measured at the 12-month follow-up. Composite success  
18 is defined as all attempted patients without a major  
19 complication, embolization, technical failure, or  
20 significant shunt measuring more than 2 mm.

21 The efficacy endpoint of the trial is to  
22 compare the closure rate at 12 months between the two

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1 arms of the study, the device closure versus surgical  
2 closure. The definition of successful closure is  
3 being defined as any patient who underwent the  
4 closure, device or surgery, with complete trivial or  
5 small residual shunt as assist by color Doppler  
6 echocardiography.

7 A fair disclosure is defined as any patient  
8 who underwent a closure, again device or surgery, with  
9 more than small residual shunt meaning moderate or  
10 large as defined by color Doppler echocardiography.

11 The residual shunt was studied by color  
12 Doppler echocardiography and the degree of shunt was  
13 graded into trivial, small, moderate, or large  
14 according to the width of the color jet at its exit  
15 from the atrial septum. This classification was  
16 reported in the journal Circulation by Boutin and her  
17 colleagues from the Hospital for Sick Children in  
18 Toronto in 1993.

19 So demonstrate that the device success is as  
20 good as surgery, we have to show that the primary  
21 efficacy success rate of the device must be shown to  
22 be within 8 percent of the primary success rate of

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1 surgery. Therefore, in simple terms, the acceptable  
2 critical difference should be within 8 percent.

3 To demonstrate safety of the device, we set  
4 acceptable rates of untoward aversive and for death  
5 and major complications to be less than or equal to 2  
6 percent for death and to be less than or equal to 10  
7 percent for major complications.

8 Let me go over the included and excluded  
9 criteria in our protocol. The inclusion criteria for  
10 the device group included any patient with secundum  
11 atrial septal defect measuring less than or equal to  
12 38 mm in diameter with significant left-to-right shunt  
13 as evidenced by either measurement of  $Q_p/Q_s$  more than  
14 or equal to 1.5 to- 1, or as evidenced by right  
15 intricardiac volume overload by echocardiography.

16 Also included patients with a clinical  
17 symptom such as paradoxical embolism or atrial  
18 dysrhythmia in the presence of a minimal shunt. A  
19 distance of more than 5 mm from the margins of the  
20 defects to the coronary sinus, AV valves, and the  
21 right upper lobe pulmonary vein was also included.

22 For the surgical group the inclusion

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1 criteria were similar to those of the device group  
2 with the exception of the size of the ASD being that  
3 there is no size limit for ASD, and no size limits for  
4 the rims if they're different.

5 This list, the exclusion criteria for the  
6 device patients, you have all of them in the package.  
7 There is no need for me to go over them. This slide  
8 also list the general exclusion criteria for both  
9 groups which are listed there. Again, I will not go  
10 over it in detail.

11 This slide again lists the exclusion  
12 criteria for the surgical patients. Again, they are  
13 similar to those of device exclusion criteria.

14 Now, let me go over our patient statement.  
15 459 patients were enrolled in the device arm and 155  
16 in the surgical arm. Of the 459 device patients 17  
17 were enrolled but did not receive a device, what we  
18 call they consented but they did not receive a device.  
19 hey were found not to be appropriate for device  
20 closure. We will talk about-them in the following  
21 slide.

22 One patient consented to undergo surgical

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1 closure but was found not to be eligible for open-  
2 heart surgery. Therefore, 442 patients underwent an  
3 attempt at device closure in the cath lab and 154  
4 patients underwent surgical closure.

5 Of the 17 patients labeled "intent to  
6 treat," six did not meet the inclusion criteria.  
7 Eight has an ASD which was too large for the device  
8 available at the time and five of them had ordeal  
9 conditions the operators felt uncomfortable to attempt  
10 device closure.

11 Let me go back to the eight patients. The  
12 eight patients who had an ASD larger than the  
13 available device at that time opted to wait for the  
14 proper size device to be available. Therefore, three  
15 of them underwent a second attempt with successful  
16 closure. Again, the third patient was found to have  
17 an ASD larger than the available device at that time.  
18 That patient opted to undergo open surgical repair.

19 This slide compares the two groups  
20 demographics. Both groups had similar percentage of  
21 females. However, as you can see, the surgical group  
22 was younger in age. Therefore, any factor associated

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1 with age, for example weight and height, was also  
2 different in both groups.

3 Also on this slide some age-related factors  
4 were different. For example, failure to thrive and  
5 respiratory infections were more common in this  
6 surgical group. Since our device group was somewhat  
7 older, these patients had more hypertension and  
8 stroke.

9 However, by echocardiography the size of the  
10 atrial septal defect in the two groups was similar, a  
11 mean of 13.3 mm for the device group and 14.2 mm for  
12 the surgical group.

13 Furthermore, the percentage of patients with  
14 right intricular volume overload was similar in both  
15 the groups. 94.1 percent of the device group compared  
16 to 96.1 percent of the surgical group had right  
17 intricular volume overload.

18 Now, let us talk about technical success for  
19 the procedure which is defined as successful  
20 deployment of the device or successful completion of  
21 the surgical procedure. Out of 442 patients who had  
22 an attempt at device deployment, 423 patients had a

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1 successful procedure. Therefore, the technical  
2 success rate is 95.7 percent, or surgical patients who  
3 underwent surgery had technical success.

4 Now, let us analyze those patients who  
5 failed a device procedure which is defined as any  
6 patient who had the device inserted but the device was  
7 recaptured or embolized and the procedure was aborted.  
8 Nineteen of 442 patients had a failed attempt.

9 Of those 19, 17 patients had medical  
10 conditions that the operator did not feel comfortable  
11 releasing the device. In one patient, however, the  
12 device embolized. In another patient the marker band  
13 of the delivery system embolized.

14 Now, let me talk about the marker band. The  
15 delivery sheath initially had a platinum marker band  
16 at the tip of the sheath to ease visualization of the  
17 sheath by fluoroscopy. This band became dislodged  
18 from the sheath and embolized. Therefore, after three  
19 incidents the manufacturing company removed this band  
20 of the sheath.

21 Of the 423 patients who had technically  
22 successful procedure, 413 had successful procedure.

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1 A successful procedure is defined as any patient who  
2 received a device or surgical closure with less than  
3 or equal to 2 mm residual shunt by color Doppler  
4 echocardiography. Therefore, 97.6 percent of device  
5 patients had a successful procedure compared to 100  
6 percent of the surgical patients.

7 Now, let us analyze the efficacy results.  
8 Again, the definition of primary efficacy result is  
9 that no significant residual shunt measuring more than  
10 2 mm by color Doppler echocardiography at the 12-month  
11 follow-up visit. Twelve-month data was available in  
12 331 device patients. 336 of them had successful  
13 closure giving a rate of 98.5 percent compared to 100  
14 percent of the surgical patients.

15 The p-value is .033 with a 90 percent  
16 confidence interval of -.052 to +0.017. Therefore,  
17 the lower band of the confidence interval is less than  
18 8 percent critical difference agreed upon as mentioned  
19 earlier.

20 This is another way of looking into success.  
21 Surgical patients are represented by the blue diamonds  
22 and device patients by the red squares. As can be

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1 seen over time, the success of device is very close to  
2 that of open-heart surgery.

3 At all points of follow-up the difference  
4 was not significant between the two arms. Although we  
5 had 100 percent successful closure for the surgical  
6 group, I would like to point out that seven surgical  
7 patients had residual shunt. However, this residual  
8 shunt was less than 2 mm in diameter.

9 Let me talk about the echo board. This  
10 consisted of two independent experienced pediatric  
11 echocardiographers from centers that were not involved  
12 in the trial. Those two physicians do not have any  
13 financial interest in AGA Medical. They only receive  
14 consultation fees.

15 They viewed a subset of the 12-month  
16 echocardiograms from both arms for this study. They  
17 concurred with the interpretations of the  
18 investigators.

19 Now, let us examine the safety results of  
20 the device and compare it to that of open-heart  
21 surgery. A data safety monitoring board was formed to  
22 assist safety of the procedures. Members were

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1 physicians with specialties in echocardiography,  
2 electrophysiology, cardio-thoracic surgery, and a  
3 statistician.

4 These members were not participants in the  
5 study and had no financial interest in the AGA  
6 Medical. They met independently to develop  
7 definitions and to adjudicate all adverse events.

8 These members developed the following  
9 definitions for major complications. Events that are  
10 life threatening, prolong hospitalization, or have  
11 long-term consequences or need for ongoing therapy.  
12 These include, but are not limited to, cerebral  
13 embolism, endocarditis, pericardial effusion with  
14 tamponade, repeat surgery, and death, which were  
15 listed in the protocol.

16 Additionally, cardiac arrhythmias requiring  
17 permanent pacemaker placement or long-term anti-  
18 arrhythmic medication and device embolization  
19 requiring immediate surgical removal, are also  
20 included as major complications.

21 They also developed the following  
22 definitions for minor complications. The device

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embolization with percutaneous retrieval, cardiac arrhythmia with treatment, phrenic nerve injury, hematoma, other vascular access site complications, retroperitoneal hematoma, surgical would complications, and other procedural complications, as listed in the protocol.

Additionally, pericardial effusion requiring medical management evidence of device associated thrombus formation without embolization (with or without treatment) and marker band embolization without known sequelae are included as minor complications.

This slide, compares the rates of major and minor complications between the two groups. 1.6 percent of the device group patients encountered major complications compared to 5.2 percent for the surgical control patients.

At 6.1 percent of the device patients had minor complications compared to 18.8 percent for the surgical group. Therefore, the overall rate of complications was 7.2 percent for the device group compared to 24 percent for the surgical control group.

1 This difference was significant.

2 This is another way of looking at rate of  
3 any complication between the two groups at anytime the  
4 difference in the-rate of any complication between the  
5 two groups was statistically significant favoring less  
6 complications for the device group.

7 This slide sort of describes all major  
8 complications encountered in both groups. Again, the  
9 total-major complication rate was 1.6 percent for the  
10 device group compared to 5.2 percent for the surgical  
11 group.

12 This is a busy slide but the slide describes  
13 the amount of complications for both groups. Again,  
14 the rate for the device group was significantly lower  
15 than that of the surgical group.

16 The FDA required a 12-month composite  
17 success which is defined as all attempted patients  
18 without a major complication, embolization, technical  
19 failure, or significant residual shunt measuring more  
20 than 2 mmby color Doppler echocardiography at anytime  
21 during this study. Patients could only fail one time  
22 and were not allowed to revert to a success over time.

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1           Therefore, this table demonstrates the 12-  
2 month composite success of 85.9 percent for the device  
3 group. However, if those cases of significant  
4 residual shunt encountered immediately after the  
5 closure and the shunt disappeared at the 12-month  
6 follow-up, which is demonstrated in 20 out of 25  
7 patients, they are allowed to revert. This would  
8 result in a 12-month composite success of 91.4 percent  
9 which is not significantly different from that of the  
10 surgical control group.

11           Now, let us evaluate the clinical utility of  
12 the Amplatzer device. The procedure time and length  
13 of hospital stay for the Amplatzer closure were  
14 significantly shorter than that of open-heart surgery.  
15 Procedure time was measured for the device group from  
16 the insertion of the venous sheath to the removal and  
17 for the surgical group from the skin incision to skin  
18 closure.

19           Therefore, to summarize our efficacy and  
20 safety results, the device successfully at 12 months  
21 is 98.5 percent which is equivalent to surgery. This  
22 meets the protocol requirement for establishing

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1 equivalence since the lower 95 percent confidence-  
2 bound is 0.052 which is less than the 8 percent better  
3 agreed upon with the FDA.

4 The device major complication rate of 1.6  
5 percent is lower than the maximum protocol specified  
6 rate of 10 percent. The overall complication rate for  
7 the device of 7.2 percent is significantly less than  
8 for the surgical control of 24 percent. There were no  
9 device related deaths and the device group had  
10 significantly lower procedure time and shorter  
11 hospital stay.

12 Therefore, ladies and gentleman, I would  
13 like to conclude that the Amplatzer Septal Occluder  
14 offers a safe, effective and less invasive treatment  
15 for closure of secundum atrial septal defects.

16 Now, it is my pleasure to introduce my  
17 colleague Dr. John Moore to share with you the results  
18 of the Fontan fenestrations. Thank you.

19 MR. MOORE: Good morning. My name is John  
20 Moore. I'm Director of Cardiology at St.  
21 Christopher's Hospital for Children in Philadelphia  
22 and Professor of Pediatrics at MCP Heiman University.

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1 I have no financial interest in the device.  
2 My expenses have been paid by AGA Medical Corporation.

3 I'm going to present to you the data  
4 regarding Amplatzer Septal Occluder closure  
5 fenestrated Fontan procedures.

6 A little background is in order because this  
7 is a little different type of indication. The  
8 incidence of all types of single ventricle heart  
9 disease, congenital heart disease, is as high as 10  
10 percent. It includes a number of complicated  
11 diagnoses such as hypoplastic left heart syndrome  
12 which is the most common in that group.

13 The modified or fenestrated Fontan procedure  
14 is a relatively recent introduction in the surgical  
15 area which has improved the prognosis of this whole  
16 patient group dramatically and has at this point  
17 become a standard palliation procedure.

18 The cartoon on the right demonstrates a  
19 patient who has hypoplastic left heart syndrome with  
20 essentially absence of left ventricle and one large  
21 ventricle which is a right ventricle. This patient  
22 has had a modified or fenestrated Fontan procedure,

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2 but that is actually the third procedure that was  
3 performed.

4 This third and final operative stage  
5 involves completion of a systemic venous baffle here  
6 shown in blue which directs "blue" blood into the  
7 pulmonary circulation directly without the benefit of  
8 a ventricular pump.

9 The fenestration here shown in purple is a  
10 punch opening in the lateral baffle which provides a  
11 vent and essentially a right-to-left shunt.

12 The aims of the fenestrated Fontan procedure  
13 are first to separate pulmonary and systemic  
14 circulations thereby increasing blood oxygen and  
15 reducing cardiac work. The fenestration reduces the  
16 Fontan operative risk because vented or shunted blood  
17 augments cardiac output and reduces central venous  
18 pressure.

19 However, after the relatively early post-  
20 operative period a fenestration may actually become  
21 dysfunctional. As I mentioned, there is a right-to-  
22 left shunt which may become a significant cause of  
cyanosis. In addition, there is the ongoing risk of

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1 paradoxical embolus through fenestration and stroke.

2 Therefore, it is often appropriate to  
3 perform closure of the fenestration. There are  
4 essentially two options for closure, the first being  
5 a fourth open-heart surgical procedure.

6 This procedure would generally follow a  
7 diagnostic catheterization demonstrating that it was  
8 safe and appropriate to close the fenestration  
9 surgically. The operative approach requires, first,  
10 a catheterization and then a fourth redo operation.  
11 The other procedure available is percutaneous device  
12 closure.

13 Percutaneous device closure may involve the  
14 use of general anesthesia and transesophageal  
15 echocardiography much as ASD closure does. The  
16 hemodynamics performed include a test fenestration in  
17 which the fenestration is balloon occluded not to size  
18 it specifically but to determine the effect of  
19 occlusion on central venous pressure and cardiac  
20 output.

21 Balloon sizing may also be performed in  
22 addition or at the same time as test occlusion. In

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1 addition, rim assessment is required. Device implant  
2 proceeds exactly as described by Dr. Cheatham in the  
3 first presentation.

4 We have a short movie here that demonstrates  
5 a Fontan procedure first. This is the baffle and I'll  
6 run the movie and show it to you. If you look right  
7 here, this is the fenestration shunting blood from the  
8 systemic venous circuit into the pulmonary venous  
9 circuit directly without passing through the loans.

10 This is the deployment of the device.  
11 First, the pulmonary venous disc is formed, the waist  
12 is formed, and the systemic venous disc is formed.  
13 The device is released and a follow-up angiogram shows  
14 the fenestration to be completely closed.

15 The study organization for this portion of  
16 the study was only slightly different. It was a  
17 single arm registry meaning that there was no surgical  
18 control group. It was also multi-center. The same  
19 independent data safety monitoring board was used to  
20 adjudicate adverse events and the same independent  
21 statistician provided statistical services for the  
22 site.

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1           The efficacy endpoint was identical as  
2 described by Dr. Hijazi. A successful closure of the  
3 fenestration at 12 months involved less than a 2 mm  
4 shunt observed by transesophageal echocardiography at  
5 one year. The same grading system was employed.

6           The safety criteria was also identical.  
7 Safety for the device was defined as a death rate less  
8 than or equal to 2 percent in a major complication  
9 rate less than or equal to 10 percent.

10           There were a few additional inclusion  
11 criteria. Obviously the patient had to have a  
12 fenestrated Fontan procedure. The opening in the  
13 baffle had to be at least five millimeters from the  
14 free atrial wall, essentially a rim requirement.

15           Finally, the central venous pressure had to  
16 be less than 15 mm of mercury during test balloon  
17 inclusion in the early hemodynamic evaluation part of  
1 8 the catheterization.

19           Exclusion criteria included if there was  
20 insufficient rim, if there was an ongoing acute  
21 infection, or inability to obtain informed-consent.

22           Demographics of this patient group were

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1 slightly different than the ASD device patients.  
2 These patients were slightly younger, mean age 7.8  
3 years. There was a predominance of male, 60 percent,  
4 as opposed to females 40 percent which is just the  
5 inverse of the ASD group.

6 As far as medical history goes, there were  
7 a few positives, congestive heart failure one patient,  
8 failure to thrive one patient, and stroke. Documented  
9 stroke had occurred already in two patients.

10 The transesophageal echocardiographic  
11 fenestration characterization showed that the average  
12 fenestration measured 4.2 mm in diameter by  
13 transesophageal echo.

14 This summarizes the patients enrolled in  
15 this registry. There were a total of 51 patients  
16 enrolled. Three patients were intent to treat  
17 patients meaning they were enrolled. They underwent  
18 catheterization but no attempt was made to place the  
19 device.

20 Of the 48 attempted patients there were two  
21 technical failures and 46 technical successes in which  
22 devices were placed. At one-year follow-up 32

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1 patients evaluated showed 100 percent meeting the  
2 primary efficacy criteria. There were no failures at  
3 that point.

4 Intention to treat patients, one failed the  
5 inclusion criteria with insufficient rim, if you will.  
6 Two had anatomical conditions resulting in inability  
7 or lack of desire of the operator to place the device.  
8 One was multiple small fenestrations. It was not  
9 feasible to close these with the Amplatzer device.

10 The other was a patient who had a damaged  
11 and malfunctioning prosthetic valve who was definitely  
12 going to require surgery and it seemed inappropriate,  
13 therefore, to place the device in that patient.

14 Technical failures were two. Both of these  
15 were related to fenestrations which were too small to  
16 place the delivery sheet and, therefore, a device  
17 could not, and probably should not have been placed.

18 As I mentioned, the primary efficacy  
19 criteria indicated successful closure at one year.  
20 Thirty-two patients evaluated at that point met the  
21 primary efficacy criteria and were successful.

22 Safety results are summarized on this slide.

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1 In the group there were two major complications or 4.2  
2 percent. One complication was a hemothorax which was  
3 related to vascular access site complications in the  
4 subclavian vein.

5 The other complication was damage to a  
6 tricuspid valve due to deployment or partial  
7 deployment of the device near and within the valve.  
8 This patient had to have surgery or tricuspid valve  
9 repair.

10 Two minor complications. One patient had a  
11 long hospital stay of one day additional because of  
12 nausea and vomiting. The other patient had an atrial  
13 arrhythmia requiring cardioversion for a total of four  
14 complications in this group.

15 Clinical utility data. The procedure time  
16 is fairly long, as you can see, but this is because  
17 these patients, as I mentioned, require a fairly  
18 extensive hemodynamic evaluation prior to device  
19 placement. In addition, many of them undergo  
20 additional interventional procedures such as  
21 transcatheter stent placement at the time of this  
22 catheterization.

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1 In fact, the placement of the device  
2 requires a very small percentage of this procedure  
3 time and this fluoroscopy time.

4 More importantly, the hospital stay of these  
5 patients is very, very short. You can see they  
6 average 1.2 days and we don't have a surgical control  
7 group but I think that speaks for itself.

8 Clinically utility of the Amplatzer device  
9 then is that it avoids morbidity and risk of repeat  
10 open-heart surgery and that the hospital stay is very  
11 short.

12 Finally, the summary of the safety and  
13 efficacy of Amplatzer closure of the fenestrated  
14 Fontan. We have a primary efficacy outcome at 12  
15 months of 100 percent. Major complication rate 4.2  
16 percent is within protocol defined limits of less than  
17 or equal to 10 percent.

18 There were no device related deaths. These  
19 results are consistent with those obtained for  
20 transcatheter closures of secundum ASD by the  
21 Amplatzer Septal Occluder device.

22 In conclusion, the data demonstrates that

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1 the Amplatzer Septal Occluder offers a safe,  
2 effective, and less invasive treatment for closure of  
3 Fontan fenestration.

4 Finally, I would like to reintroduce Dr.  
5 Hijazi who will summarize our presentation.

6 DR. HIJAZI: Thank you. Good morning again.  
7 My name is Ziyad Hijazi. The sponsor of this study  
8 has worked with the FDA and the circulatory panel to  
9 conduct a sound clinical trial to assist the safety  
10 and effectiveness of the Amplatzer Septal Occluder for  
11 two indications; secundum ASD closure and Fontan  
12 fenestration closure.

13 The clinical study results meet the  
14 endpoints of safety defined in the protocol.  
15 Furthermore, in the secundum ASD arm of the trial, the  
16 device group had significantly lower complication  
17 rates than the surgical control group.

18 The clinical study results meet the endpoint  
19 for efficacy defined in the protocol. The secundum  
20 ASD group had the success rate of 98.5 percent in 20  
21 years which is statistically equivalent to the  
22 surgical control group. Aiso, the Fontan

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1 fenestrations group had a success'rate of 100 percent.

2 The clinical utility of the device group  
3 demonstrated a significantly shorter procedure time  
4 and shorter hospital stay than the surgical control  
5 group.

6 It is my pleasure to share with you my own  
7 personal experience with the device. To date I have  
8 done over 420 closures with the Amplatzer Septal  
9 Occluder. About 220 in the United States and the  
10 remainder abroad.

11 In 10 cases I could not implant the device.  
12 These patients underwent surgical closure. Four  
13 patients had device embolization with successful  
14 retrieval in the cath lab in three patients and  
15 subsequent device implantation.

16 The fourth patient required surgical  
17 treatment and at the same time the surgeon closed the  
18 ASD. Therefore, 409 patients had successful  
19 implantation. All but two had successful closure of  
20 their defects.

21 Inconclusion, the Amplatzer Septal Occluder  
22 is safe and effective for closure of secundum ASD and

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1 Fontan fenestrations. Thank you for your attention.

2 DR. TRACY: Thank you very much. At this  
3 point I'll ask the FDA to present their findings.

4 MS. BUCKLEY: Good morning. My name is  
5 Donna Buckley and I am a mechanical engineer in the  
6 Interventional Cardiology Devices Branch of the Office  
7 of Device Evaluation. I am also the lead reviewer for  
8 the Amplatzer Septal Occlusion, or ASO device  
9 submission, PMA No. P000039.

10 Today Dr. Stuhlmuller, the medical officer  
11 of this submission, and I will present the FDA summary  
12 for the Amplatzer ASO submission. This device is a  
13 transcatheter septal defect closure device used in the  
14 treatment of atrial septal defects and fenestrated  
15 Fontans.

16 You'll be asked to discussion and make  
17 recommendations on the sponsor's PMA submission. Your  
18 points of discussion of the clinical study results and  
19 labeling recommendations will be taken into  
20 consideration by FDA in their evaluation of the  
21 application.

22 Finally, you will be asked to vote on the

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1       approvability of this device.

2               The FDA summary will provide a brief  
3       overview of the following: the FDA review team, device  
4       description, nonclinical evaluation, clinical  
5       evaluation, and questions to the panel.

6               Members of the FDA review team include  
7       myself, Donna Buckley, and Dr. John Stuhlmuller from  
8       the Office of Device Evaluation, Mr. John Dawson from  
9       the Office of surveillance and biometrics who served  
10      as a statistical reviewer, and Ms. Liliane Brown from  
11      the Office of Compliance who coordinated FDA  
12      inspection of the investigational sites.

13              The AS0 Occluder is a double-disc design  
14      with a connecting waist. It is made from a nitinol  
15      wire mesh with polyester material stitched into the  
16      discs. The left atrial disc is larger than the right  
17      atrial disc.

18              There are 26 sizes available based on the  
19      connecting waist diameter. The occluder sizes range  
20      from 4 mm to 38 mm in diameter. The occluder is sized  
21      to match the connecting waist diameter to the  
22      stretched defect diameter.

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1           The delivery catheter is 6F to 12F in size  
2 based on occluder size.    The occluder is packaged  
3 separately and manually attached to the delivery cable  
4 prior to loading into the delivery catheter.

5           In vitro or bench testing is outlined in  
6 Section 1.4 of the FDA Summary in your Panel Pack. It  
7 was performed to evaluate the mechanical integrity of  
8 the AS0 system.

9           Biocompatibility testing of the device  
10 components was conducted in accordance with ISO  
11 Standard 10993.   Animal studies were conducted in a  
12 porcine model on the Amplatzer System.

13           The results of the in vitro or bench,  
14 biocompatibility, and animal testing submitted  
15 demonstrate the integrity and functionality of the  
16 device for its intended use.

17           Dr. Stuhlmuller will now summarize the  
18 clinical evaluation of the device.

19           DR. STUHMULLER:   Good morning.   My name is  
20 John Stuhlmuller.   I am a medical officer in the  
21 Interventional Cardiology Devices Branch in the  
22 Division of Cardiovascular and Respiratory Devices.

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1 I am going to provide a brief overview of the clinical  
2 information contained in the PMA.

3 The sponsor has provided clinical data for  
4 two proposed INDICATIONS FOR USE in the PMA. The  
5 first indication for use is closure of secundum atrial  
6 septal defects. The second indication is for closure  
7 of fenestrations following Fontan procedures.

8 Information has been provided for five  
9 different clinical data sets of part of the PMA.  
10 Information on the pivotal data sets has been provided  
11 in the Panel Packs.

12 First is the pivotal data set from the Phase  
13 IIB registry for atrial septal defect closure. A  
14 total of 459 patient were enrolled in this registry.

15 Second is the pivotal data set for closure  
16 of fenestrations following Fontan procedures. A total  
17 of 51 patients were enrolled in the registry.

18 Non-pivotal data sets not included in the  
19 Panel Packs include Phase I, Phase IIA and continued  
20 access patients.

21 The device patients were enrolled in a non-  
22 randomized open-label, multi-center registry. The

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1 surgical control patients were also enrolled in a non-  
2 randomized open-label, multi-center registry.

3 Surgical patients were prospectively and  
4 retrospectively identified. All patients completed a  
5 prospective one-year follow-up.

6 Patient outcome assessment was made using a  
7 composite clinical endpoint termed Composite Clinical  
8 Success at 12 months. The intent of this endpoint was  
9 to evaluate safety and effectiveness at 12 months.  
10 That was residual shunt rate at 12 months. It was not  
11 intended to incorporate all residual shunts prior to  
12 12 months.

13 The individual clinical endpoints  
14 incorporated into assessing a Composite Clinical  
15 Success include: major complications, embolization,  
16 technical failure, and presence of a significant  
17 residual shunt. Additional individual secondary  
18 safety and effectiveness endpoints were also  
19 evaluated.

20 Technical success defined as device  
21 deployment or completion of surgery was seen in 423 to  
22 442 device patients and 154 of 154 surgical patients.

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1 Procedure success defined as a residual shunt less  
2 than 2 mm in patients who were technical successes was  
3 seen in 413 of 423 device patients and 154 of 154  
4 surgical patients.

5 Six-month closure defined as residual shunt  
6 of less than or equal to 2 mm in patients who were  
7 technical successes was seen in 376 of 387 device  
a patients and 154 of 154 surgical patients.

9 Twelve-month closure defined as residual  
10 shunt less than or equal to 2 mm in patients who were  
11 technical successes was seen in 326 of 331 device  
12 patients and 149 of 149 surgical patients.

13 Twelve-month composite success defined as  
14 all patients attempted without major complications,  
15 embolization, technical failure, and presence of a  
16 significant residual shunt was seen in 311 and 362  
17 device patients and 146 of 154 surgical patients.

18 Major complications were seen in seven of  
19 442 device patients and eight of 154 surgical  
20 patients. Minor complications were seen in 27 and 442  
21 device patients and 29 of 154 surgical patients.  
22 Overall, 32 of 442 device patients experienced a

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1 complication and 37 of 154 surgical patients  
2 experienced a complication.

3 The pivotal cohort for closure of  
4 fenestrations following Fontan procedures were  
5 enrolled in a prospective open-label, single-arm  
6 registry without a control group.

7 Patient outcome assessment was completed at  
8 12 months. Effectiveness was defined as successful  
9 closure of less than a 2 mm residual shunt at 12-month  
10 follow-up. Safety was evaluated by analysis of  
11 potential anticipated and unanticipated adverse  
12 events.

13 Occluders were implanted in 46 of 48  
14 attempted patients. Successful closure was  
15 demonstrated in 32 of 32 patients evaluated at 12  
16 months.

17 Adverse events were evaluated in the 48  
18 patients in which device placement was attempted. A  
19 total of four adverse events were seen. Two major and  
20 two minor adverse events were seen.

21 Next will be the panel questions presented  
22 by Donna Buckley.

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1 MS. BUCKLEY: To support the ASD indication,  
2 the sponsor has submitted data from a prospective,  
3 non-randomizedconcurrentlycontrolledstudycomparing  
4 device closure to surgical closure. The study was  
5 designed to assess individual endpoints and composite  
6 endpoints.

7 Question 1a. Please discuss whether  
8 individual endpoints, composite endpoints, or a  
9 combination of both should be used to evaluate the  
10 safety and effectiveness of the Amplatzer ASD device?

11 Question 1b. The sponsor is seeking  
12 approval for device sizes from 4 mm to 38 mm.  
13 Approximately 89 percent of devices implanted in the  
14 pivotal ASD study were between 10 mm and 28 mm. Is  
15 there sufficient data to support approval of the  
16 entire range of devices (4 mm to 38 mm) or a specific  
17 range of device sizes?

18 Question 1c. Based on the data provided on  
19 ASD patients and the suggested analysis of the data  
20 from question 1a., please discuss whether these data  
21 provide reasonable assurance of safety and  
22 effectiveness.

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1 To support the fenestrated Fontan  
2 indication, the sponsor has submitted data from a  
3 single arm registry with 48 patients.

4 Question 2. Based on the data provided on  
5 fenestrated Fontanpatients and the suggested analysis  
6 of the data from question 1a., please discuss whether  
7 these data provide reasonable assurance of safety and  
a effectiveness.

9 A summary of the Physician Training Program  
10 has been provided in Section 5 of the Panel Package.

11 Question 3a. Please discuss any  
12 improvements that could be made to the training  
13 program.

14 Question 3b. More than one device was  
15 placed in 10 ASD patients. Please discuss training  
16 issues regarding the placement of multiple devices in  
17 a single patient.

18 One aspect of the pre-market evaluation of  
19 a new product is the review of its labeling. The  
20 labeling must indicate which patients are appropriate  
21 for treatment, identify potential adverse events with  
22 the use of the device, and explain how the product

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1 should be used to maximize benefits and minimize  
2 adverse effects. Please address the following  
3 questions regarding the product labeling

4 Question 4a. Please comment on the  
5 INDICATIONS FOR USE section as to whether it  
6 identifies the appropriate patient populations for  
7 treatment with this device.

a Question 4b. Please comment on the  
9 CONTRAINDICATIONS section as to whether there are  
10 conditions under which the device should not be used  
11 because the risk of use clearly outweighs any possible  
12 benefit.

13 Question 4c. Please comment on the  
14 WARNING/PRECAUTIONS section as to whether it  
15 adequately describes how the device should be used to  
16 maximize benefits and minimize adverse events.

17 Question 4d. Please comment on the  
18 OPERATOR'S INSTRUCTIONS as to whether it adequately  
19 describes how the device should be used to maximize  
20 benefits and minimize adverse events.

21 Question 4e. Please comment on the  
22 remainder of the device labeling as to whether it

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1 adequately describes how the device should be used to  
2 maximize benefits and minimize adverse events.

3 The Panel Package includes the available  
4 one-year data for the Amplatzer AS0 device. Long-term  
5 adverse effects that may be associated with device  
6 implantation include late thrombosis formation, the  
7 risk of endocarditis, problems with late operation,  
8 and arrhythmias.

9 Question 5. Based on the clinical data  
10 provided in the PMA, do you believe that additional  
11 follow-up data or post-market studies are necessary to  
12 evaluate the chronic effects of the implantation of  
13 the Amplatzer device. If so, how long should patients  
14 be followed and what endpoints and adverse events  
15 should be measured? Thank you.

16 DR. TRACY: Thank you very much.

17 At this point we'll begin the open committee  
18 discussion and I'm going to ask Dr. Robert Williams  
19 who was the lead reviewer to begin with her questions  
20 for the sponsor and then we'll go around the rest of  
21 the panel after she's completed.

22 DR. WILLIAMS: I just have a few questions

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1 to start. I was wondering in looking at the patients  
2 at the first evaluation after implantation, what do  
3 you believe is the sensitivity to thrombi that would  
4 be associated with the surface on either the right or  
5 the left atrial surface of the device?

6 MR. LOCK: My name is Ken Lock and I'm the  
7 clinical programs manager AGA Medical. I'm an  
8 employee of AGA Medical. I will have Dr. Hijazi  
9 answer this question.

10 DR. HIJAZI: I think in our patients,  
11 especially being a trial done under the FDA auspices,  
12 we have been extremely vigilant looking at any  
13 patient's echocardiogram in the post-implantation  
14 period and the follow-ups. One of the things that we  
15 look very clearly at is the presence of formation of  
16 thrombosis.

17 Clearly we have not seen any reported  
18 incidence of thrombosis and that goes with the  
19 clinical data that none of our patients had TIAs or  
20 strokes. I think echocardiography is pretty sensitive  
21 to detect small clots. Maybe less than 1 mm maybe not  
22 but I think the important thing is the- clinical

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1 outcome of these patients.

2 DR. WILLIAMS: And I saw in one place where  
3 TEE was recommended as an aid in another place where  
4 it was required. In your current indications is it a  
5 required part of the procedure or just recommended?

6 DR. HIJAZI: This is Ziyad Hijazi again. I  
7 think it is required. It's a must. TEE is required  
8 for device implantation. The other thing that we may  
9 be adding also giving the operator an option is the  
10 intracardiac echo if it's available. Either  
11 transesophageal echo or intracardiac echo should be  
12 required prior to device implantation.

13 DR. WILLIAMS: Okay. Another question was  
14 the indications prohibiting strenuous activity. Is it  
15 for one month or six months now?

16 MR. LOCK: This is Ken Lock. We are  
17 recommending one month.

18 DR. WILLIAMS: One month. And, finally,  
19 there was an indication of phrenic nerve injury. I'm  
20 sorry. Was that in the device group or in the surgery  
21 group?

22 MR. LOCK: This is Ken Lock. I'll have to

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1 check to make sure. I'm pretty sure it was in the  
2 device group but I'll check on that.

3 DR. WILLIAMS: What was the theory about how  
4 that might have occurred?

5 MR. LOCK: I'll have to get details on that  
6 and answer it later.

7 DR. WILLIAMS: It's a minor question. Those  
8 are my questions for the moment. I reserve the right  
9 to be stimulated by the other members of the panel.

10 DR. TRACY: Okay. Thank you.

11 Dr. White.

12 DR. WHITE: Thank you. My name is Chris  
13 White. I'm an adult cardiologist, interventional  
14 cardiologist.

15 I guess my question, No. 1, revolves around  
16 the nitinol composition and the nickel. There is  
17 nowhere I saw about any concern about nickel allergy.  
18 We know that's prevalent among the population. Do you  
19 have concerns about what a nickel allergic patient  
20 will do with this device?

21 MR. LOCK: This is Ken Lock. I will have  
22 Dr. Hijazi respond to that question.

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1 DR. HIJAZI: Obviously the nitinol, as we  
2 all know, is an alloy from nickel and titanium. As  
3 Dr. White mentioned, a large percentage of people have  
4 nickel allergy.

5 As a matter of fact, two of the patients in  
6 the trial have documented nickel allergy and they came  
7 to me and I knew they had nickel allergy. I told  
8 them, "Your option is either to take the risk or have  
9 open-heart surgery." The opted to take the risk and  
10 we implanted the devices in both patients and one of  
11 them is now two and a half years follow-up and the  
12 other one is one year and no clinical findings at all.

13 I do not think implanting the device inside  
14 the vascular system is similar to the contact  
15 manifestations of nickel allergy that is prevalent in  
16 the general population.

17 DR. WHITE: I also wanted you to comment on  
18 the fact that only three-quarters of your patients  
19 have been followed at one year for the primary  
20 efficacy. Did I miss that number? 331?

21 MR. LOCK: That is correct. This is Ken  
22 Lock. 331 of the patients available for a one-year

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1 visit.

2 DR. WHITE: Why- did you pick a primary  
3 efficacy endpoint which was incomplete by the time you  
4 present the data? I mean, why would you pick one  
5 year's data as being your primary efficacy and then  
6 bring us an incomplete data set?

7 MR. LOCK: This is Ken Lock. The original  
8 protocol required analysis to look at 110 patients  
9 from each group so in talking with the FDA they  
10 requested that we include all patients that we had  
11 available to follow up on and that's why we have the  
12 331 patients.

13 DR. WHITE: Okay. Let me get this straight.  
14 You met the number at one year for follow-up of 110  
15 and then you continued to enroll patients so those  
16 have not been completely followed yet?

17 MR. LOCK: That's correct.

18 DR. WHITE: In the protocol there was  
19 concern about implanting the device in presumably  
20 older patients who had had heart failure decompensated  
21 left ventricular failure, recent MIs. Will that also  
22 be part of the contraindication package? How will you

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1 deal with an assessment of LV function before the ASD  
2 closure?

3 MR. LOCK: This is Ken Lock. I'll let Dr.  
4 Hijazi answer this question.

5 DR. HIJAZI: Ziyad Hijazi. As we are all  
6 clinicians, I do believe that these patients if they  
7 are managed well and if they are not dying, I don't  
8 think implantation of the device should be a problem  
9 in these patients.

10 As a matter of fact, it may be of more  
11 benefit for them rather than to undergo open heart  
12 surgery to close an ASD with them. I do believe that  
13 if a patient has left ventricular dysfunction and has  
14 an ASD with left-to-right shunt that requires a  
15 closure.

16 After the device gets approved I would be  
17 able to implant the device in these patients.  
18 However, during the protocol and the study period, we  
19 try to avoid any patients with such conditions like  
20 left ventricular dysfunction.

21 DR. WHITE: Let me just see if I understand.  
22 You did a study for the safety and efficacy of this

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1 device and you excluded those patients. Now after  
2 approval you want me to implant in those patients?

3 DR. HIJAZI: If there are patients which are  
4 very real, as you know, with ASD and they have  
5 significant left ventricular dysfunction and the  
6 closure there is beneficial. I do not think that  
7 device or closure should be contraindicated for that.

8 DR. WHITE: Then why did you exclude them  
9 from this trial?

10 DR. HIJAZI: Initially for the study we  
11 wanted to do plain straightforward secundum ASD in  
12 patients that we encountered on a daily basis.

13 MR. LOCK: This is Ken Lock. We will  
14 include in the labeling that it is a contraindication  
15 for patients who have heart failure MIs. That will be  
16 in the labeling.

17 DR. WHITE: Can you tell me also in your  
18 contraindication there were patients who were  
19 considered to be poor candidates for catheterization.  
20 It says, "Any patient whose size or condition would  
21 cause the patient to be a poor candidate for cardiac  
22 catheterization." Can you give me an example of

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1 someone who is a poor candidate for cardiac  
2 catheterization? I don't know if I've ever met that  
3 person.

4 DR. HIJAZI: An example of a poor candidate  
5 is a patient who, let's say, has significant left  
6 ventricular dysfunction and they are dying for  
7 somebody to attempt to take these patients to the cath  
8 lab to close their ASD I think will be a poor  
9 judgement.

10 DR. WHITE: I guess from the provider's side  
11 of this equation, when I read the package labeling I  
12 would like specific things. I would like to know what  
13 you consider to be a problem. This vague thing about  
14 poor candidates, I don't understand really because for  
15 different doctors it's different.

16 I think if there are specific issues that  
17 you think are related to this device that would make  
18 catheterization a problem, then that ought to be  
19 specifically listed in order to help us understand  
20 what it is.

21 Ziyad, can you comment on the difference  
22 between -- this application is for ASD but immediately

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1 upon the release of this device PFOs are going to get  
2 on the horizon. Is there a difference in the  
3 treatment of PFO, patent foramen ovale, and ASD?

4 DR. HIJAZI: This is Ziyad Hijazi again.  
5 Technically speaking there is no different. As a  
6 matter of fact, a few of the patients in this cohort  
7 had PFO with minimal shunt and TIA or dysrhythmia that  
8 we close with the Amplatzer Septal Occluder.

9 DR. WHITE: So in the umbrella of approval  
10 for the ASD would also include the PFO patients?

11 DR. HIJAZI: We're not seeking that for PFO.  
12 That would be operator dependent because there is  
13 another device, the Amplatzer PFO Occluder  
14 specifically designed for the PFO. If this device  
15 gets approved and you have a patient with a PFO with  
16 left-to-right shunt and you want to close it, it's --

17 DR. WHITE: Is it a clinical difference?

18 DR. HIJAZI: No.

19 DR. WHITE: And I guess my last comment is  
20 that I don't -- I understand the difficulty of doing  
21 a randomized trial and I wasn't involved in the trial  
22 when you came in 1997, but your groups are not

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1 comparable. To say that you have a controlled trial  
2 here is a little specious. I mean, you've got an  
3 adult group for your heavily weighted adult group.  
4 Your pediatric group is -- there's no attempt at  
5 matching for equivalence.

6 I'm not sure that's required but I think it  
7 kind of -- I think just to set the present and make  
8 sure we all understand, these groups are not  
9 comparable, I don't think. They are just a different  
10 population of patients.

11 Perhaps you could comment on why they are  
12 different, Ziyad. Why did you grab more adults? Why  
13 was there not anybody getting operated on in this  
14 setting?

15 MR. LOCK: This is Ken Lock. There are two  
16 parts to that. The first part, the difference, we  
17 believe, in the populations was attributed to referral  
18 patterns of the investigators in the trial.

19 The surgical control investigators were  
20 pediatric cardiologists and they would refer their  
21 patients to surgery and they were enrolled into the  
22 study.

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1           The adult cardiologists were referred from  
2 a broader base of patients of adults seeking a less  
3 invasive procedure perhaps or there are adult  
4 cardiologists referring them to a site that had the  
5 device available. That would account for the  
6 difference of the populations and how we got the  
7 populations. I'll have Kinley Larntz here speak to  
8 the second part of the question.

9           DR. LARNTZ : Perfect timing. I'm Kinley  
10 Larntz. I served as the independent statistician.  
11 I'm Professor Emeritus, University of Minnesota. I  
12 also work as a consultant to companies and to the FDA  
13 occasionally.

14           You're right. I mean, look, there's a big  
15 age difference, right? The key feature of any -- and  
16 it wasn't a randomized trial so you are liable to get  
17 differences and that's what happened. The key feature  
18 statistically that I could figure out was does this  
19 age difference make any difference statistically, and  
20 so we, didn't report.

21           I apologize that Dr. Hijazi didn't do all  
22 the covariate analysis for you on the screen. Maybe

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1 you would prefer that he did, but we did a lot of  
2 covariate analysis. We used age and also the symptoms  
3 that we saw as covariates; failure to thrive,  
4 respiratory problems.

5 It turned out that doing those covariate  
6 analysis -- and this is what we would have to do to  
7 try to adjust in some way without doing a formal  
8 matching. We didn't do a formal matching, I  
9 understand, although I did a little bit of that in one  
10 example.

11 Age didn't have an effect on anything. It  
12 didn't have an effect on complication rates. It  
13 didn't have an effect on closure rates. It didn't  
14 have an effect on anything. Every analysis I did with  
15 age just turned out to be the same result as if you  
16 didn't have age in the equations.

17 I agree in randomized trials. I'm a  
18 statistician. I should agree with that, right? In  
19 fact, the best analysis we can do is to try to adjust  
20 for what the differences were and in doing that  
21 adjustment we found basically -- not basically but  
22 exactly the same effects, the same size effects.

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1 Everything went through the same way.

2 DR. WHITE: I'm not criticizing the fact  
3 that you didn't randomize these patients. I would not  
4 have asked you to do it. I think the reason the  
5 complications don't show is because it's a safe  
6 procedure with low complications in each group.

7 But you can't tell me that operating on a  
8 range of adult patients for ASDs, which were not done  
9 because adults didn't get operated on, wouldn't have  
10 shown maybe some difference. You gave surgery every  
11 benefit of the doubt in your analysis and that's fine.  
12 I think this isn't to compare surgery but it's just  
13 not a comparable group and not a good thing to do.

14 I'm finished.

15 MR. DILLARD: Dr. Tracy, sorry to interrupt.  
16 Jim Dillard. Just a couple comments. I don't usually  
17 do this but I think in this case it might be a little  
18 bit important for contextual purposes. I think Dr.  
19 White brings up some great issues.

20 A couple of things from the FDA's  
21 perspective, the fact about sort of additional  
22 patients. I mean, one of the questions that you had

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1 is the difference between 110, which I think was  
2 really sort of the primary number for the study,  
3 versus the continued access number.

4 One of the things that we do struggle with  
5 in designing trials is allowing a sponsor to continue  
6 to-gather some data over longer periods of time and at  
7 what point in time do you bring the data before a  
8 panel when you also don't have much experience with a  
9 product. Sometimes we at the FDA look to a larger  
10 safety database and a longer term, even though the  
11 effectiveness numbers may be somewhat different in  
12 terms of the statistical calculation.

13 I think that is certainly the case here  
14 where we felt like a larger body of information for  
15 safety might certainly be relevant in an area where we  
16 really didn't have very much understanding of the  
17 technology. I think that is where we see a little bit  
18 of a difference here and certainly something that the  
19 FDA felt pretty strongly about.

20 I'm sorry. I'm just going over a couple of  
21 notes here. Safety information and really the larger  
22 dataset about embolization also. I mean, that was

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1 certainly an issue that we looked to and thought that  
2 a larger dataset would help us analyze the issue about  
3 embolization.

4 About the control patient population here  
5 also. I agree certainly with what the sponsor said at  
6 this point. One of the other struggles that we had,  
7 and I think even back to 1997 since probably none of  
8 the members here were actually at that panel meeting,  
9 but one of our concerns when we started looking at  
10 some sort of randomized concurrently controlled study  
11 which really wasn't feasible at the time.

12 Then we looked at what other options we had  
13 available to us for a control group. One of the  
14 considerations was really how contemporary was the  
15 data. When we look back the dataset that we might  
16 have had available if we didn't do something  
17 prospective in terms of a contemporary control group  
18 would have been really looking back at older surgical  
19 procedures.

20 I think the tradeoff here was to try to get  
21 new surgical data in order to compare the two patient  
22 populations. I think, as usual, we all struggle with

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1 what the appropriate control group is. In this case  
2 we thought the contemporary nature of the data might  
3 be important for this particular product. Just a  
4 couple of general products. Thank you.

5 DR. TRACY: Dr. Skorton.

6 DR. SKORTON: Thank you. I just have a  
7 couple questions. One of them has to do with the  
8 section on instructions for physicians on using the  
9 device. It has to do with the use of imaging methods  
10 during the procedure.

11 In the precaution section, and in the  
12 question that was asked by Dr. Williams, you mentioned  
13 the importance of using one technique, ultrasound. In  
14 the procedural area and in the demonstration that you  
15 showed, you showed angiography. That seems needlessly  
16 redundant to me.

17 I would like to ask why you have to do both.  
18 If you're going to do echocardiography, why do you  
19 need to also do additional angiographic study?

20 DR. HIJAZI: Ziyad Hijazi again. As an  
21 operator in the cath lab, I think any imaging modality  
22 will be very helpful for the operator to place the

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1 device in the correct position. We do angiography  
2 because it gives a road map and a location in more  
3 space than echocardiography.

4 When you do TEE, as you are aware, you just  
5 see a confined space. You do not have the entire  
6 field in front of you to see where you would open the  
7 disc or the waist or something like that. I think  
8 most, if not all, operators prefer to have both  
9 fluoroscopy as well as echocardiography to guide you  
1b during the implantation.

11 However, there are people in Germany, for  
12 example, for small size ASDs the entire procedure is  
13 done under TEE alone without fluoroscopy. In my  
14 opinion if you try to do this for larger ASD, you will  
15 create more problems rather than trying to save two to  
16 three minutes fluoroscopy. That's why I think we use  
17 fluoroscopy judiciously with TEE during the procedure.

18 DR. SKORTON: Thank you. Then I have a  
19 question for the statistician. Can you go over again  
20 how you came up with 8 percent as the predicted  
21 difference? I know it was done by a lower limit 95  
22 percent confidence limit, because I agree with Dr.

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1 White that this is not a randomized trial. I would  
2 like to know statistically how you came up with that  
3 95 percent confidence limit. How you calculated it.

4 DR. LARNTZ: Oh, how I calculated the 95  
5 percent confidence limit?

6 DR. SKORTON: Urn-hum.

7 DR. LARNTZ: I used an exact comparison of  
8 two binomial proportions using exact test. I gave a  
9 lower limit of 5.2 percent. I'm not quite sure. Are  
10 you asking where the 8 percent came from?

11 DR. SKORTON: Yes.

12 DR. LARNTZ: Okay. That's what I assumed  
13 you were asking. Of course, the standard answer from  
14 a statistician is that is not a statistical question.  
15 The 8, percent is the standard answer we give, but the  
16 8 percent was provided in the protocol in the IDE so  
17 that was considered the standard that **was** to be met  
18 for the primary endpoint in the protocol.

19 That was set up -- I have to admit set up  
20 before I got involved and it was deemed, if I might  
21 say, and I'll elaborate as best I can  
22 nonstatistically, and I apologize for that, but if

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1 you're using a less invasive procedure perhaps with  
2 some other advantages compared to surgery, you're  
3 willing to tolerate a slightly lower final closure  
4 rate for the device.

5 Based on considerations of how much lower,  
6 what we wanted to do was prove that it was no worse  
7 than 8 percent worse. I hope that explains it as best  
8 I can to do that.

9 DR. SKORTON: Let me tell it back to you to  
10 see if I understand. You didn't actually calculate 8  
11 percent. That was an arbitrary figure and it's a  
12 little bit more in favor of the device than the actual  
13 calculated lower limit would be.

14 DR. LARNTZ: That's correct. The calculated  
15 lower limit is 5.2 percent for the **lower** bound for  
16 equivalence so we met better than 8 percent.

17 DR. SKORTON: Sure. I agree. I just wanted  
18 to point out that it was an arbitrary thing. It  
19 **wasn't** calculated.

20 DR. LARNTZ: That's correct.

21 DR. SKORTON: Then the last thing is just a  
22 comment. I just want to weigh in agreeing with Dr.

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1 White, both sides of Dr. White's remarks. I'm not  
2 sure that it would have been important to do a  
3 prospective randomized control trial.

4 I'm not sure that's important. But I don't  
5 think we have a comparable control group in this  
6 trial. It may not be necessary to have one to make  
7 the decision but, just for the record, I don't believe  
8 this is a comparable controlled group. It may not  
9 have been possible to get one but this isn't one.

10 DR. TRACY: Dr. Zahka.

11 DR. ZAHKA: I have a few technical questions  
12 about the echocardiographic aspects of the study. It  
13 was mentioned that seven out of 155 surgical patients  
14 had some residual shunting. Now, what was the  
15 comparable number for the device patients?

16 MR. LOCK: This is Ken Lock. Those seven  
17 patients were patients that were reviewed by the Echo  
18 Board and they found that they had a trace or less  
19 than 2 mm residual shunt in the cohort that was  
20 reviewed.

21 As far as the complete closure of the device  
22 group, there was 304 out of 331 patients that had

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1 complete closure. The remaining 27 patients had a  
2 trace or a trivial residual shunt.

3 DR. ZAHKA: And that was at one year?

4 MR. LOCK: That was one year, correct.

5 DR. ZAHKA: And as the echocardiographers,  
6 the independent echocardiographers reviewed the video  
7 tapes, were there any measurements actually made on  
8 the video tapes that the echocardiographer would then  
9 see?

10 MR. LOCK: This is Ken Lock. I'll have Dr.  
11 Kleinman comment on that.

12 DR. KLEINMAN: Good morning. My name is Dr.  
13 Charles Kleinman. I'm a pediatric cardiologist. I'm  
14 the Director of Clinical Cardiology at the Nemours  
15 Cardiac Center in Orlando at the Arnold Palmer  
16 Children's Heart Institute.

17 I was one of the Echo Review Board members  
18 and was compensated on a per diem basis for my time on  
19 the Echo Review Board. I do not have any financial  
20 interest in AGA Medical and my expenses for today's  
21 trip are being borne by AGA.

22 We did review video tape of the

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1 echocardiograms. As you know, it can be a little  
2 difficult to do accurate measurements down the line on  
3 an echocardiographic view using an analog image of  
4 what was originally digital data.

5 Very few of the echocardiograms that were  
6 submitted had digital measurements on the video tape  
7 that were done by the individual investigators,  
8 although several did.

9 In the shunts that were seen in the surgical  
10 group, it was quite clear that these were rather  
11 trivial shunts and they were well visualized and one  
12 could see the millimeter or centimeter marks on the  
13 analog image. It was quite clear that these were well  
14 less than two millimeters in diameter.

15 In most cases were in the range of less than  
16 1 millimeter in diameter but clearly were visualizable  
17 as color flow shunts across the margins of the defect.

18 I was also wondering whether the  
19 echocardiographic reviews looked at the pre-procedure  
20 and post-procedure prevalence of aortic regurgitation  
21 or mitral regurgitation or, for that matter, tricuspid  
22 regurgitation.

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1 MR. LOCK: This is Ken Lock. The only echos  
2 that were reviewed by the Echo Board were the primary  
3 efficacy echos at one year so they did not see any  
4 pre-echos.

5 DR. ZAHKA: And are there any data available  
6 that speak to the issue of whether or not aortic  
7 regurgitation or mitral regurgitation or tricuspid  
8 regurgitation increases in severity after device  
9 placement.

10 MR. LOCK: This is Ken Lock. There is no  
11 data reported in the PMA. I'm wondering if Dr. Hijazi  
12 would like to step back up and comment further on  
13 that.

14 DR. HIJAZI: This is Ziyad Hijazi.  
15 Obviously when we implant a device in a patient and we  
16 do echocardiograms, we just don't look at the residual  
17 shunt. We look at the mitral valve as well as the  
18 vent because in a couple of instances when we implant  
19 a device, the left atrial disc may be close to the  
20 mitral valve leaflet and may result in mitral  
21 regurgitation. To my knowledge, there have not been  
22 cases that reported in this Phase IIB of patients that

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1 had mitral regurgitation.

2 I know of one case abroad where the device  
3 was very big and resulted in severe mitral  
4 regurgitation that the operator did not deploy the  
5 device, just took the device out and sent that patient  
6 for surgery.

7 DR. ZAHKA: Can you comment on aortic  
8 regurgitation?

9 DR. HIJAZI: In all honesty, Dr. Zahka, I do  
10 not think there is any case to my knowledge that  
11 resulted in aortic regurgitation due to a device  
12 implantation.

13 DR. ZAHKA: Thank you.

14 DR. TRACY: Dr. Hopkins.

15 DR. HOPKINS: For the record, I was here in  
16 1997 as a member of this panel. At that time, as I'm  
17 sure the investigators remember, I was extremely  
18 concerned about the design of the trial. I'm sure a  
19 review of the transcripts would show that I felt  
20 strongly that a randomized prospective trial could  
21 have been done and it was not done.

22 I have a number of questions and they relate

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1 really to the control side as much as to the  
2 experimental side. First of all, as was pointed out  
3 by earlier panel members, there are really two sets of  
4 overall questions here.

5 One is the safety and the efficacy of this  
6 device as compared, to arbitrary chosen endpoints;  
7 specifically the two percent death rate and the 10  
8 percent major complication rate, which I am going to  
9 assume was chosen with discussions with the FDA.

10 I would point out, and as I recall I pointed  
11 out in 1997, that even historical controls for  
12 surgical ASD closure for relatively contemporary  
13 series, and by that I mean the '90s and late '80s,  
14 would have listed a death rate for open-heart surgery  
15 at 5 and 10,000, well below 1 percent much less 2  
16 percent. I did have the question and I think you  
17 answered it was how were those arbitrary endpoints  
18 actually chosen.

19 The series of questions I have relate a  
20 little bit to the surgical arm. Was there a standard  
21 surgical protocol that the surgeons participating in  
22 this study were to follow that approached the rigor of

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1 the technical protocol that you provided your  
2 cardiologists who were implanting this device. Or did  
3 you simply say do your ASD the way you would normally  
4 do it and we'll take your data?

5 MR. LOCK: This is Ken Lock. That is  
6 correct. A protocol was provided to the prospective  
7 sites to enroll their prospective patients not looking  
8 at the type of surgery that they would perform, the  
9 techniques, I should say. Then the retrospective  
10 patients-we went back and pulled the patient files and  
11 didn't really look at the type if it was a modified  
12 procedure.

13 DR. HOPKINS: As I've gone through your nine  
14 major surgical complications, there are at least one  
15 that I would ask why it was a major instead of a minor  
16 which was the wound complication, which I thought was  
17 a minor complication by your protocol.

18 The major complication involving thrombosis  
19 of the femoral artery was a complication of femoral  
20 artery cannulation which is not standard procedure in  
21 today's world of cardiac surgery. The complication of  
22 two sternal wires causing pain requiring removal which

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1 was listed as a major complication. Most of us today  
2 do not use wire. I haven't used wire on a pediatric  
3 sternum in 15 years.

4 A transverse sternotomybroke down on one of  
5 the major complications. Once again, it's not  
6 standard surgical procedure. I have some concerns  
7 about claims that this is equivalent to or better than  
8 surgery when, in fact, we don't have a randomized  
9 prospective trial.

10 Now, I've gone through your data multiple  
11 times and I get confused as I go through so I'm going  
12 to ask your help. It appeared that while there were  
13 essentially no residual shunts in the surgical arm as  
14 I recall it, there were small and trivial shunts. Did  
15 I read your data properly that when these occurred  
16 that most of those had actually closed at 12 months?

17 MR. LOCK: This is Ken Lock. Regarding the  
18 device group?

19 DR. HOPKINS: Yes.

20 MR. LOCK: Yes. Most have closed over time.

21 DR. HOPKINS: Okay. And in there surgical  
22 patients, and at least in one place, seven surgical

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1 patients were noted as having residual shunts. Were  
2 those secondary ASDs that were missed or were they  
3 margin defects?

4 MR. LOCK: This is Ken Lock. I do not know  
5 the answer to that question.

6 DR. HOPKINS: It's an important question in  
7 the sense that the protocols are different because  
8 most ASD patients are not cathed prior to surgery and  
9 you are operating based upon pre-operative echo data.

10 MR. LOCK: We'll have to gather that data.  
11 Actually, Dr. Kleinman --

12 DR. HOPKINS: Do you know the answer to that  
13 of those seven?

14 DR. KLEINMAN: Charles Kleinman. Yes, I do  
15 know the answer to that and they appear to be margin  
16 defects in all seven cases echocardiographically.

17 DR. HOPKINS: Were any of the patients who  
18 were excluded from the device protocol included in the  
19 surgical arm?

20 MR. LOCK: This is Ken Lock. I believe  
21 there were a couple patients.

22 DR. HOPKINS: -- who failed inclusion

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1 criteria for device and were included?

2 MR. LOCK: That is correct.

3 DR. HOPKINS: Of the 30 -- I think it was 37  
4 patients who were added retrospectively. Is that  
5 correct?

6 MR. LOCK: Ken Lock. Yes, that's correct.

7 DR. HOPKINS: How many of the major/minor  
8 complications in the overall surgical group were  
9 accounted for by this 37?

10 MR. LOCK: This is Ken Lock. I will have to  
11 check on that number for you.

12 DR. HOPKINS: For the record, I would have  
13 to say just grabbing a handful of retrospective  
14 patients and throwing them into the surgical arm  
15 without listing what proportion of the complications  
16 are attributable by that group raises really grave,  
17 grave concerns in my mind. As I said, in '97 I don't  
18 think it. should have been necessary.

19 In the procedure, you do have 105 minutes of  
20 cath time as the analysis. As I recall, this came up  
21 in '97. What amount of radiation exposure is this?

22 DR. HIJAZI: This is Ziyad Hijazi.

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1 DR. HOPKINS: Particularly for the small  
2 size pediatric patient.

3 DR. HIJAZI: We have listed in the package  
4 with the fluoroscopy time and immediate fluoroscopy  
5 time was usually within 15 minutes. However, there  
6 were some cases that were complicated that may require  
7 a little bit longer, for example, as Dr. Moore  
a mentioned in his presentation, the fluoroscopy time  
9 would be slighter longer.

10 DR. HOPKINS: But the total time was on  
11 average 15 minutes?A

12 DR. HIJAZI: Average 15 minutes or less,  
1 3 yes.

14 DR. HOPKINS: For a statistician did you  
15 plot visual plots of the subtypes of complications  
16 versus age? What I'm specifically referring to is  
17 that in the pediatric population post-pericardiotomy  
18 syndrome is extraordinarily common, as high as 40 or  
19 50 percent, particularly over the last couple of years  
20 for some reason.

21 -Some of your other minor complications that  
22 actually did make it into the major when it created

1 tamponade are a little more common in the adult so  
2 when we begin I share the concern about the ages here  
3 in that the different ages have different sort of  
4 nature of their complications.

5 The question really for the clinician and  
6 the parents is not independent of age. It is very  
7 dependent on age because the patient exist at a point  
8 in time at a given age. The question is for my three-  
9 year-old child what is the complication rate between  
10 the two options and what is the mortality rate between  
11 the two options?

12 I'm a little concerned. I can understand  
13 statistically when you look at a lump of minor  
14 complications versus minor complications, but if you  
15 look at the subtypes and plot them versus age, did you  
16 note anything?

17 DR. LARNTZ: This is Kinley Larntz. The  
18 answer is that we did not do any analysis on the  
19 subtypes and the reason is the numbers were pretty  
20 small for the subtypes. The only thing I can say is  
21 we looked and divided up the groups into quartiles by  
22 age.

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1 I wanted specifically to look at the  
2 complication rates for younger versus -- by quartiles  
3 in the whole study dataset. That analysis by quartile  
4 showed that in each case the surgery group had a  
5 larger complication rate than the device for younger  
6 patients.

7 My memory will fail me here but I think the  
8 lowest quartile was like less than three years of age  
9 or something like that. In each of those quartiles  
10 there was a considerable advantage of the same size  
11 and magnitude of an advantage with respect to  
12 complication rates. But for individual complications  
13 I don't think there were enough to do that analysis  
14 that you're talking about. I didn't do it anyway.

15 DR. HOPKINS: On the first part of your  
16 answer there in terms of the complication rates  
17 between the four quartiles, are you saying that there  
18 was a difference in complication rates amongst the  
19 four quartiles? In other words, there was more  
20 advantage to having the ASD closed younger or older?

21 DR. LARNTZ: What I should do is find the  
22 exact data for you which I can do in just a second.

1 What I think I said, I hope I said, is that each  
2 quartile there was an advantage for the device over  
3 the surgery group. There was no particular trend in  
4 complication rate across time so complication rates  
5 were similar across time.

6 DR. HOPKINS: For all complications?

7 DR. LARNTZ: For all complications. And I  
8 did not break that down by individual complications.

9 DR. LASKEY: That's on page 49 of the Panel  
10 Pack.

11 DR. LARNTZ: Thank you.

12 DR. TRACY: Which section?

13 DR. LASKEY: Table 41.

14 DR. LARNTZ: Thank you. Right.

15 DR. LASKEY: Yellow sticky.

16 DR. HOPKINS: I did see that when I reviewed  
17 the data but, once again, the nature of the  
18 complications does have some effect on clinical  
19 decision making, particularly since I think it's  
20 probably the intent of all the pediatric cardiologists  
21 in the world that nobody would get to the age of 10  
22 with an ASD still present.

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1           On the fenestrated Fontan why was the size  
2 of the residual shunt limit chosen to be the same as  
3 in the larger ASDs of 2 mm as an efficacy criteria  
4 when surgically we try very hard not to make  
5 fenestration larger than 4 mm? In effect, you're  
6 saying that a 50 percent reduction in fenestration  
7 would be efficacious, which is not the same criteria  
a you're using in normal ASD.

9           MR. LOCK: This is Ken Lock. I would like  
10 Dr. Moore to come forward to address this question.

11           MR. MOORE: I'm John Moore. The definition  
12 was chosen simply because there was no criteria that  
13 we could identify in the literature and for  
14 consistency with the study data all together.

15           Clearly there are in the study small ASDs  
16 that are not unlike fenestrations in terms of their  
17 size which you'll see if you look at the details of  
18 the fenestration. Most of them are 4 or 5 mm punch  
19 fenestrations. There were certainly some larger than  
20 that.

21           DR. HOPKINS: And do you recall -- I looked  
22 for this and I couldn't find it. Are these patients

1 after the device closure of the fenestration routinely  
2 anti-coagulated?

3 MR. MOORE: They have the same anti-  
4 coagulation recommendations as the ASD patients. That  
5 is, aspirin is recommended for six months.

6 DR. HOPKINS: Because most of our Fontans  
7 are kept on anti-coagulation because they are Fontans,  
8 not because of closure. I'm just wondering if the  
9 slightly higher persistence of the shunts was actually  
10 due to clinical anti-coagulation for being a Fontan.

11 MR. MOORE: As I indicated, the Coumadin,  
12 etc., is not recommended specifically in this  
13 protocol, just the aspirin.

14 DR. HOPKINS: Thank you.

15 DR. TRACY: At this point I think we'll take  
16 a 15-minute break. It's 11:00 by my watch. Let's be  
17 back by 11:15.

18 (Whereupon, at 11:00 a.m. off the record  
19 until 11:18 a.m.)

20 DR. TRACY: All right. We'll resume our  
21 questioning. I believe Dr. Hopkins has one more  
22 question.

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1 DR. HOPKINS: Sorry. It raises the same  
2 questions, you may recall, from four years ago.

3 There is one question that I had. In the  
4 protocols and data and also during the presentations  
5 there was reference to proof of complete  
6 endothelialization of the device after six months.  
7 What is the nature of that proof?

a MR. LOCK: This is Ken Lock. What we had  
9 done is some animal testing on 12 Yucatan pigs that we  
10 looked at at three months and they were completely  
11 endothelialized at that time.

12 DR. HOPKINS: Do we have any human data  
13 whatever? Anybody gotten run over by a car or  
14 anything?

15 MR. LOCK: This is Ken Lock. As a matter of  
16 fact, we do have one patient that we do have a slide  
17 we could show on that.

18 DR. HOPKINS: You don't have to show me.

19 MR. LOCK: We do have one patient, yes.

20 DR. HOPKINS: That does show complete on  
21 both sides?

22 DR. HIJAZI: Endothelialization of the

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device, yes.

2 DR. HOPKINS: Thank you.

DR. TRACY: Dr. Aziz.

4 DR. AZIZ: I've just got a few questions.

5 I enjoyed the presentation. I think it was very lucid  
6 and helped me as a surgeon to follow exactly what you  
7 folks are doing.

8 You mentioned, Dr. Hijazi, that there were  
9 12 additional months of data collection and 465  
10 patients and that a number of these patients were from  
11 overseas although they were not analyzed in this data  
12 analysis. You mentioned there were no adverse events  
13 reported. Was the follow-up fairly rigid?

14 DR. HIJAZI: That's a good question. The  
15 patients have been followed-up by their local  
16 cardiologist there. To my knowledge nobody has called  
17 me to tell me that that patient we have done together  
18 has this adverse event or that. But the four  
19 embolizations that I reported, those were encountered  
20 while I was there so I know that.

21 If there were other complications, it was  
22 not reported to me or to the AGA. As a matter of

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1 fact, for the clinical trial internationally all  
2 patients that receive the Amplatzer device were  
3 reported and we would have known about that.

4 DR. AZIZ: And the 'people who were  
5 implanting these devices were local physicians or  
6 folks from here going out to help them implant them?

7 DR. HIJAZI: The initial proctoring or  
a training physicians from there contact the company and  
9 the company decides on a proctor. Then a proctor goes  
10 there and they proctor the physicians three to five  
11 cases in each center.

12 DR. AZIZ: Let me just ask you some  
13 theoretical questions. Most of these patients with a  
14 device that have been implanted, the mean age is about  
15 18 years old. Looking ahead I'm sure a number of them  
16 will probably come for bypass surgery or valve  
17 replacements. Do you see any potential problems  
18 lifting the heart and surgically manipulating it that  
19 might cause either kinking or displacement or problems  
20 with the device?

21 DR. HIJAZI: That's a good question. This  
22 is Ziyad Hijazi again. Not to my knowledge. I think

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1 once the device endothelializes, which takes anywhere  
2 from probably three months to six months for the  
3 device to be endothelialized, I do not think that  
4 lifting the heart or punching the heart would cause  
5 any problem.

6 Even in the real couple of cases that we had  
7 to take to the cath lab to close a residual shunt,  
8 going beside the device with a sizing balloon back and  
9 forth, that device is completely lodged there. It  
10 does not move at all. Actually, I remember with  
11 another device about five years ago the residual shunt  
12 was large requiring closure in the OR.

13 I went to the surgery to look and the  
14 surgeon had to use three knives to cut around. The  
15 device is totally impeded in the tissue so it's very  
16 difficult for the device to move during cardiac  
17 surgery or during anything else.

18 DR. AZIZ: I think most surgeons obviously  
19 do an ASD closure very well, and apart from I think  
20 the marginal echo defects, hopefully we don't see much  
21 leakage. If you had a patient who had an ASD repair  
22 done surgically and had a significant shunt, could

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