FDA Executive Summary

Prepared for the
September 23, 2014 meeting of the
FDA's Pediatric Advisory Committee

H020003
Medtronic Contegra® Pulmonary Valved Conduit,
Models 200 (unsupported) and 200S (supported)

INTRODUCTION

In accordance with the Pediatric Research Equity Act, this review provides a safety update based on the postmarket experience with the use of the Medtronic Contegra® Pulmonary Valved Conduit in pediatric and adult patients since approval. The Medtronic Contegra® Pulmonary Valved Conduit is a glutaraldehyde-crosslinked, heterologous bovine jugular vein with a competent tri-leaflet venous valve. It was approved on November 21, 2003 by the Center for Devices and Radiological Health under Humanitarian Device Exemption (HDE) application H020003.

The purpose of this review is to provide the Pediatric Advisory Committee with postmarket safety data so the committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This executive summary will include summaries of the premarket clinical study, 7-year postmarket follow-up of the premarket clinical study, postmarket medical device reporting (MDR) for adverse events, and the peer-reviewed literature associated with the device.

INDICATIONS FOR USE

The Contegra® Pulmonary Valved Conduit is indicated for correction or reconstruction of the right ventricular outflow tract (RVOT) in patients aged less than 18 years with any of the following congenital heart malformations:

- Pulmonary Stenosis
- Tetralogy of Fallot
- Truncus Arteriosus
- Transposition with Ventricular Septal Defect (VSD)
- Pulmonary Atresia

In addition, the conduit is indicated for the replacement of previously implanted, but dysfunctional, pulmonary homografts or valved conduits.

BRIEF DEVICE DESCRIPTION

The device is a glutaraldehyde-crosslinked, heterologous bovine jugular vein with a competent tri-leaflet venous valve and a natural sinus slightly larger in diameter within its lumen than the diameter of the adjacent conduit.

The device is available in 6 sizes in even increments between 12 and 22 mm in inside diameter, measured at the inflow end. The overall length of the device is about 10 cm, except

for the 12 mm models, which are approximately 7 cm in length. The valve and valve sinus are located at approximately the middle of the device.

The device is available in two models: one without external ring support (Model 200), and the other with ring support modification (Model 200S). The latter consists of an attachment of two polyester-knit-cloth covered polypropylene rings sutured to the adventitial layer of the device (with polytetrafluoroethylene suture). One ring is attached at the level of the commissures, and the other is attached at the level of the annulus of the valve leaflets.

REGULATORY HISTORY

The Contegra® Pulmonary Valved Conduit was granted Humanitarian Use Device (HUD) designation on April 24, 2002 by FDA's Office of Orphan Products Development. Medtronic conducted a clinical investigation of the device in support of an HDE application. This investigation involved pooled patients from the European Companion Study, which began in May 1999, and the United States Phase II IDE Study, which began in December 2001 and was conducted under IDE G990260. Medtronic submitted the HDE application to FDA on May 13, 2002. Subsequently, the HDE was approved on November 21, 2003.

PREMARKET DATA: CLINICAL INVESTIGATION

The clinical investigation for the Contegra® Pulmonary Valved Conduit was a prospective, non-randomized, multi-center investigation, with centers in Europe and in the United States.

Enrollment Criteria

Inclusion Criteria

- Male or female subjects, less than 20 years of age
- Female subjects of childbearing potential having a negative urine pregnancy test 24 hours prior to procedure
- Subject requires surgical reconstruction or replacement of his/her natural right pulmonary outflow tract (RVOT) or replacement of failed, previously implanted homograft or composite conduit in the RVOT
- Subjects and/or parents or guardians have been adequately informed, and provide written informed consent with regard to participation in the clinical study and what will be required of them and their child in order to comply with the protocol and its requirements

Exclusion Criteria

- Subjects 20 years of age or older
- Female subjects of child bearing potential, having a positive urine pregnancy test 24 hours prior to procedure
- Subjects who are pregnant or lactating
- Subjects requiring multiple heart valve replacement other than a Ross procedure

- Subjects in need of the surgical implantation of the study device for a Fontan procedure
- Subjects who have active endocarditis
- Subjects who have a major, or progressive non-cardiac disease (e.g., liver failure, renal failure, cancer) that significantly increases the surgical risk to the subject or that results in a life expectancy of less than 6 months
- Subjects known to have the Acquired Immune Deficiency Syndrome (AIDS) Virus or known to be HIV positive
- Subjects who are known intravenous drug users
- Subjects held in a juvenile detention facility or who are prison inmates
- Current participation in a clinical study of another investigational device or drug
- Subjects (or parents/guardians) unwilling or unable to provide written Informed Consent, or follow protocol requirements

Clinical Investigation Endpoints

Key Safety Endpoints

- Thrombus
- Thromboembolism
- Hemorrhage
- Endocarditis
- Hemolysis
- Nonstructural dysfunction
- Structural deterioration
- Catheter intervention
- Reoperation
- Explant
- Death

Key Effectiveness Endpoints

- Peak gradient
- Mean gradient
- Valvular regurgitation
- Contegra-related malfunction

Although not stipulated in the clinical protocols for the 2 studies in the clinical investigation, the composite safety/effectiveness endpoints "Conduit failure" and "Conduit success" were used by the FDA during its evaluation of the clinical investigation data.

Clinical Investigation Results

At the time of the HDE application, the clinical investigation data were obtained from 237 patients implanted at 16 centers (135 patients at 6 European centers and 102 patients at 10 United States centers). The cumulative follow-up for these patients was 307.7 patient-years, with a median follow-up of 1.0 year (range 0 years to 3.5 years). Preoperative data and major outcome data are presented in the tables below.

Table 1: Preoperative Data (N=237)

Variable	Category	n	%
Age at Implant	Less than 3 months	46	19.4
	3 to 12 months	37	15.6
	13 to 24 months	44	18.6
	25 months to 5 years	48	20.3
	6 to 10 years	33	13.9
	Greater than 10 years	29	12.2
Gender	Male	138	58.2
	Female	99	41.8
Primary Indication for Surgery	Replacement of Previous Conduit	77	32.5
	Tetralogy of Fallot	62	26.2
	Truncus Arteriosus	38	16.0
	Aortic Valve Disease	21	8.9
	Double Outlet	15	6.3
	Pulmonary Atresia	13	5.5
	Transposition of Great Arteries	8	3.4
	Pulmonary Stenosis	3	1.3

Table 2: Mortality Rates Following Implant with the Contegra® Pulmonary Valved Conduit

European Companion Study and US Study (N=237)	Early Events[1] n (% of patients)	Late Events[2] n (%/patient-year)[3]	Freedom From[4] Death at 1 Year (SE)	Freedom From[4] Death at 2 Years (SE)
All Death	22 (9.3%)	6 (2.1%)	88.1% (2.7%)	87.3% (3.9%)
Non Device-Related[5]	18 (7.6%)	0 (0.0%)	92.1% (2.3%)	92.1% (3.3%)
Device-Related or Unexplained	4 (1.7%)	6 (2.1%)	95.6% (1.8%)	94.8% (2.7%)
Device-Related	2 (0.8%)	5 (1.8%)	97.0% (1.5%)	96.2% (2.4%)
Unexplained	2 (0.8%)	1 (0.4%)	98.6% (1.1%)	98.6% (1.5%)

Notes:

1. ≤30 days postoperative if the patient was discharged from the hospital, or at any time after implant if the patient was not discharged from the hospital
2. Greater than 30 days postoperative if the patient was discharged from the hospital
3. Calculations were based on 284.0 late patient-years.
4. Kaplan-Meier method was used to estimate survival and Peto's formula was used for the calculation of the standard errors of these estimates.
5. Twelve early deaths were cardiac and six early deaths were noncardiac.

Table 3: Morbidity Rates Following Implant with the Contegra® Pulmonary Valved Conduit

European Companion Study and US Study (N=237)	Early Events[1] n (% of patients)	Late Events[2] n (%/patient-year[3])	Freedom From[4] Event at 1 Year (SE)	Freedom From[4] Event at 2 Years (SE)
Endocarditis	1 (0.4%)	2 (0.7%)	98.6% (1.0%)	98.6% (1.5%)
Thrombus[5]	5 (2.1%)	6 (2.1%)	95.4% (1.8%)	93.7% (3.0%)
Reoperation[6,7]	3 (0.8%)	22 (7.6%)	92.4% (2.3%)	86.1% (4.1%)
Explant	1 (0.4%)	11 (3.8%)	97.6% (1.4%)	92.0% (3.3%)
Minor Hemorrhage[8]	12 (4.2%)	2 (0.7%)	94.4% (2.0%)	94.4% (2.9%)
Major Hemorrhage[9]	31 (10.5%)	4 (1.4%)	88.0% (2.9%)	88.0% (4.1%)
Catheter Intervention[7,10]	2 (0.4%)	39 (13.5%)	86.8% (3.0%)	80.2% (4.7%)

Notes:

1. ≤30 days postoperative
2. Greater than 30 days postoperative
3. Calculations were based on 289.7 late patient-years.

4. Kaplan-Meier method was used to estimate survival and Peto's formula was used for the calculation of the standard errors of these estimates.
5. There were four (4) additional cases of focal thrombus deposition on the valve surface, on the conduit, or at the pulmonary artery anastomosis of the conduit which were considered by the core lab pathologist to be of insufficient amount to be primary valve thrombosis or to interfere with valve function.
6. Reoperation includes explant and surgical repair involving the Contegra device.
7. One patient had two early events.
8. Two patients had two early events.
9. Three patients had two early events and one patient had four early events.
10. Catheter intervention includes balloon dilation or stent placement in the branch PA, PA bifurcation, and/or distal anastamosis.

Table 4: Risk Factors Associated with Time to Death (All Causes) (n=237)

Risk Factor	Relative Risk	95% Confidence Interval	P-Value
Age at Implant			
Less Than 3 Months	4.81	1.99 - 11.61	0.0005
Concomitant Procedure			
Mitral/Tricuspid Valve Repair	20.42	5.96 – 70.44	< 0.0001
Aortic Valve/Root Replacement	8.62	2.60 – 28.38	0.0004
Ventricular Septum Repair	4.56	1.50 – 13.97	0.0082

Cox Proportional Hazards Survival regression analysis was used to assess the association of risk factors and time to event.

Table 5: Risk Factors Associated with Time to Reoperation (n=237)

Risk Factor	Relative Risk	95% Confidence Interval	P-Value
Age at Implant			
Less Than 24 Months	4.11	1.39 – 12.04	0.0105

Cox Proportional Hazards Survival regression analysis was used to assess the association of risk factors and time to event.

Table 6: Risk Factors Associated with Time to Explant (n=237)

Risk Factor	Relative Risk	95% Confidence Interval	P-Value
Primary Indication for Surgery			
Tetralogy of Fallot	16.05	1.92 – 132.53	0.0102
Truncus Arteriosus	12.44	1.38 – 111.63	0.0246

Cox Proportional Hazards Survival regression analysis was used to assess the association of risk factors and time to event.

Literature-Based Controls

Since the 237 patients evaluated for the HDE did not provide sufficient statistical power to evaluate Contegra conduit success in the clinical investigation, literature-based controls derived from homograft clinical studies were used in the review of the clinical results.

Table 7: Comparative Literature (Homograft vs. Contegra® Pulmonary Valved Conduit)

Author/yr	# pts	Mean age (SD or range) d=day m=month y=year	Death (%)		Freedom From reop @1yr[4] (%)	Catheter intervention- % of pts having a cath interv. (%)	Regurgitation	
			Early	Freedom From @1yr			# pts eval.	≥ mod regurg (%)
Medtronic, Contegra 2003	237	2.0 y[1] (1d-19y)	9	88	92	12.2	95[2]	21[2]
Albert, 1993	139	3.0 y (6d-17y)	17	83[3]	98[3]			
Baskett, 1996	44	6.2y (3d-20y)	7	93[3]	95[3]		38	29
Bielefield, 2001	223	2.8y (5d-17y)	14	84[3]	97[3]			
Chan, 1994	41	3.1y[1](3m-28y)				9.8	43	35
Dittrich, 2001	23	1.9y (5d-9y)	13	--	93	4.3	20	15
LeBlanc, 1998	76	3.1y (6d-19y)	5	93	96			
Perron, 1999	84	26d (1d-3m)	11	81	91	20.2		
Schorn, 1997	63	1.3y (±0.9y)	27	--	92	12.7		
Stark, 1998	405	6.8y (--)			97[3]	3.2		
Tam, 1995	56	3.6y[1](1d-24y)	16	84[3]	100		39	36
Tweddell, 2000	205	6.9y (3d-48y)	11	89[3]	95			

[1]median

[2]at one year
[3]estimated from graph in article
[4]For Homograft references: Freedom from reoperation is explant; for Medtronic, Freedom from reoperation includes explant and surgical repair.
shaded cells: no data available

The clinical data demonstrated that the device performed as expected with regard to hemodynamic performance and the incidence of conduit-related adverse events. It was concluded that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available or alternative forms of treatment when used as indicated in accordance with the directions for use.

It is expected that the device will undergo replacement due to pediatric patient growth. It is an interim device that provides the physician with a tool to manage the patient until the patient attains growth to allow consideration of other alternatives for their congenital cardiac repair.

POSTMARKET DATA: THE IDE CLINICAL STUDY – FINAL RESULTS

There was no post-approval study ordered as a condition of approval for the Contegra HDE. The IDE study used to support the HDE application was officially terminated on April 26, 2007. A total of 386 patients were enrolled throughout the study: 165 patients at 8 centers in Europe and 221 patients at 10 centers in the United States. The implant period for these patients was from May 12, 1999 to April 30, 2004. Preoperative data and major outcome data available through September 11, 2006 are presented in the tables below.

Table 8: Preoperative Data

All patients analyzed: N=374; n=number per subgroup

Variable	Category	%	(n/N)
Age at Implant	Less than 3 months	19.5	(73/374)
	3 to 12 months	17.1	(64/374)
	13 to 24 months	16.6	(62/374)
	25 months to 5 years	20.6	(77/374)
	6 to 10 years	12.8	(48/374)
	Greater than 10 years	13.4	(50/374)
Gender	Male	58.6	(219/374)
	Female	41.4	(155/374)
NYHA Classification[1]	I	38.5	(42/109)
	II	54.1	(59/109)
	III	6.4	(7/109)
	IV	0.9	(1/109)
Cardiovascular Presentation[2]	Pulmonary Stenosis	46.3	(173/374)
	Tetralogy of Fallot	37.2	(139/374)
	Pulmonary Insufficiency	33.7	(126/374)
	Pulmonary Atresia	32.4	(121/374)
	Truncus Arteriosus	27.0	(101/374)
	Failed Repair	22.2	(83/374)
	Failed Homograft	21.1	(79/374)
	Congestive Heart Failure	17.6	(66/374)
	Pulmonary Hypertension	15.5	(58/374)
	Failed Composite Conduit	12.6	(47/374)
	Double Outlet	12.0	(45/374)
	Transposition of Great Arteries	9.1	(34/374)
	Systemic Hypertension	2.1	(8/374)

Bacterial Endocarditis	1.3	(5/374)
Ross Procedure	0.5	(2/374)
Rheumatic Etiology	0.3	(1/374)

Notes:
1. NYHA classification not obtained for patients less than four years of age at implant.
2. Patients may have had more than one cardiovascular presentation.

Table 9: Summary of Mortality and Morbidity Data

All patients analyzed: N=374; n=number per subgroup

	Early[1] Events		*Late[2] Events*		*Freedom from Event (%)*			
	n	% of Patients	n	%/Pt-Yr[3]	1 Year	SE	2 Years	SE
All Death	32	8.6	16	1.4	88.3	1.7	87.4	1.9
Not Device-Related	30	8.0	8	0.7	89.9	1.6	89.9	1.8
Device-Related or Unexplained	2	0.0	8	0.7	98.2	0.8	97.2	1.0
Device-Related	0	0.5	7	0.6	98.8	0.6	97.7	0.9
Unexplained	2	0.5	1	0.1	99.4	0.4	99.4	0.5
Structural Deterioration	0	0.0	7	0.6	99.7	0.3	99.3	0.5
Nonstructural Dysfunction	3	0.8	47	4.1	95.0	1.3	92.5	1.6
Reoperation[4]	3	0.5	65	5.6	93.3	1.4	88.7	1.9
Explant	1	0.3	51	4.4	96.6	1.0	95.9	1.2
Repair	2	0.5	14	1.2	96.3	1.1	91.7	1.6
Catheter Intervention[5]	2	0.3	115	9.9	86.8	1.9	80.8	2.4
Device-Related	2	0.3	56	4.8	94.9	1.3	91.1	1.7
Not Device-related	0	0.0	59	5.1	91.8	1.6	89.0	1.9
Hemolysis	9	2.4	11	0.9	95.4	1.2	95.4	1.3
All Hemorrhage[6]	83	15.5	31	2.7	82.2	2.2	81.8	2.4
Major Hemorrhage	66	11.8	7	0.6	86.6	2.0	86.6	2.1
Minor Hemorrhage	17	4.0	24	2.1	94.6	1.3	94.3	1.4
Thromboembolism	0	0.0	0	0.0	100.0	0.0	100.0	0.0
Thrombosis[7]	9	2.1	14	1.2	94.4	1.3	93.4	1.5
Endocarditis	1	0.3	13	1.1	98.5	0.7	97.8	0.9

Notes:
1. ≤30 days postoperative if patient was discharged from hospital, or at any time after implant if the patient was not discharged from the hospital
2. Greater than 30 days postoperative, if the patient was discharged from the hospital
3. Calculations are based on 1135.9 late patient-years for mortality and 1159.7 late patient-years for morbid events.
4. One patient had an early repair and an early explant.
5. One patient had two early catheter interventions.
6. Seven patients had two early major hemorrhages, one patient had three early minor hemorrhages, one patient had one early major and one early minor hemorrhage, three patients had three early major hemorrhages, one patient had four early major hemorrhages, and one patient had seven early major hemorrhages.
7. One patient had two early thromboses.

Table 10: Summary of Mortality and Morbidity Data (continued)

All patients analyzed: N=374; n=number per subgroup

	Freedom from Event (%)									
	3 Years	SE	4 Years	SE	5 Years	SE	6 Years	SE	7 Years	SE
All Death	87.0	2.2	86.4	2.7	86.4	3.3	86.4	5.0	86.4	18.4
Not Device-Related	89.5	2.1	89.5	2.5	89.5	3.0	89.5	4.6	89.5	16.7
Device-Related or Unexplained	97.2	1.2	96.6	1.5	96.6	1.9	96.6	2.8	96.6	10.3
Device-Related	97.7	1.0	97.7	1.3	97.7	1.5	97.7	2.3	97.7	8.5
Unexplained	99.4	0.5	98.8	0.9	98.8	1.1	98.8	1.7	98.8	6.2
Structural Deterioration	99.3	0.6	98.0	1.2	98.0	1.4	96.1	3.0	92.8	14.4
Nonstructural Dysfunction	91.7	2.0	88.6	2.8	83.6	3.9	83.6	5.8	80.8	25.0
Reoperation	85.1	2.4	82.3	3.1	76.0	4.1	70.3	6.4	65.3	27.2
Explant	95.1	1.5	95.1	1.9	94.3	2.5	94.3	3.8	94.3	16.0
Repair	88.9	2.1	86.1	2.8	80.7	3.7	75.3	5.9	70.5	22.1
Catheter Intervention	77.3	2.9	72.2	3.7	70.5	4.5	69.4	7.0	66.6	27.2
Device-Related	89.1	2.2	86.0	3.0	84.1	3.8	82.9	6.0	80.0	25.3
Not Device-Related	87.4	2.3	84.0	3.0	84.0	3.6	82.8	5.8	82.8	19.8
Hemolysis	94.9	1.6	94.9	1.9	94.1	2.5	94.1	4.0	94.1	16.2
All Hemorrhage	80.9	2.8	80.4	3.4	80.4	4.2	79.2	6.3	79.2	20.9
Major Hemorrhage	86.6	2.4	86.6	2.9	86.6	3.6	86.6	5.4	86.6	18.3
Minor Hemorrhage	93.4	1.8	92.8	2.3	92.0	2.9	88.8	5.0	88.8	17.2
Thromboembolism	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0

Thrombosis	93.4	1.7	93.4	2.1	93.4	2.5	93.4	3.8	93.4	13.8
Endocarditis	97.4	1.1	95.6	1.7	93.7	2.5	93.7	3.7	93.7	13.5

POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

The Pediatric Medical Device Safety and Improvement Act of 2007 amended section 520(m) of the Food and Drug Administration Amendments Act and now allows HDEs indicated for pediatric use and approved on or after September 27, 2007, to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). The ADN was defined to be the number of individuals affected by the disease or condition per year (i.e., annual incidence) multiplied by the number of devices reasonably necessary to treat an individual. The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 amended the ADN definition to be the number of such devices reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States, and FDA has interpreted that to imply that the calculation of the ADN should be 4,000 multiplied by the number of devices reasonably necessary to treat an individual.

Section 613(b) of the FDASIA states that an HDE holder of a HUD for which an HDE was approved prior to the enactment of FDASIA on July 9, 2012 may submit an HDE supplement (21 CFR 814.108) requesting an exemption from the profit prohibition for a HUD. In March 2013, the firm requested a determination that the Contegra Pulmonary Valved Conduit device met the conditions of either subclause (I) or (II) under section 520(m)(6)(A)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the FDASIA, so that the device might be sold for profit. The HDE supplement request was approved by the FDA on April 11, 2013. The approved ADN for the Contegra Pulmonary Valved Conduit device was 4,000.

As stated in section 520(m)(8) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted.

Table 11: Annual Distribution Numbers of the Contegra Pulmonary Valved Conduit Device

Calendar Year (Jan - Dec)	Total Sales	Total Implants	Total Pediatric Implants	Age Unknown
2003	58	1	1	0
2004	328	135	126	6
2005	304	158	151	4
2006	460	287	271	13
2007	648	430	387	31
2008	630	459	402	41
2009	503	375	328	36
2010	563	449	396	33
2011	612	399	360	26
2012	518	378	343	15
2013	350	357	322	25
2014-July	306	170	155	11
Note:				

1. Contegra implants are not required to be registered; therefore, there are only approximately 65% of U.S. implants that are registered.
2. There were a total of 241 implants where age was not listed; therefore, it is unknown if these were pediatric or adult patients. Note that the 241 total is not included in the "Total Pediatric Implants" column.

POSTMARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of Manufacturer and User Facility Device Experience (MAUDE) Database

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MAUDE database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting, including rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs include, but are not necessarily limited to:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MAUDE data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MAUDE data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDR Data associated with Contegra Valved Conduit

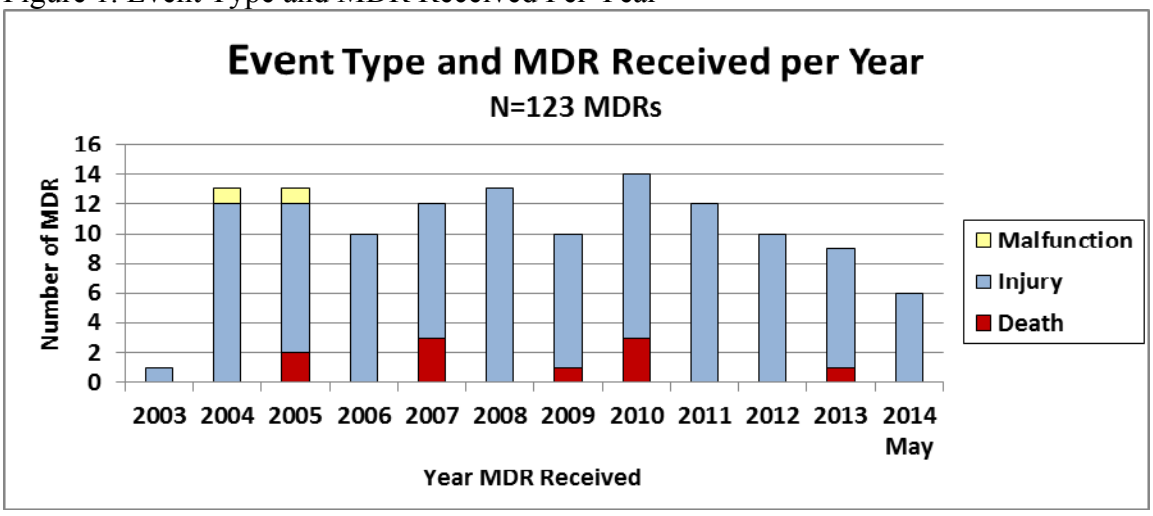
FDA received 125 MDRs related to the **Contegra Valved Conduit** in the FDA's MAUDE database between November 21, 2003 and May 31, 2014. Two of the 125 MDRs were excluded from the MDR data set, including one duplicate MDR submitted by 2 different reporting sources on a same event and another MDR submitted based on a published article of a case series which is covered by FDA's literature review (reference the POSTMARKET DATA LITERATURE REVIEW section of the Executive Summary) for the Pediatric Advisory Committee (PAC). Therefore, the following MDR analyses are based on the data of **123 MDRs**, and include the following demographic data shown in Table 12:

Table 12. Patient Demographic Data

Reporting Country	(reported in 105 MDRs)		MDR Count
	United States (US) : Outside US	**49.5% : 50.5%**	(52 : 53)
Patient Gender	(reported in 91 MDRs)		
	Male : Female	**58% : 42%**	(53 : 38)
Patient Age	(reported in 98 MDRs)		
	Range	**12 days – 32 years**	
	Average	**6.2 ± 6 years**	
	Pediatric : Adult	**99% : 1%**	(**97** : 1)
Pediatric (≤ 21 Year)	**(reported in 97 MDRs)**		
	Range	**12 days – 21 years**	
	Average	**5.9 ± 5.5 years**	

The event types reported in the 123 MDRs include death (10 MDRs), serious injury[1] (111 MDRs) and malfunction[2] (2 MDRs). The event type and the number of MDR received per year between 2003 and 2014 are provided in Figure 1 below. The number of MDR received each year has remained stable, ranging between 9 and 14 reports per year over the past 10 years.

Figure 1. Event Type and MDR Received Per Year



Individual review of the 123 MDRs also provided for categorizing the reported problems based on the major events reported in the MDRs. Additionally, to determine the peri-

[1] Serious injury, per regulatory definition (CFR 803.3), includes event that is life-threatening or results in permanent impairment or necessitates medical or surgical intervention(s).
[2] Malfunction event is defined as device not performing as intended, but no patient adverse effects and no intervention(s) are required.

procedural and post-implant timing of the adverse events, the "time to event occurrence" (TTEO) for the 123 MDRs was calculated. The TTEO was based on the implant duration specified in the Event Text of the MDRs or calculated as the time period between the Date of Implant and Date of Event. The event types, the reported problems and the TTEO are shown in the following Table 13.

Table 13. Event types, Reported problems and TTEO of the 123 MDRs

		Event Type			
Reported Problem	**MDR Count**	**Death**	**Serious Injury**	**Malfunction**	***TTEO Range (Mean)**
Peri-procedural Event, n=11					
Inadequate device size	7	1	5	1	< 1 day
Coronary Artery Compression	1	0	1	0	< 1 day
Bleeding	1	0	1	0	< 1 day
Discolored solution in container	1	0	1	0	< 1 day
Breakage of container	1	0	0	1	< 1 day
Post- implant Event, n=112					
**Stenosis	78	2	76	0	0.3 – 168 (44) months
Thrombus/embolism	9	4	5	0	0.1 – 30 (4) months
Conduit dilation/aneurysm	8	0	8	0	0.2 - 22 (7) months
Infection/endocarditis	7	2	5	0	0.3 - 51 (13) months
***Structural valve deterioration	4	0	4	0	41 - 135 (77) months
Pulmonary insufficiency/regurgitation	4	0	4	0	1.7 - 56 (29) months
Conduit intimal dehiscence	1	1	0	0	9 months
Explant for other cardiac surgery	1	0	****1	0	12 months
Total,	**123**	**10**	**111**	**2**	

* TTEO: Time to event occurrence

** Stenosis includes but is not limited to the following events such as calcification, mineralization, stenosis, host tissue overgrown and pannus formation.

*** Structural valve deterioration includes events such as wear, tears, holes or disruption of the valve.

**** The MDR represents the only adult patient reported in the 123 MDRs.

Based on the review of the event text included in the 123 MDRs and the TTEO calculation, 11 MDRs were identified as peri-procedural events where reported problems were identified within 24 hours of the Contegra implantation. The remaining 112 MDRs were identified as post-implant events where the problems were observed beyond 1 day post implant. Each of the reported problem categories falling under the Peri-operative or Post-implant events and included in Table 2 are further summarized as follows.

A. Peri-procedural Event (n =11 MDRs, including 1 death)

Inadequate device size *(n=7 MDRs, including 1 death)*

The most frequently reported problem of the peri-procedural events was inadequate device size (7 MDRs), including device size too large, too small, or too long. One of the 7 events of inadequate device size involved a death of an infant who had a truncus arteriosus and a regurgitant truncal valve and required an urgent valve replacement. An incorrect sized valve was distributed erroneously to the hospital and it was not a suitable size for the patient. The surgeon implanted another manufacturer's homograft into the patient, and the patient did not survive the surgical procedure.

For the remaining 6 events where inadequate device size was identified, 5 patients required valve conduit replacement on the same day of the surgery. In the other patient,

the Contegra valved conduit was not implanted, as the surgeon identified that the size of the device was smaller than desired prior to the implant surgery.

According to the manufacturer analysis, the results of the investigation include the following:

- Patient-Prosthesis Mismatch – 2 MDRs
- No conclusion – 2 MDRs (The device was not returned to the manufacturer for analysis).
- Device met manufacturing specifications – 2 MDRs, including the event of distribution error.
- Device sized incorrectly during the manufacturing process – 1 MDR

For the reported event where the device sized incorrectly during the manufacturing process, the manufacturer has reported taking actions to retrain the technicians and the inspectors.

***Coronary Artery* Compression** (n = 1 MDR)
One report noted that the supported Contegra valved conduit had to be explanted 5 hours post implant due to ST depression and cardiac arrest of a 9-year-old girl. The patient was taken back to the operating room and extracorporeal membrane oxygenator (ECMO) was initiated. The supported Contegra device was replaced with an unsupported Contegra device. The surgeon stated it was possible that the rings on the supported Contegra device were too stiff for this patient and contributed to the post-operative complications by compressing the patient's coronary artery.

Please note that a review of the current Instruction for Use (IFU) of the Contegra Valved Conduit did not find coronary artery compression in the list of potential adverse events.

Bleeding *(n = 1 MDR)*
There was one report of bleeding from a hole in the conduit. The hole was repaired with a stitch during the implant surgery. The device remained implanted with no consequences reported for the patient.

Discolored solution in container *(n = 1 MDR)*
One report noted discolored glutaraldehyde solution in the Contegra jar. The device was replaced intra-operatively. No patient complication was reported.

Breakage of container *(n = 1 MDR)*
One report cited difficulty opening the product jar during set-up. The bottom of the jar broke during the lid removal. The conduit was not implanted and there was no patient involvement.

B. Post-Implant Event (n=112 MDRs, including 10 deaths)

Stenosis *(n=78 MDRs, including 2 deaths)*
Stenosis was the most frequently reported problem in the MDRs of the Contegra device. Of the 78 MDRs reporting stenosis, 2 MDRs noted patient death. The event text of the 2 MDRs is summarized as follows:

1. MDR# 2025587-2010-00038

A one-day-old male patient with multiple congenital heart abnormalities had a placement of the Contegra valved conduit and partial closure of an atrial septal defect (ASD). The patient developed multiple complications post implant including arrhythmia, diaphragm paralysis, increasing shunting across the ventricular septal defect (VSD) and required multiple interventions such as inotropic support, intubations, gastrostomy and pulmonary artery stenting. Three months post implant, the patient was re-admitted to the hospital for Contegra explant, Dacron patch closure of the VSD and suture closure of ASD when significant narrowing of both pulmonary arteries and residual (congenital) VSD were found. Post Contegra explant, the patient had multiple admissions for pneumonia and respiratory distress. The patient subsequently expired 6 months post Contegra explant. There was no information regarding the causal relationship between the death and Contegra device.

2. MDR# 2025587-2010-00051

A patient, age and gender unknown, underwent a re-operation for a replacement of Contegra device and expired on the same day. The implant duration was not reported. The Contegra device reportedly had calcified due to an aneurysm on the aorta which had bulged into the Contegra valve conduit. According to the manufacturer analysis, the cause of death is unknown. However, it was reported as unrelated to the device.

For the remaining 76 non-fatal stenosis events, the majority of the patients required valve replacement surgery and/or additional interventions such as angioplasty, stenting, or transcatheter pulmonary valve procedure.

For the 78 MDRs involving stenosis, the reported time to event occurrence ranged from 0.3 to 168 months (14 years). According to the manufacturer analyses, the reasons for stenosis include, but are not necessarily limited to the following: calcification, mineralization, host tissue overgrown, intimal tissue proliferation, pannus formation, and anatomical positions which were likely related to patient factors. There were also 7 MDRs noting that the stenotic Contegra device was explanted due to patient outgrowth.

Thrombus/embolism *(n= 9 MDRs, including 4 deaths)*

Thrombus/embolism was reported in 9 MDRs. The thrombus/embolism was identified between 4 days and 5 months post Contegra implant. There were 4 patient deaths and the remaining 5 patients required device explant. The event text of the 4 MDRs involving patient death is summarized as follows:

1. MDR# 2025587-2005-00093

A surgeon alleges valve-related death due to possible thromboembolic event. The 12-day-old male patient expired 4 or 5 days following implant due to clotting of the Contegra device. The manufacturer's investigation with the healthcare profession found the cause of death was pulmonary embolism. The inspection done at the user facility revealed a thin thrombus noted on the valve leaflet, as well as dislodged thrombus seen at the distal anastomosis.

2. MDR# 2025587-2007-00110

A 19-month-old female patient expired 5 months post Contegra implant. An autopsy revealed a small lumen due to thrombus within the conduit. The healthcare professional reported the death to be non-device related. No detailed information is available regarding this case.

3. MDR# 2025587-2007-00033

A 3 month-old patient expired 2 weeks post Contegra implant. The valve explanted at autopsy was returned to the manufacturer, with the presence of thrombus noted on the leaflets. The surgeon stated that the death is not due to the valve, but likely due to the cardiac status of the patient, the clinical/surgical history and the patient's small size.

4. MDR# 2025587-2010-00063

A 4-year-old patient was noted to have metabolic acidosis during an outpatient cardiac catheterization for conduit and branch PA stenosis 2.5 years post Contegra implant. Severe RV-PA conduit obstruction was noted on angiography due to thrombus. Prior to any interventions, the patient acutely decompensated. CPR was initiated and a stent was emergently placed across the RV-PA conduit with immediate improvement. The patient subsequently developed stent thrombosis and required TPA treatment with a complication of a large bilateral intracranial hemorrhage with hydrocephalus, 6 hours post TPA initiation. After aggressive medical management, the family decided to withdraw support and patient expired shortly thereafter. Based on the physician's report, the death was precipitated by bilateral intracranial hemorrhage with hydrocephalus, secondary to TPS treatment.

In the 5 non-fatal thromboembolic cases, other clinical presentations were also reported, including pulmonary regurgitation/insufficiency, conduit dilation, reduced leaflet mobility, or right ventricle outflow tract obstruction. According to the manufacturer analysis, the exact causes of the events were not known, however, thrombotic host material lining the outflow of the valve leaflets was noted in one MDR and patient factors were cited in the other MDR.

Dilation/aneurysm *(n=8 MDRs)*

A total of 8 MDRs noted dilation or aneurysm of the valved conduit. The patients required a replacement of valved conduit between 0.2 and 22 months post implant. Based on the manufacturer's analyses reported in 3 of the 8 MDRs, the dilation/aneurysm of valved conduit was likely due to pulmonary hypertension. For the other 5 cases of dilation/aneurysm, no conclusion can be drawn as the explanted devices were not returned to the manufacturer.

Endocarditis or infection *(n=7 MDRs, including 2 deaths)*

Seven MDRs noted endocarditis or infection between 9 days and 51 months post implant of Contegra device. Two of the 7 endocarditis/infection events involved patient death. The event descriptions for the 2 fatal events are summarized as follows:

1. MDR # 2025587-2005-00065

The surgeon of the 4-year-old male patient reported that the conduit was difficult to suture due to thick and stiff wall tissue. However the case was completed with no patient complications. Subsequently, it was reported that the patient expired and the

cause of death was acute endocarditis. The causative organism was identified as Streptococci. The information of implant duration was not provided in the report. The manufacturer analysis on the returned device revealed that the wall thickness measurements were comparable to the measurement data from other Contegra conduit products. The manufacturer concluded that the endocarditis from the Streptococci would not have originated from the valved conduit.

2. MDR# 2025587-2009-00001

It was reported that a 6 month-old male patient visited his doctor for diarrhea, vomiting and ear infection approximately 1.5 months post implant of Contegra device. On the way home from the doctor visit, the patient arrested and expired. An autopsy was not performed. Of note, the patient's medical history includes Tetralogy of Fallot with absent pulmonary valve syndrome, imperforate anus with colostomy, trisomy 21 and gastric tube for feeding. According to the manufacturer's analysis, the healthcare professional suggested that the death was not related to the conduit.

Of the remaining 5 endocarditis/infection events, the organisms were reported in 3 MDRs, including Gram –positive Cocci (1 MDR), culture-negative bacteria (1) and Staphylococci with a possible fungal infection (1). The patients typically required antibiotic treatment and/or a replacement of the valve conduit.

Structural valve deterioration (SVD) *(n=4 MDRs)*
Four MDRs cited structural valve deterioration. The valve deterioration includes wear, tears, holes or disruption of the valve. The patients required a replacement of the valved conduit between 41 and 135 months (up to 11 years) post implant. Please note that SVD is a known complication associated with bioprosthetic heart valves and is addressed in the IFU of the device.

Pulmonary insufficiency/regurgitation *(n= 4 MDRs)*
Pulmonary insufficiency or regurgitation was noted in 4 MDRs and the patients required replacement of the Contegra device between 1.7 and 56 months post implant. One of the 4 MDRs indicated that the pulmonary valve had become insufficient due to anatomic distortion which had contributed to the re-operation. The cause of the insufficiency/regurgitation was not available in the other 3 MDRs.

Conduit intimal dehiscence *(n=1 MDR, a death of a 27-month-old female patient)*
The patient who was implanted with a Contegra valved conduit suddenly died 9 months post implant at an outside institution. The cause of death on the autopsy was "pulmonary arterial intimal dehiscence". The patient was seen by the cardiologist 10 days prior to the death and there were no issues with the conduit. The echocardiogram performed 11 days prior to the patient's death noted a widely patent conduit, although there was an overall peak instantaneous gradient of 55 mmHg. According to the manufacturer's narrative, the device history review of this device was reviewed and no anomalies were noted that would have impacted this event. It was reported that the cause of patient death was due to dehiscence of the conduit. However, without the device, a conclusive cause of the dehiscence of the conduit could not be determined.

Device explant due to other cardiac surgery *(n= 1 MDR, on the only adult patient)*

A 32-year-old male patient required an aortic root surgery due to severe aortic root dilation conduit. The Contegra device with a transcatheter heart valve was explanted during an aortic root surgery. There were no adverse patient effects.

Summary of MDR Review

- The reported coronary artery compression by the supported rings of the Contegra device is not addressed in the current device IFU.
- Although the conduit intimal dehiscence reported in one of the MDRs is considered as a known complication of prosthesis deterioration which is addressed in device IFU, the suddenness of the event onset was relatively unexpected as reported.
- The inadequate device size reported in 7 MDRs appeared be related to different factors, including user's selection for adequate valve size, a product distribution error, manufacturing process control, or others.
- Other events reported in the MDRs reflect known complications associated with the bioprosthetic devices and are addressed in the IFU of Contegra device.

POSTMARKET DATA LITERATURE REVIEW

A search of the PubMed database was conducted on June 30, 2014 for articles published after HDE approval of the Contegra (November 21, 2003) using the following search terms: "Contegra" OR "Bovine Jugular vein "OR "Pulmonary valved conduit". A total of 135 articles were found. Titles and abstracts were reviewed to exclude the following records: non-English publication (n=1), non-human or animal models (n=7), non-clinical data (n= 15), not Contegra (n=6), case reports (n=26), editorials/comments/Report/Reviews (n=14), full text not available (n=3), and studies without safety or effectiveness data (n=2).

This yielded 61 full text articles that were assessed for eligibility and the following articles were excluded: studies with mean or median age > 22 years (n=3), non-systematic review (n=1), articles with ≤ 10 study device or subjects (n=4), studies on procedures/techniques (n=4), studies involving off-label use of device (n=2), studies with combined outcomes (n=1). Thus, a total of 46 final articles were included in the qualitative data analysis[1-46].

There were 23 retrospective studies, 13 prospective cohort studies, 2 systematic reviews and 8 unspecified study designs. Twenty-eight (28) studies were conducted in Europe, six (6) studies were performed in the US and 1 was a joint study of USA and Europe patients. The remaining 11 studies were conducted in Canada, Saudi Arabia Pakistan or the country was unspecified. The sample sizes ranged from 10 to 193 patients or 31-232 Contegra conduits. The patients' ages at implant ranged from 2 days to 73.5 years. The mean ages for the studies ranged from 7.3 months to 16 years. The mean follow-up times ranged from 9 months to 7 years.

Death

The incidence of early mortality (defined as death occurring in-hospital or within 30 days of surgery or discharge) ranged from 0 to 30%[1,2,4-19,21,23,24,26-29,31-40,42-44] and late mortality (defined as any mortality beyond 30 days post device implant) ranged from 0 to 8.3%[1,2,4,6-12,14-19,21,23,24,29,31-34,36,38,42,44] (Of note: studies that reported high early mortality rates of 14-30% tended to have small sample sizes of 10-16 subjects[6,26,39] and 43 subjects[32]).

Of the two systematic reviews, one reported early and late mortality rates of 3.2–10.9% and 0–4%[46] respectively. The other reported early mortality rate of 3.4% and a late mortality rate of 2.2%, and indicated that mortality was sometimes unrelated to the conduit[45].

Eight studies reported early or late mortality rates of 0% during the follow-up period[11,12,15,21,24,37,41,42].

Of the studies that reported deaths rate > 0%, seventeen studies specified that all of the deaths were unrelated to the Contegra conduit[2,8-10,13,14,16-19,23,26,29,33,35,39,40]. In eleven other studies the relatedness of deaths to the Contegra conduit were not specified[1,4-6,27,28,31,32,34,43,44] such as the following reported deaths: 3 early and 2 late deaths of cardiac causes by Albanesi et al[1], 3 early deaths by Boethig et al[4], 3 late deaths due to infection, pulmonary embolism and sudden cardiac death after reoperation reported by Pawelec-Wojtalik et al[32] and 1 death due to recurrent fungal septicemia[34].

Contegra conduit related deaths were found in 4 studies. The reported Contegra-related death rate ranged from 1.2 to 3.4%[7,27,36,38].

Four studies did not evaluate death or mortality as endpoints[3,20,25,30].

Survival (time-to-event analysis)

Twelve (12) studies calculated and reported patient survival data[2,9,10,17,20,21,25,30,34,38,40,46]. The all-cause death-free survival rates were reported as 94%[23] at < 6 months, 96%[28,38] at 3 years, 91- 94%,[8 32] at 4 years, 80%-100[7,18,19,36] at 5 years, 95.7%[1] at 7 years, 91.8%[16] at 8 years and 81-100[18,44] at 10 years.

Brown et al[9] comparing Contegra and Pulmonary homograft conduits with respect to patient survival, conduit durability, and performance in neonates, children and young adults reported similar survival rates for the Bovine jugular vein (BJV) and Pulmonary homograft (PH) cohorts at 2 years (BJV, 95%; PH, 93%) and 10 years (BJV, 95%; PH, 89%) [9]. Among subgroups of patients implanted with different sizes of Contegra Conduit, Fiore et al reported that 5 and 10 year survival of patients implanted with the 12-14 mm size (group 1) Contegra conduit was significantly lower than survival in patients implanted with the 16-18mm (group 2) or 20-22 mm size (group 3) Contegra conduit (at 5 years: group 1, 81%; group 2, 95%; and group 3, 100%, and at 10 years: group 1, 80%; group 2, 99%; and group 3, 100%)[18]

Thrombosis

Seven articles reported data on thrombosis[4,7,30,36-38,42]. Sfyridis et al in a retrospective analysis of 34 patients (mean age 10.9 years) implanted with the Contegra conduit reported early (11 days post initial surgery) conduit replacement in a 3 year old patient as a result of recurrent valve thrombosis[37]. Four other patients in that study developed valve thrombosis as early as 2-4 days post-implant (the patients had associated heparin antibodies) but resolved completely with anticoagulation therapy. The total thrombosis rate was 14.7% (5/34)[37]. Shebani et al reported 1 death directly due to complete conduit thrombosis in the early post-operative period[38]. Besides this death, thrombosis developed on the valve cusps of five conduits at a median time interval of 78 days (range 12—210 days) after implant. All cases

were receiving aspirin at 2.5 mg/kg /day and all cases resolved with continuation of aspirin therapy [38] – a total thrombosis rate 9.4% (6/64) was observed in that study.

Tiete et al in a study of 29 pediatric patients, mean age 3.39 years, who underwent RVOT reconstruction with the Contegra reported that two infants age 1.8 and 3.5 months experienced thrombus formation at the conduit valve 2 weeks post-operative. The thrombus formation was attributed to mismatch in valve sizes (both had 12-mm size conduit) causing a relatively low blood flow and an incomplete valve leaflet motion. The total thrombosis rate was 6.9%[42].

A 2-year freedom from thrombosis rate of 95.2% was reported by Boethig et al in a prospective multicenter study of 104 patients, mean age 6.0 years, implanted with the Contegra[4]. The thrombosis rates in the remaining three studies ranged from 0.5 to 1.5%[7,30,36].

Thromboembolism

One death, that occurred 3 months post implant, was reported by Pawelec-Wojtalik et al[32] in 43 patients after reoperation to repair a RVOT aneurysm. The authors indicated that this late death was probably caused by pulmonary thromboembolism, but it was not certain whether the graft was the source of the emboli[32].

Endocarditis

Sixteen studies reported cases of endocarditis[1,4,7,14,17,18,20,27,30,32,33,35,36,38,43,44] . The reported rates of endocarditis in the literature were in the range of 0% to 11.3% at different follow-up times (up to a median of 7.6 years). Studies reporting: up to 1-year follow-up observed proportions of 3.5%[7], 1.6%[38] and 0.74%; approximately a 2-year follow-up observed proportions of 0.96%[4], 1.08%[17], 1.49%[14], 4.65%[32], and 5.2%[27], approximately 3-year follow-up observed proportion of 2.3%[36], 4-year follow-up observed proportions of 0.52%[33], 0.86%[18], 7.0%[35] and 11.3%[1], approximately 5 and 6-year follow-up observed proportions of 8.6%[30] and 7.4%[43] respectively. A 5-year freedom from endocarditis rate of 92% was reported by Breymann and colleagues[7]. A recent publication by Albanesi et al[1] reported a graft infection rate of 11.3% (12 of 106 patients) in Contegra implanted patients, median age 13 years (range 0-54) at a median follow-up time of 4.4 years, despite the lifelong endocarditis prophylaxis[1] in the patients. In that study, graft infection was found to be significantly associated with Tetralogy of Fallot (HR 0.06, $P = 0.01$), systemic-to-pulmonary shunt (HR=64.71, $P < 0.01$) and hypothermia (HR=0.77, $P < 0.01$).

Stenosis

Twenty (20) articles reported the occurrence of distal stenosis in the Contegra conduit[4,7,9,12,13,17,19,21,22,25,27,28,34-36,38,39,43-45].

The freedom from severe distal Contegra stenosis ranged from 68-100%[17,21,25,27,38,45] at 1 year, 49 to 80%[4,21,27,45] at 2 year and 75-100%[22,34,45] at 3 years.

The freedom from moderate Contegra stenosis at 1, 2 and 3 years was reported by Morales et al in a study of 76 patients, median age 1.6 years, implanted with 77 Contegra as 100%, 92% and 82 % respectively[28] .

Shebani et al reported distal stenosis rate of 11.6% in 64 Contegra implanted in 62 patients during a median follow-up of 14 months[38]

Articles reporting on the5 and 10 year freedom from severe distal Contegra stenosis observed ranges from 73 to 80%[7,36,43] and 52 to 79 %[9,19], respectively. Five (5)-year and 10-year freedom from moderate stenosis rates were up to 75% and 74.6% , respectively[44]. A severe stenosis rate of up to 12.5%, occurring < 3months post Contegra implantation, was also reported[27]. Boethig et al investigating 104 Contegra implanted children for risk factors for distal stenosis, in the prospective European multicenter study, concluded that age <2 years was the main factor for development of distal stenosis[4]. Other investigators found that younger age and small pulmonary arteries (graft size ≤ 20 mm) increase the risk of development of distal conduit stenosis and graft replacement[27,36].

Two studies that evaluated the Contegra with pulmonary homograft found no significant difference between Contegra and pulmonary homografts with regard to the development of distal stenosis[9,19]. However, one study found that patients with Contegra developed moderate conduit stenosis faster than patients implanted pulmonary homograft. The rate of freedom from moderate stenosis was 85.4% and 75.1% at 5 years and 59.2% and 35.8% at 10 years for homografts and Contegra respectively (p =0.01)[44].

Christenson et al[13] studied 120 children treated with aortic homografts and Contegra grafts for RVOT reconstruction, with a mean follow up to 115 months (homograft group) and 64 months (Contegra group), reported fibrocalcification and stenosis (within 2 years) in 1 Contegra patient (1.1%) vs 8 patients in the homograft group (6.7%).

Aneurysmal Dilatation/Pseudoaneurysm

Five (5) articles[16,28,32,38,42] reported cases of aneurysmal dilation often located in the proximal anastomosis. Dave et al observed dilatation and aneurysm formation in 4 patients (13%, in high pulmonary pressure group)[16]. In a prospective study of 64 consecutive Contegra implants in 62 patients, median age 13.8 months, Shebani et al reported that 16 (27.5%) conduits developed significant dilatation during the follow-up period (median follow up of 14 months) that led to severe regurgitation. The proportion of subjects that developed pseudoaneurysm (3.9%) in a study of 76 patients implanted with 77 Contegra for RVOT reconstruction by Morales et al [28] is comparable to the proportion that developed pseudoaneurysm reported by Tiete et al 3.4%[42] in 29 implanted patients at 14 months post-implant.

Explantation

Fourteen articles reported freedom from explantation or explantation rates[2,4,5,7-11,18,19,21,23,36,38]. In the Boethig et al study, a freedom from explantation rate of 89.9% at 2 years was reported and the authors indicated that this was comparable to pulmonary homograft [4].

Arenz et al reported 100 % freedom from explantation at 42 months in a study of 10 patients implanted with the Contegra[2] while Shebani et al documented 4 explantations (one endocarditis and three for conduit dilatation) in 64 patients (4 early mortality) during a median follow up of 14 months[38]. Other studies reported freedom from explantation rates were 60 - 98%[7,9,11,18,23,36] at 5 years and 68 to 90%[9,19] at 10 years. However in a retrospective

analysis of 216 patients who received Contegra (n = 153) and cryopreserved pulmonary homograft (n= 63), Brown et al found the longevity of the Contegra to be significantly better than pulmonary homograft with a freedom of explantation rate at 5 and 10 years of 97% and 90% versus 81% and 69%, for Contegra and PHs, respectively (P =0.0002)[9]. Similarly, in a retrospective analysis that compared pediatric patients who received small caliber (12-14mm) Contegra (n=52) and pulmonary homograft (10-15 mm)(n=32) by Fiore et al[19], the freedom from explantation was found to be significantly better for Contegra than pulmonary homografts (Contegra 85% vs PH 47% P<0.001)[19] at 10 years.

Conduit dysfunction

There were 7 studies that reported conduit dysfunction rates[2,9,17-19,46,25]. The freedom from conduit dysfunction was reported as 100%[17,46] at 1 year, 76- 90%[9,19] at 5 years and 82-90%[9,18,19] at 10 years. Kadner et al reported 2 cases of graft dysfunction (3%) caused by formation of a stenotic membrane at the distal anastomosis in 67 Contegra conduits at 12 and 8 months post implant[25]. A 100% freedom from dysfunction/failure at 42 months was reported by Arenz et al in 10 patients of median age 194 days implanted with the Contegra[2].

In a retrospective analysis of 84 children (mean age 8.4 months) who received the conduits (Contegra n = 52) or (pulmonary homograft n = 32) with mean follow-up time for Contegra 4.4 years and for PH, 5.9 years , the freedom from conduit dysfunction was significantly worse in the homograft cohort (71% and 24% at 5 and 10 years, respectively) compared with Contegra (90% and 85% at 5 and 10 years, respectively, P < 0.001)[19]. Brown et al found similar outcomes in a retrospective analysis of 153 Contegra and 63 PH cohorts: the freedom from conduit dysfunction was significantly worse in the homograft cohort (73% and 47% at 5 and 10 years, respectively) compared to Contegra (90% and 82% at 5 and 10 years, respectively; P < .001)[9].

Conduit failure

Nine papers reported freedom from conduit failure[2,4,9,18,19,28,30,33,46]. The reported conduit failure rates were 59-75%[4] at 2 years, 50-92%[9,18,19,30,46] at 5 years and 67-90%[9,19,33] 10 years. Brown et al in their analysis of 10 year outcomes of 153 patients (mean age 8.4 years) implanted with the Contegra and 63 patients (mean age 10.8 years) implanted with Pulmonary homograft for RVOT reconstruction found the 5 year and 10 year freedom from conduit failure was higher for the Contegra group than for pulmonary homograft group (Contegra, 86% and 82% vs PH, 76% and 65% at 5 and 10 years respectively)[9]. In a retrospective analysis of 84 subjects (Contegra n= 52, PH n=32) under 2 years of age, Fiore et al reported higher rates of freedom from conduit failure for the Contegra cohort at 5 and 10 years compared to the pulmonary homograft (BJV, 85% and 67% vs PH, 75% and 45%, respectively), but the difference was not significant (p =0.06)[19]. In the retrospective study 76 patients (median age 1.6 years) implanted with the Contegra, Morales et al reported freedom from reoperation for conduit failure at 1 and 3 years of 98.3% and 93.1%, respectively. All conduit failures (n=3) were caused by pseudoaneurysm at the proximal stenosis[28] comparable to freedom from reoperation for conduit failure of 100% reported by Arenz et al[2].

Regurgitation

Sixteen papers reported on regurgitation[2,13,14,16,22,26-28,31,36,38-40,42,44,45].

Severe Regurgitation

The freedom from severe regurgitation at 12 months was 91-97%[28,39], 84-88%[27,28,45] at 2 years, 73-81%[28,38,45] at 3 years, and 75% at 5 years[44].

Palma et al investigating risk factors for dysfunction and failure of the bovine Contegra valved conduit for RVOT reconstruction 156 patients mean age 5.4 years reported 12 (7.7%) patients developed conduit valve regurgitation greater than 2+ with no evidence of aneurismal formation during a mean follow up of 58 months[31] In a small group of 16 patients treated with Contegra of the 12 survivors severe valvular regurgitation was present in 1 (8.3%) patient at 22 months follow-up[39]. In Arenz et al[2], graft valve regurgitation increased in 5 of 10 patients treated with Contegra but this never exceeded grade 2,

Moderate Regurgitation

A moderate pulmonary regurgitation rate of about 16% at approximately 2 years was demonstrated in two studies[27,36] Dave et al reported moderate or more regurgitation rates of 15% at 6 years[16], and 82.8% at 9 years[13] . In a non-randomized study of patients implanted with the Contegra conduit (n=50) and Aortic homograft (n=88), a moderate valvular regurgitation of 8.0% was reported for the patients Contegra versus 3.4 % of aortic homografts patients [40] . Tiete et al reported one case of severe regurgitation (3.4%), at mean follow-up of 10.2 months, that was caused by fibrous peel of the valve and not by leaflet destruction[42]. In a study of 120 patients treated with aortic homograft (mean age 6.4 years) and 85 Contegra patients (mean age 4.8 years) conducted by Christenson et al, moderate valvular regurgitation was seen in 3.4% (homografts) vs 7.2% (Contegra grafts)[13].

Mild Regurgitation

The outcomes of Contegra were also evaluated in 67 patients (mean age 16 years) implanted with the device. After a mean follow-up of 26.4 months there was absent or trivial valve regurgitation in 76% of the patients and mild regurgitation in 24%[14]. Mertz et al reported a much higher absence or mild regurgitation rate approximately 92% in 11 of 14 subjects that underwent RVOT reconstruction with the Contegra conduit[26].

Reoperation/Surgical intervention

Freedom from reoperation ranged from 89-98%[17,28,34,37,42] at 1 year, 62-93%[4,14,17,40] at 2 years, up to 93%[28] at 3years, 90-100%[2,5,8,34] at 4 years, 78-91%[36,40,46] at 5 years and 89% at 9 years[13]. In the study by Albanesi et al comprised of 106 Contegra conduits implanted in patients of mean age 13 (range 0-54), reoperation was performed in 12 cases (11.3%) due to bleeding, in 10 cases (9.4%) because of graft infection and in 10 cases (9.4%) because of structural deterioration of the Contegra graft[1].

Catheter Intervention

In one study, the freedom from reintervention (balloon dilatation) for the Contegra graft was reported as 58.2% and 43.7% after 6 months and 12 months, respectively[41]. For catheter-based interventions involving balloon and stent to the Contegra conduit, the freedom from re-intervention reported ranged from 92 to 99 %[17,28] at 1 year, 86 to 93 %[17,28] at 2 years and 74 to 90%[7,16,46] at 5 years.

Meyns et al[27] studied 58 patients with a mean age of 9 years. After a mean follow-up of 23 months, 17 (29%) conduits required an intervention (balloon dilatation or stent).

In a prospective study of 78 Contegra conduits implanted in 72 consecutive patients with mean age of 9.2 years, Rastan et al[34] reported that percutaneous right ventricular outflow tract re-interventions were performed in 24.4% (19) of patients after a mean of 12.9 months post implant, while Dave et al [16] observed a 16.5 % (28/170) catheter interventions at a median interval of 13.3 months in 170 Contegra implants.

Structural deterioration

Two papers Albanesi et al[1] and Sfyridis et al[37] reported structural deterioration. The former investigated 106 patients with heart anomalies implanted with the Contegra and reported structural deterioration rate of 9.4% of Contegra graft that led to subsequent reoperation[1]. The latter study reported no structural deterioration after a mean follow-up of 85 months in 34 consecutive patients, mean age of 10.9 years, implanted with the Contegra.

Conduit or Valve Degeneration

Eleven papers reported on conduit or valve degeneration[4,5,7,8,12,21,26,31,34,38,43]. The rates for reported conduit or valve degeneration ranged from 0 to 4.7%[26,38] at approximately 1 year, 0%[12,21,34] at 2 to 3 years, 0 to 1.8%[5,7,8] at 4 years, 0%[31] at 5 years and 5.6%[43] at 6 years. Boethig et al 2012 however reported a 2-year freedom from conduit degeneration rate of 49.8% in 104 conduits which comprises of the stenosis, insufficiency, thrombosis and dilatation[4].

Bleeding

Albanesi et al reported a perioperative bleeding rate of 11.3% in patients implanted with the Contegra which all led to reoperation[1]. A bleeding rate of 5.7%, that required re-exploration, was also reported by Palma et al[31] in 156 patients implanted with the BJV (Contegra conduit). One case of bleeding was reported by Mert et al as a major post- operative complication among 14 patients, mean age of 40.89 months, implanted with the Contegra[26].

Hemolysis

There was only one (1) study that evaluated hemolysis[3]. A total of 60 patients of median age 1.6 years (range 2 days to 17.4 years) were evaluated for hemolysis after Contegra implantation. Regular blood tests were conducted to determine haptoglobin, plasma-free hemoglobin, reticulocytes and hemoglobin levels at pre implant, before discharge and at regular intervals post discharge. After a mean of 3.3 years of follow-up, the authors reported there was no indication of clinical relevant hemolysis.

Literature Conclusions

Although short and long term studies have reported impressive performance of the Contegra BJV conduit, the literature search shows this device has some inherent considerations. The distal stenosis rate of Contegra appeared comparable to pulmonary homografts[9,19] (but in one case was worse at 5 and 10 years[44]). Younger age at implant and small conduit size were found to increase the risk of distal stenosis[4,27,36].

A number of studies showed Contegra to have substantially better performance with respect to explantation (through 5 and 10 years) and conduit dysfunction (through 5 and 10 years). Freedom from explantation in the premarket was 97.6% and 92.0% at 1 and 2 years, respectively. Performance in literature is comparable at 2 years (~90%) and shows, continued performance, roughly 80-90% proportions through 5 and 10 years, respectively.

One study reported conduit failure rates were comparable to pulmonary homografts through 5- years and worse for Contegra at 10 years (absolute difference of 10%).

The freedom from mortality rates in the literature, which all appear to be well above 90% beyond 1-year) are better than those presented in the premarket submission (88% at 1-year) provided by the sponsor in support of device approval. One article presented evidence in support of a univariate association of increasing survival rate with increasing conduit size, however, conduit size is associated with body size and age of the patient which are independent risk factors for mortality[18].

The freedom from catheter intervention rates of 92 -99 %[17,28] and 86 -93 %[17,28] at 1 and 2 years respectively, reported in the literature are comparable to the rates reported for the premarket data 86.6% and 80.2% at 1 and 2 years respectively.

The 1-year incidence of endocarditis in the premarket was 1%. The 1-year (3.5%[9] and 1.6%[40]) and 2-year (0.96%[6], 1.08%[18], 1.49%[10], 4.65%[34], and 5.2%[29]) approximate incidences reported in literature are in line with, and some higher than the 1-year incidence observed in the premarket study.

The reported rates of pseudoaneurysm in the literature ranged from 3.2 to 13%. Given that this adverse event was not captured as a separate endpoint in the premarket study a comparison to the premarket cohort data could not be made.
Several clinical outcomes are comparable between literature and premarket studies. For example, the 2 year freedom from thrombosis of 95% reported in the literature is comparable to the 2-year rate in the premarket cohort 93.4%. The freedom from explantation rate of 94.3% at 5 years reported for the premarket cohort is in the range of reported rate of freedom from explantation 60-98% reported at 5 years in the literature. Similarly the freedom from reoperation rates at 5 years reported in the literature 78-91% is comparable to that of the premarket 76% at 5 years.

There were certain limitations (e.g. different definitions) in the data extractions for some clinical outcomes. While some studies reported data on conduit deterioration, other studies reported conduit or valve degeneration. These two endpoints were not clearly defined in the papers. Therefore the two endpoints were collected separately. However in the study by Boethig et al 2012 conduit degeneration included stenosis, insufficiency, thrombosis and dilatation at 2 years with a lower freedom from conduit degeneration rate of approximately 50% at 2 years compared to other studies[4]. Thus the definition for conduit degeneration may not be consistent with structural deterioration used by some authors or in the premarket study. The endpoint thromboembolic events used in the IDE protocol definition includes acute myocardial infarction that occurs after operation if the patient possesses normal coronary arteries or if the patient is less than 40 years of age. Albanesi et al reported 6 cases (5.7%) of myocardial ischemia and 2 cases (1.9%) cerebrovascular events separately in the perioperative period[1]. Palma et al reported similar rate (1.9%) of neurological events in 156 patients after Contegra conduit implantation.

However, there is insufficient information in those studies to directly attribute these events to thromboembolism as defined in the IDE study.

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