Executive Summary

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

H020003

Prepared by the Center for Devices and Radiological Health
for the September 12, 2017, Pediatric Advisory Committee Meeting

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INTRODUCTION

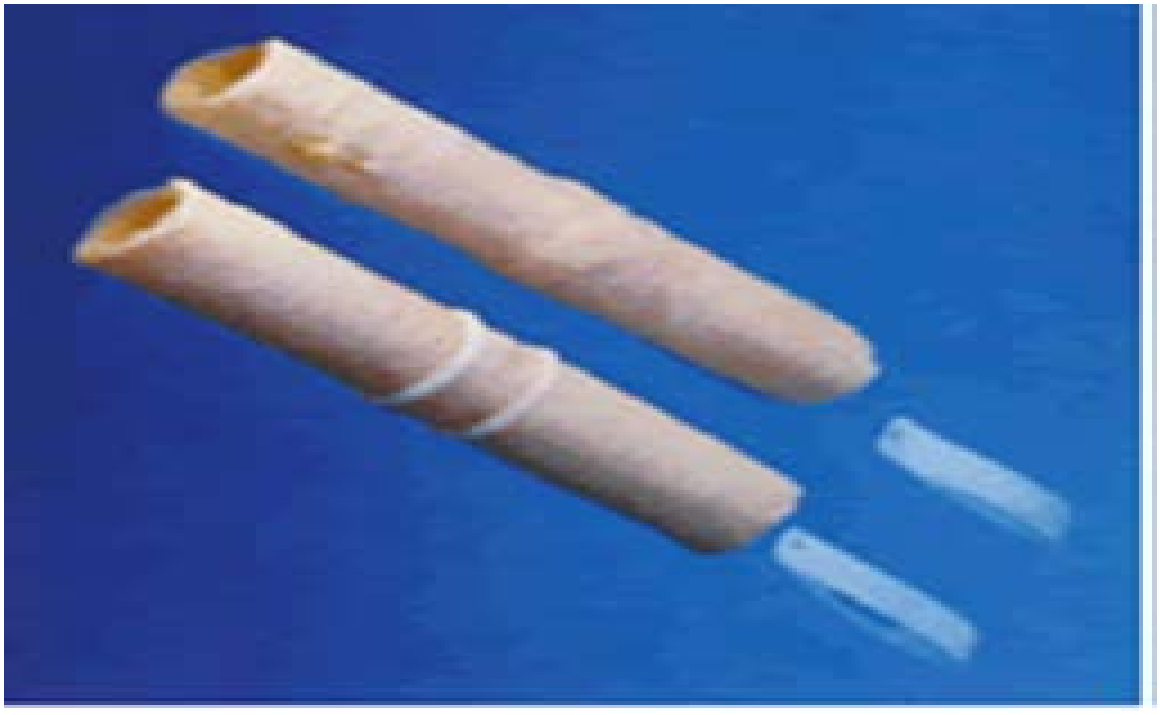
In accordance with the Pediatric Medical Device Safety and Improvement Act, this document provides the Pediatric Advisory Committee (PAC) with post-marketing safety information to support its annual review of the Contegra® Pulmonary Valved Conduit ("Contegra"). The purpose of this annual review is to (1) ensure that the Humanitarian Device Exemption (HDE) for this device remains appropriate for the pediatric population for which it was granted, and (2) provide the PAC an opportunity to advise FDA about any new safety concerns it has about the use of this device in pediatric patients.

This document summarizes the safety data the FDA reviewed in the year following our 2015 report to the PAC. It includes data from the manufacturer's annual report, post-market medical device reports (MDR) of adverse events, and peer-reviewed literature.

BRIEF DEVICE DESCRIPTION

Contegra is a glutaraldehyde-crosslinked, heterologous bovine jugular vein with a competent tri-leaflet venous valve. The device is available in 6 sizes in even increments between 12 and 22 mm inside diameter, measured at the inflow end. The device is available in two models (Figure 1): one without external ring support (Model 200), and one with ring support modification (Model 200S).

Figure 1. Contegra 200 and 200S (ring-supported) Models



INDICATIONS FOR USE

Contegra 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

Contegra is also indicated for the replacement of previously implanted, but dysfunctional, pulmonary homografts or valved conduits.

REGULATORY HISTORY

April 24, 2002:	Granting of Humanitarian Use Device (HUD) designation for Contegra (HUD #020003)
November 21, 2003:	Approval of Contegra HDE (H020003)
April 11, 2013:	Approval to profit on the sale of Contegra

DEVICE DISTRIBUTION DATA

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) allows HDEs indicated for pediatric use 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). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. However, it is to be noted that unless the sponsor requests to update their ADN based on the 21st Century Cures Act, the ADN will still be based on the previously approved ADN of 4,000. The approved ADN for Contegra is 4000 tests total per year. Since the last PAC review, a total of 372 devices were sold in the U.S., and 172 devices were implanted. At least 163 of the devices were implanted in pediatric (<22 years) patients.

MEDICAL DEVICE REPORT (MDR) REVIEW

Overview of MDR Database

The MDR database is one of several important post-market surveillance data sources used by the FDA. Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MDR 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 in a "real world" setting/environment, including:
    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - off-label use
    - 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 post-market 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.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR 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.

MDRs Associated with Contegra

There were 109 MDRs regarding Contegra identified in the FDA's MDR database between June 1st, 2016 and May 31st, 2017. Of these, 84 were identified as unique MDRs. The remaining 25 MDRs are excluded from the MDR data analysis for this year's presentation since these MDRs described events reported in literature that were either presented to the PAC previously, or are discussed in the Literature Review section of this document. Therefore, the MDR analysis is based on the review of 84 unique MDRs, all submitted by the manufacturer.

Patient Demographic Data

The reporting country information is included in all 84 MDRs, and includes 75 MDRs received from the United States (US) and 9 from outside of the US (OUS). Patient gender information is included in 84 MDRs; 50 involved males and 34 involved females. Patient age is included in 83 MDRs; 81 are pediatric patients and 2 are adults. TABLE 1 summarizes this information.

TABLE 1: Patient Demographic Data (Total 84 MDRs; 81 involve pediatric patients)

Demographic Data		Value	Number of MDRs containing the demographic
Reporting Country	US : OUS	89% : 11%	75 : 9 (84 Total)
Patient Gender	Male : Female	60% : 40%	50 : 34 (84 Total)
Patient Age	Pediatric : Adult	98% : 2%	**81** : 2 (83 Total)
Pediatric Only Age Range: 1 month – 20 years Average Age: 9.8 ± 5.3 years			

Reported Events

The 84 MDRs were individually reviewed and analyzed to determine the primary reported events. Additionally, the "time to event occurrence" (TTEO) was either obtained from MDR event text or calculated as the period between the Date of Implant and the Date of Event. The primary reported event by patient age group and the TTEO ranges and means are outlined in TABLE 2 below.

TABLE 2: Primary Reported Event by Patient Age and TTEO for 2017 PAC Review

Primary Reported Event	Total MDR Count	Patient Age (year)			TTEO (month)	
		Pediatric (<22)	Adult (≥21)	Age not reported	Range	Mean
Stenosis	**37**	36	1		3 - 160	73
Device replaced (reason not provided)	**35**	34		1	3 - 158	71
Regurgitation	**5**	4	1		50 - 136	87
Arrhythmia	**2**	2			0 - 0.3	0.15
Aneurysm	**2***	2			0.1 - 17	8.5
Infection/Endocarditis	**1**	1			37	--
Increased pressure gradient	**1**	1			133	--
Thrombus	**1**	1			0.07	--
Grand Total	**84**	81	2	1		

***** One of the 2 MDRs of aneurysm involved a patient death in this reporting period. The remaining 83 MDRs represent injury events.

The primary reported events in the MDRs this year as compared with those in 2016 is shown in TABLE 3 below. The number of MDRs increased from 58 in 2016 to 84 in 2017. The types of primary reported events are similar, with "Stenosis", "Device replacement" and "Regurgitation" remaining as the most frequently reported events for both years. Although "Arrhythmia", "Aneurysm" and "Thrombus" were not reported in 2016, these events reported in 2017 are known complications as reflected in the device's labeling. The details of the events are included in the MDR section below.

TABLE 3: Comparison of Primary Reported Event for Contegra MDRs in 2016 and 2017

Primary Reported Event	2016 PAC	2017 PAC
	MDR Count (%)	MDR Count (%)
Stenosis	28 (48 %)	37 (44 %)
Device replacement (reason not provided)	22 (38 %)	35 (42 %)
Regurgitation	2 (3.4 %)	5 (6 %)
Arrhythmia	0	2 (2.3 %)
Aneurysm	0	2 (2.3 %)
Infection/Endocarditis	2 (3.4 %)	1 (1.2 %)
Increased pressure gradients	1 (1.7 %)	1 (1.2 %)
Thrombus	0	1 (1.2 %)
Conduit tear/breakdown	2 (3.4 %)	0
Device sizing issue	1 (1.7 %)	0
Total	**58**	**84**

The primary events reported in the 84 MDRs, involving one death and 83 injuries are summarized by the reported event/problem below. Of the 84 MDRs, 79 noted that the patient required a valve replacement subsequent to the reported event.

Stenosis (n=37 MDRs, including 36 pediatric patients)

Stenosis was the most frequently reported event. In these 37 reports, stenosis (in conjunction with calcification, obstruction, pulmonary regurgitation or insufficiency and/or elevated pressure gradients) was identified between 3 months and 13.3 years post implant. Of the 37 stenosis reports, 2 reports reflect early and mid-term events. Both involved pediatric patients who required reconstruction or replacement of the valved conduit between 3 months and 1 year post Contegra implant, due to stenosis and elevated pressure gradients. The manufacturer noted in one of the reports that the physician did not attribute the event to a device malfunction. In the other report, no specific causes were identified as neither additional information nor the device was available for manufacturer's investigations. The 35 remaining reports reflected stenosis events where patients required interventions between 2 and 13.3 years post implant. The interventions included valve-in-valve transcatheter pulmonary valve (TPV) implantation (22 MDRs), device surgical replacement (11), angioplasty (1) and stenting (1).

Device replacement[1] – reason not reported (n=35 MDRs; including 34 pediatric patients)

Thirty-five reports indicate that Contegra was replaced between 3 months and 13.2 years post implant, including 34 involving pediatric patients. The causes of the device replacement were not reported. Of the 34 pediatric reports, 4 reported that the device was replaced within 2 years post Contegra implant, but no failure mechanism or other patient adverse effects were reported. In the remaining 30 pediatric reports, limited information was provided despite the manufacturer's attempts to obtain more details from the healthcare provider. An analysis was conducted on the patient age and the TTEO of the device replacement. The Contegra devices were implanted in these 30 patients during their infancy or early or middle childhood. It is not unanticipated that patients would need a device replacement by 6.75 years, on average, post Contegra implant, given the patient outgrowth and the tissue degeneration known to be associated with the bio-prosthetic valves.

Regurgitation (n= 5 MDRs, including 4 pediatric patients)

Valve regurgitation was reported as the reason for valve replacement in 5 MDRs. Of these 5 reports, 4 involved pediatric patients who required valve replacement between 5.7 and 11.7 years post Contegra implant. One of the 4 pediatric patients required a surgical replacement whereas the other 3 had a valve-in-valve replacement with a transcatheter pulmonary valve (TPV). Of note, one of pediatric patients receiving a TPV was a 20-year-old patient who was pregnant with twins and had had Contegra implanted for more than 8 years. Although the patient had mild pulmonary insufficiency, the physician was concerned that the patient's pregnancy would exacerbate the patient's condition and determined to replace the Contegra device with the TPV.

According to manufacturer, none of these Contegra devices were returned for analysis and the causes of the regurgitation cannot be determined. The manufacturer noted in one report that the

[1] The "replacement" is defined as the intervention taken to replace or substitute the function of Contegra device, including replacing the Contegra valved conduit surgically or via a transcatheter valve-in-valve procedure, without removing the Contegra device.

event occurred 6 years post implant and it is unlikely that the event was due to device manufacturing.

Arrhythmia (n=2 MDRs; 2 pediatric patients)

Arrhythmia was reported in 2 pediatric patients. One patient developed arrhythmia and heart failure immediately after implant. The patient was treated with an Extracorporeal Membrane Oxygenation (ECMO) and medication and subsequently implanted with a permanent pacemaker due to sick sinus syndrome, 6 weeks after the valve implant. The other patient required a permanent pacemaker 8 days post Contegra implant. The type of the arrhythmia and other information were not provided in the report.

Aneurysm (n=2 MDR; 2 pediatric patients, including one patient death)

A newborn with a history of truncus arteriosus and a prior Rastelli type procedure required a repeat conduit replacement due to tracheal compression by a conduit aneurysm 2 weeks post the first Contegra implantation. The patient expired due to pneumonia and sepsis 6 days later. According to the manufacturer, neither autopsy nor explant information was reported. The physician stated that the patient's death was not related to the Contegra device. Conduit dilatation (e.g. aneurysm) is a known complication and is included in the potential adverse event section of the Instructions for Use (IFU) for the device. However, tracheal compression by a conduit aneurysm has not been reported in MDRs or literature.

The other patient, a 4-year-old, developed a "significant aneurysm due to peripheral pulmonary stenosis and elevated right ventricular pressure" 17 months post Contegra implant. Subsequently, the Contegra device was explanted and replaced 21 months post implant. No further adverse patient effects were reported.

Infection/Endocarditis (n=1 MDR; 1 pediatric patient)

The Contegra device in a pediatric patient was explanted and replaced 37 months post implant due to suspected endocarditis. No infective organism was identified. The healthcare provider reported that the device was not suspected as a cause of the endocarditis.

Increased pressure gradients (n=1 MDR; 1 pediatric patient)

One report noted increased pressure gradients across the valve 11 years after a Contegra was implanted in a 20-year-old patient. The Contegra device was replaced valve-in-valve with a TPV due to patient outgrowth and increased gradients. Following the procedure, the gradients decreased and no other adverse patient effects were reported.

Thrombus (n=1 MDR; 1 pediatric patient)

Two days 2 post-Contegra implant, a pediatric patient was in a hypercoagulable state and presented emergently in cardiac arrest "due to a clot occluding the device". The device was explanted and replaced. No other adverse patient effects were reported. According to the manufacturer, the product specimen was not returned for device evaluation and no definitive conclusions could be drawn.

Conclusions Based on the MDR Review

1. Although conduit dilatation (e.g. aneurysm) is a known event and noted in the IFU, tracheal compression by a conduit aneurysm has not been reported previously in MDRs or literature. This specific adverse event is not explicitly addressed in the device IFU.
2. The majority of the other MDRs received in this reporting period reflected either peri-procedural or mid- to long-term events which are known events and have already been addressed in the device IFU.

CONTEGRA LITERATURE REVIEW- 2017

Purpose

The objective of this systematic literature review is to provide an update on safety events associated with the use of Contegra.

Methods

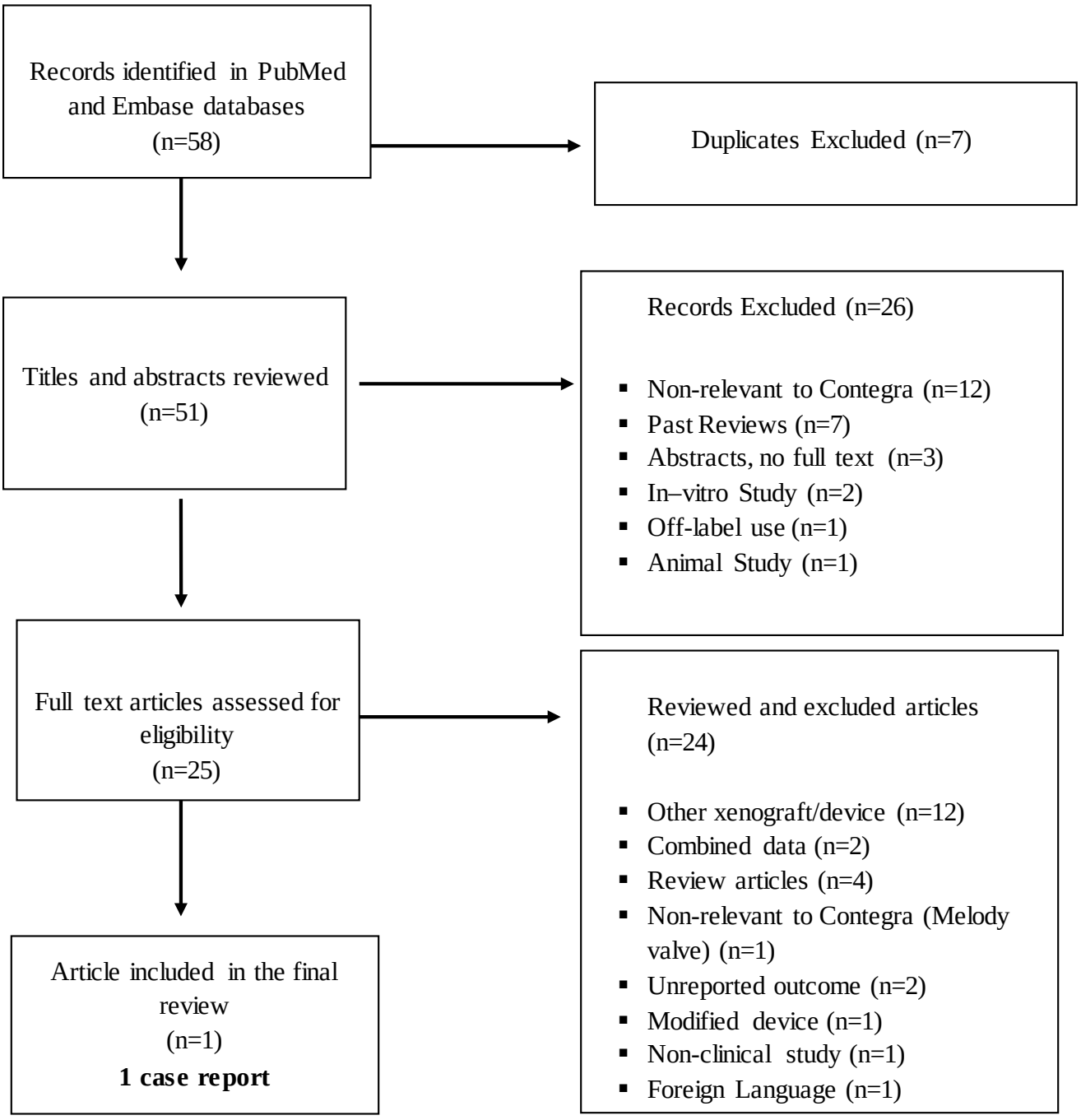
A search of the PubMed and Embase databases were conducted for published literature using the search terms: "Contegra" OR "Bovine Jugular Vein" OR "Pulmonary Valved Conduit," which were the same terms used in the previous 2016 literature review. The search was limited to articles published in English from 06/01/2016 through 05/31/17.

A total of 58 (11 Pubmed and 47 Embase) articles were retrieved. Seven (7) articles were duplicates. The remaining 51articles were subjected to review of titles and abstracts, and the following articles were excluded: one (1) article on animal study**,** one (1) article on off-label use ("left heart"), two (2) articles on *in-vitro* study, three (3) articles were Abstracts/posters only, seven (7) were articles previously reviewed, and twelve (12) articles were non relevant to this device (Melody valve and other conduits).

Twenty-five (25) articles were retained for second pass review. Of the 25 articles reviewed for full text during the second pass, twelve (12) articles were on other xenografts/devices, four (4) articles were review papers, two (2) articles did not report separate data for Contegra (Contegra was evaluated with other xenografts but no separate data reported for Contegra), one (1) article was not relevant to this device (Melody valve), two (2) articles had unreported outcomes, one (1) article involved a modified Contegra, one (1) article was a non-clinical study, and one (1) article was in a foreign language. Thus,

one article was retained for the final review analysis. Figure 2 depicts the article selection process and criteria for exclusion.

FIGURE 2: Article Retrieval and Selection



Results

A total of one (1) article was reviewed in the final analysis. This was a case report of one patient reported by Falchetti and colleagues from Belgium.

Case Report

Falchetti et al. ***Contegra 12 mm: How Long Can It Last?*** World J for Pediatric and Congenital Heart Surgery. 2016 Dec 7, pg. 1-3. PMID: 27927942

The authors reported an exceptional case of freedom-from-failure for a 12 mm Contegra conduit which was implanted in an infant and lasted 16 years. The patient was originally a 4-month old female weighing 3kg (6.6 lbs), who was referred to the facility from another country with diagnosis of Type I Truncus Arteriosus (TA), a large Ventricular Septal Defect (VSD), Right Ventricular Hypertrophy (RVH), well-developed Pulmonary Artery branches, a right-sided Aortic arch, and grade 2/4 truncal valve regurgitation. The RVOT was reconstructed with a 12 mm size Contegra conduit. The main pulmonary artery measured 9 mm diameter resulting in an artery/device mismatch Z-score of +2.5. The VSD was repaired by using a Gore –Tex patch. The early post-operative period was complicated by pulmonary hypertension, but the child recovered quickly and was discharged 16 days post-intervention.

After 16 years the patient was referred back to the original surgical team because of the need for reoperation for conduit failure. The examination showed a healthy 16-year old female patient, weighing 33kg (~73lbs) and 156 cm height, without signs of right heart decompensation.
Trans-thoracic echography (TTE) showed a competent truncal valve, conduit stenosis with a pressure gradient of 110 mm Hg across the RVOT without evidence of regurgitation, normal right and left ventricular function, and normal development of the pulmonary arteries. Computed tomography scan showed mild shrinkage of the conduit to minimal inner diameter of 9 mm and moderate peripheral calcifications. The reoperation consisted of replacement of the degraded conduit with a composite 22 mm pulmonary homograft and a Gore-Tex patch, and closure of the residual atrial septal defect. The explanted conduit showed no neo-intimal formation and only moderate calcifications. The specimen histopathology showed spots of fibrin in occasional nodules, some peripheral calcifications, and intact valve leaflets.

The authors believe that the overall condition and performance of the conduit after 16 years post-implantation may be an exception for a small size conduit (12 mm) in young patients. They also state that it is unclear if the type of Truncus Arteriosus (Type I -with a main pulmonary artery segment) and/or the body surface area of this 4-month old infant (as opposed to a neonate) may have contributed to the longevity of the conduit. An additional factor that could have played a role in the successful survival outcome is the moderate degree of device oversizing. The authors also believe that the surgical technique of a distal everting suture avoiding contact of the conduit's outer layer with the bloodstream could have contributed to the prevention of distal stenosis of the conduit.

Given the absence of signs of right ventricular failure and significant right ventricular hypertrophy, the authors questioned whether some conduits are being replaced too early because of stricter follow-up and failure definition. The authors admitted that the observations from this report cannot entirely answer the question about how long the Contegra can last.

Discussion of the literature

Falchetti et al. reported successful and long term use of a 12 mm size Contegra conduit despite the presence of significant risk factors for conduit failure [1,2,4] (such as: a. age ((< 1 year -low BSA/body weight)), b. small conduit size (12 – 14 mm) and c. elevated pulmonary pressure). While conduit stenosis with a gradient of 110 mmHg across the RVOT was observed, there was no evidence of regurgitation. Other factors that could have contributed to the longevity of the device in this patient include the specific type of malformation, the surgical technique (i.e., conduit distal everting suture), and the device mismatching/oversizing (Z-score of +2.5).

Hickey et al[3] reported that the Z-score of +1 to +3 is associated with optimal longevity, which is consistent with the Falchetti et al findings. The article by Falchetti et al. indicated that the use of a distal everting suture, avoiding contact between the outer layer of the conduit and the bloodstream may have contributed to the absence of distal stenosis.

Conclusion on the Literature Review

Review of literature published from 06/01/16 through 05/31/17 revealed:

- One case of Contegra12 mm conduit implanted in an infant 4- month old with freedom-from-failure duration of 16 years. The findings include:
    - Conduit stenosis with gradient of 110 mmHg across the RVOT, moderate calcification, fibrin nodules and intact valve leaflets
    - No evidence of conduit regurgitation
    - Right ventricular hypertrophy
    - Normal right and left ventricular function

Besides the conduit stenosis/degradation and increased pressure gradient that required device replacement there were no reports of other adverse events (e.g. endocarditis). However, the ability to draw conclusions from this literature review regarding the safety, effectiveness and longevity of the device is very limited given that the observations are based on a single patient report.

SUMMARY

The FDA identified an adverse event, tracheal compression by conduit aneurysm, during this review period. Although conduit dilatation (e.g. aneurysm) is a known complication, tracheal compression by conduit aneurysm as an outcome of conduit dilatation has not been reported previously. The FDA plans to ask the PAC experts whether a recommendation to the manufacturer is warranted to explicitly call out "compression of nearby organ/structures such as trachea by conduit aneurysm" as a potential outcome of conduit dilatation in the Contegra IFU. The other adverse events reported in MDRs in this review period are known events and have been addressed in the IFU.

The literature review identified one case of a 12 mm Contegra conduit implanted in a 4-month old infant that lasted 16 years. No safety issues were reported in literature during the review period.

The FDA believes that the HDE for this device remains appropriate for the pediatric population for which it was granted. The FDA will continue our routine monitoring of the annual distribution and most importantly the safety and probable benefits of the device.

REFERENCES

1. Mery CM, et al. Risk factors for development of endocarditis and re-intervention in patients undergoing right ventricle to pulmonary artery valved conduit placement. J Thorac Cardiovasc Surg. 2016 Feb. 151(2): 432-9.

2. Niemantsverdriet MB, Ottenkamp J, Gauvreau K, Del Nido PJ, Hazenkamp MG, Jenkins KJ. Determinants of right ventricular outflow tract conduit longevity: a multinational analysis. Congenital heart disease. May-Jun 2008; 3(3):176-184.

3. Hickey EJ, McCrindle BW, Blackstone EH, et al. Jugular venous valved conduit (Contegra) matches allograft performance in infant truncus arteriosus repair. European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery. May 2008; 33(5):890-898.

4. Shebani SO, et al. Right Ventricular Outflow Tract reconstruction using Contegra valved conduit: natural history and conduit performance under pressure. Eur J Cardiothorac Surg. 2006 Aug. 30(2): 418.

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