Executive Summary

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

H020003

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INTRODUCTION

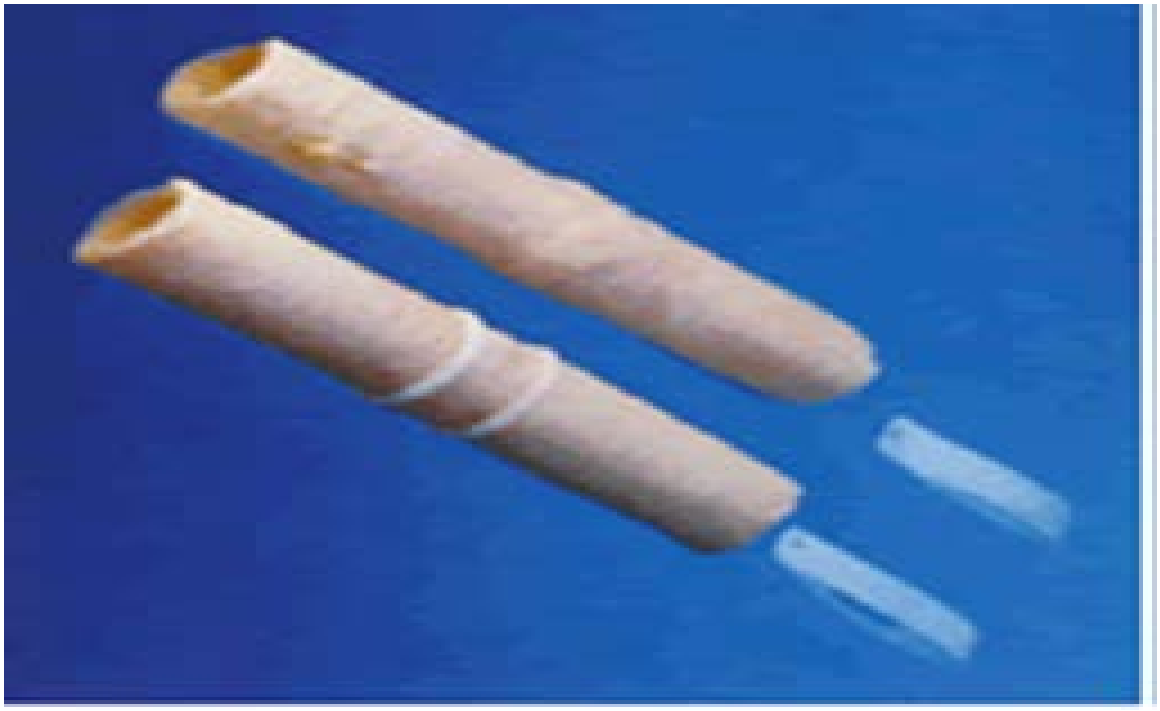
In accordance with the Pediatric Medical Device Safety and Improvement Act, this document provides the Pediatric Advisory Committee (PAC) with postmarketing safety information to support its annual review of the Contegra® Pulmonary Valved Conduit ("Contegra"). The purpose of this annual review is to (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, postmarket 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

FDASIA amended section 520(m) of the FD&C Act to allow devices with HDEs indicated for use in pediatric patients or a pediatric subpopulation to be sold for profit; the number of devices distributed in any calendar year cannot exceed the Annual Distribution Number (ADN) for each device. The ADN is defined as the number of devices reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States. The FDA has interpreted this to mean that the calculation of the ADN should be 4,000 multiplied by the number of devices reasonably necessary to treat an individual. For Contegra, one device is reasonably necessary to treat an individual; therefore the ADN for this device is 4,000. Annual distribution of Contegra has not yet exceeded the ADN. Since the last PAC review, a total of 747 devices were sold in the U.S., and 428 devices were implanted. At least 399 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 postmarket 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 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.
- 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 79 MDRs regarding Contegra identified in the FDA's MDR database between 06/01/2015 and 05/31/2016. Of these, 58 were identified as unique MDRs. The remaining 21 MDRs were 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 in 2014 or 2015, or are discussed in the Literature Review section of this document. Therefore, the following MDR analysis is based the review of the 58 unique MDRs, all submitted by the manufacturer.

Patient Demographic Data

Reporting country information is included in all 58 MDRs; 52 are from the United States (US) and 6 are from outside of the US (OUS). Patient gender information is included in 37 MDRs; 25 involved males and 12 involved females. Patient age is included in 53 MDRs; 48 are pediatric patients and 5 are adults. TABLE 1 summarizes this information.

TABLE 1: Patient Demographic Data (Total 58 MDRs; 48 involve pediatric patients)

Demographic Data		Value	Number of MDRs containing the demographic
Reporting Country	US : OUS	90% : 10%	52 : 6 (58 Total)
Patient Gender	Male : Female	68% : 32%	25 : 12 (37 Total)
Patient Age	Pediatric : Adult	91% : 9%	**48** : 5 (53 Total)
Pediatric & Adult Age Range Average Age Pediatric Only Age Range Average Age		2 months – 51 years 10.9 ± 9.2 years 2 months – 21 years 8.8 ± 5.5 years	

Reported Problems

The 58 MDRs were individually reviewed and analyzed to determine the primary reported problems. Additionally, the "time to event occurrence" (TTEO) was either obtained from MDR event text or calculated as the time period between the Date of Implant and Date of Event. The primary reported problem by patient age group and the TTEO are outlined in TABLE 2 below.

TABLE 2: Primary Reported Problem by Patient Age and TTEO for 2016 PAC Review

Primary Reported Problem	Total MDR Count	Patient Age (years)			TTEO (months)	
		Pediatric (≤ 21)	Adult (> 21)	Age not reported	Range	Mean
Stenosis	28	26	1	1	0.2-165	76
Device replacement (reason not provided)	22	17	3	2	2.7-120	74
Regurgitation	2	1	0	1	0-112	56
Infection/Endocarditis	2	1	1	0	2-102	52
Conduit tear/breakdown	2	1	0	1	0-33	17
Increased pressure gradients	1	1	0	0	101	--
Device sizing issue	1	1	0	0	0.2	--
Total	**58**	**48**	**5**	**5**		

The primary problem reported in the MDRs this year was compared with those in 2015 as shown in Table 3 below. The number of MDRs increased from 30 in 2015 to 58 in 2016. The types of primary reported problems are similar, with "Stenosis" remaining as the most frequently reported problem for both years. There were no new problems reported this year. The number of MDRs with "Device replacement" as their primary reported problem appeared to increase, whereas the report of "Device sizing issue" decreased. The analyses of the primary reported problems are detailed in the following section.

TABLE 3: Comparison of Primary Reported Problem for Contegra MDRs in 2015 and 2016

Primary Reported Problem	2015 PAC MDR Count (%)	2016 PAC MDR Count (%)
Stenosis	12 (40%)	28 (48%)
Device replacement (reason not provided)	5 (17%)	22 (38%)
Regurgitation	2 (6.7%)	2 (3.4%)
Infection/Endocarditis	1 (3.3%)	2 (3.4%)
Conduit tear/breakdown	1 (3.3%)	2 (3.4%)
Increased pressure gradients	2 (6.7%)	1 (1.7%)
Device sizing issue	4 (13.4%)	1 (1.7%)
Thrombus	1 (3.3%)	0
Bleeding	1 (3.3%)	0
Death	1 (3.3%)	0
Total	**30**	**58**

All 58 MDRs were reported as injuries. There were no deaths or malfunctions reported. The events are summarized as follows:

Stenosis (n=28 MDRs, including 26 pediatric patients)

Stenosis was the most frequently reported problem. In these 28 reports, stenosis (e.g. calcification, obstruction, elevated pressure gradients, and pulmonary insufficiency) was identified between 0.2 and 165 months post implant. Of the 28 stenosis reports, 2 reports reflect early and mid-term events. Both involved infant patients who required device replacement between 5 days and 5 ½ months post Contegra implant, either due to branch pulmonary artery (PA) stenosis or PA obstruction. According to the manufacturer's investigations, no device or manufacturing issues were identified. The 26 remaining reports reflected calcification/stenosis events where patients required interventions between 2 and 13 years post implant. The interventions included valve-in-valve transcatheter pulmonary valve (TPV) implantation (17 MDRs), device explantation (7), hybrid surgical/catheter procedure (1) and stenting (1).

Device replacement[1] – reason not reported (n=22 MDRs; including 17 pediatric patients)

Twenty-two reports indicate that Contegra was replaced between 2.7 and 120 months post implant, including 17 involving pediatric patients. The exact causes of the device replacement were not reported; however, 3 of 17 MDRs involving pediatric patients indicated possible factor(s) associated with the device replacement. These 3 MDRs noted patient outgrowth of the device (or a need for a larger valve size) between 5 to 10 years post Contegra implant. In the remaining 14 pediatric reports, limited information was provided despite the manufacturer's attempts to obtain more details from the healthcare provider. An analysis of the patient age and the TTEO of the device replacement for these 14 reports revealed that the Contegra devices were implanted in these patients during their infancy or early childhood. It is not unanticipated that patients would need a device replacement 6 years post Contegra implant, given the patient outgrowth and the tissue degeneration known to be associated with the bio-prosthetic valve, especially in pediatric patients.

Regurgitation (n=2 MDRs, including 1 pediatric patient)

A pediatric patient required a balloon dilatation for stenting and a valve replacement with a TPV via a valve-in-valve procedure 9 years post Contegra implant due to pulmonary regurgitation. The other patient, age not reported, had pulmonary regurgitation post Contegra implant and the Contegra device was explanted and replaced. Based on event investigations and an analysis of explanted device, the manufacturer concluded that the product met all manufacturing specifications and no issues were identified.

Infection/Endocarditis (n=2 MDRs, including 1 pediatric patient)

[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.

One report noted that the Contegra device was explanted and replaced with a homograft in an eleven-month-old infant 2.4 months post Contegra implant due to infection. The explanted device was not returned to the manufacturer. The cause of the infection and the type of organism(s) were not reported. No other adverse patient effects were reported. The other report indicated that an adult patient developed pulmonary endocarditis with bilateral septic pulmonary emboli and required device replacement 8 ½ years post implant. Although the root cause of the event cannot be determined, the manufacturer indicated that endocarditis beyond 1 year of heart valve implant is largely a community-acquired event. In addition, the patient had a history of intravenous drug abuse. Based on the investigation, the manufacturer noted that the endocarditis was unlikely to be attributed to the device and/or manufacturing process.

Conduit tear/breakdown (n=2 MDR, including 1 pediatric patient)

One report noted that a pediatric patient underwent a balloon valvuloplasty which resulted in tears in the posterior wall of the main pulmonary artery 33 months post Contegra implant. After an unsuccessful attempt of TPV placement, the Contegra device and the TPV were explanted and replaced with another valved conduit. The manufacturer's investigation concluded that the events were related to the patient's anatomy and co-morbidities and were not attributed to the Contegra device. The other report indicated the conduit tissue breakdown and the patient (age not reported) required a replacement post Contegra implant. The explanted device was not returned to the manufacturer. The manufacturer performed a device history records review and determined that the product met all manufacturing specifications and no issues were identified that would have impacted this event.

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

One report noted increased pressure gradients across the valved conduit in a 12-year-old pediatric patient 8 and ½ years post Contegra implant. The 16 mm Contegra valved conduit was replaced with a 20 mm TPV via a transcatheter valve-in-valve procedure. The Contegra device remained in the patient and was not returned to the manufacturer for analysis. The root cause of the elevated pressure gradients could not be determined. The manufacturer indicated that it is possible the patient had outgrown the device and there is no indication of a product quality issue.

Device sizing issue (n=1 MDR, 1 pediatric patient)

One report (involving an infant patient) noted the Contegra device was explanted 8 days post implant. Although the exact causes of the device explant were not provided, the report noted that the 12 mm Contegra was replaced with a 10 mm valved conduit. This event might be similar to the device sizing issue which had been reviewed by the previous PACs and addressed via modifications to the device Instructions for Use (IFU) in 2015. The number of MDR of device sizing issue decreased from 4 reports last year to 1 report this year.

After the PAC 2014 review relevant to a device sizing issue identified in 7 MDRs, the manufacturer modified the IFU in 2015. The modifications include adding a statement in the Warnings and Precautions section to further address the device size issue, "The size of the conduit is based on the inside diameter of the inflow side (end). The outflow side (end) may be larger". The IFU also contains the following information about device size:

- "The Contegra Pulmonary Valved Conduit consists of a heterologous (bovine) jugular vein with a tri-leaflet venous valve and a natural sinus slightly larger in diameter than its lumen." and
- "The Contegra Pulmonary Valved Conduit is sized in even increments between 12 and 22 mm (inside diameter), measured at the inflow end."

Conclusions Based on the MDR Review

1. No death reports or new safety issues were identified based on the MDR review for this reporting period.
2. The majority of the MDRs received in this reporting period reflect long-term events which are known and addressed in the device IFUs.
3. The number of MDR with device sizing issue appears to be declining this year. The decrease may be attributable to the IFU update made in 2015 or other factors.

CONTEGRA LITERATURE REVIEW- 2016

Purpose

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

Methods

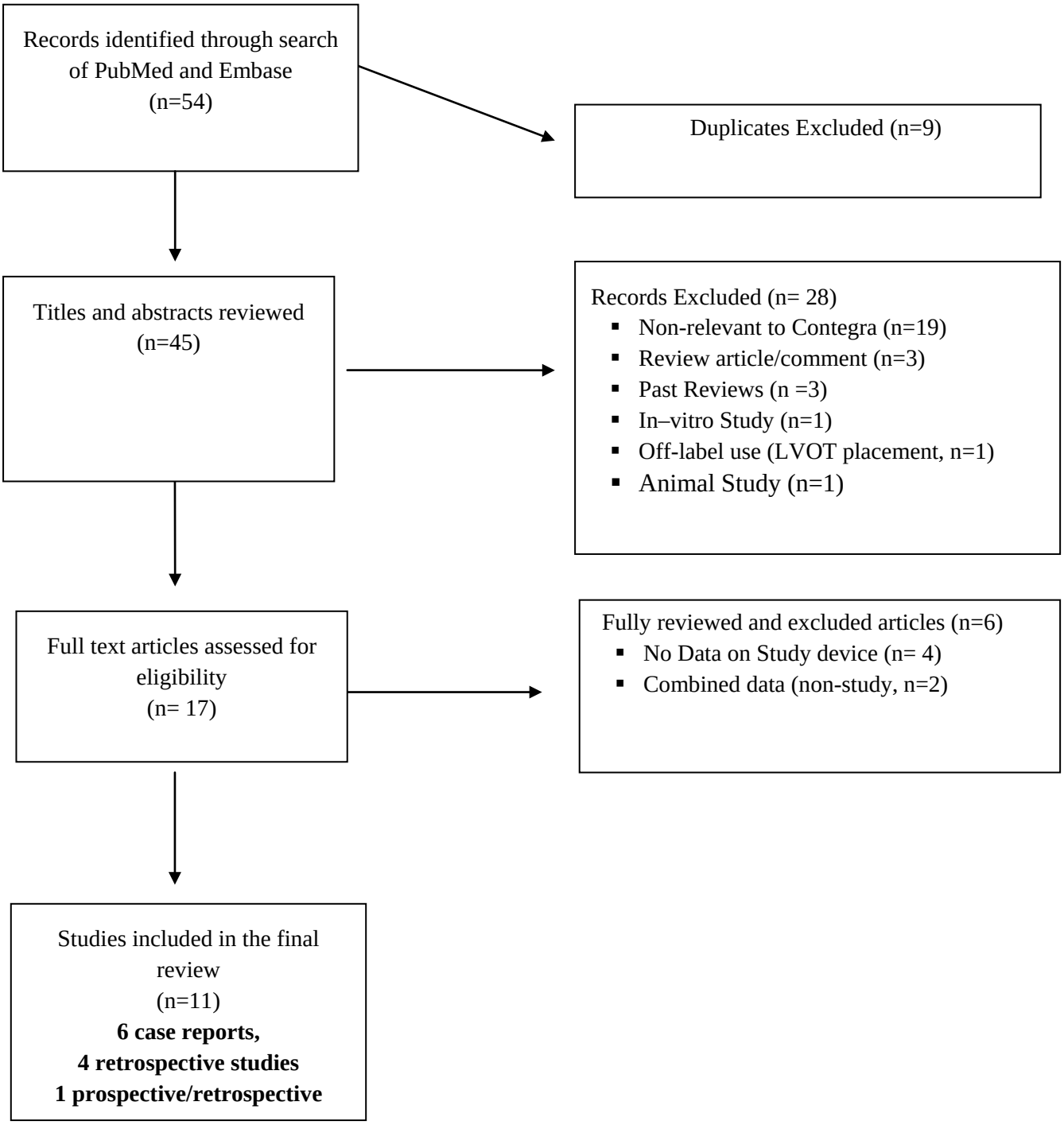
A search of the PubMed and Embase databases were conducted for published peer-reviewed literature. The search was conducted using the search terms: "Contegra" OR "Bovine Jugular vein" OR "Pulmonary valved conduit," which were the same terms used in last year's literature review. The search was limited to articles published in English from 05/31/2015 through 05/31/16.

A total of 54 articles were retrieved. Nine (9) articles were duplicates. The remaining 45 articles were subjected to first pass review of titles and abstracts and the following articles were excluded: one (1) article on animal study**,** 19 articles not relevant to Contegra,

3 articles that were previously reviewed, 3 review articles/comments, 1 article on off-label use of Contegra (Left ventricular outflow tract placement), and 1 article on in-vitro study. Seventeen (17)

articles were retained for second pass review. Of the 17 articles reviewed for full text during the second pass, 4 articles reported no data on Contegra, 2 articles did not report separate data for Contegra. Thus, a total of 11 articles were retained for the final review analysis[1-11]. Figure 2 depicts the article retrieval and selection process including the criteria for exclusion.

FIGURE 2: Article Retrieval and Selection



Results

A total of eleven (11) articles were completely reviewed for the analysis including 6 case reports[2,4,5,7,10,11], 4 retrospective studies[1,3,6,9] and 1 prospective/retrospective study[8]. Of the 6 case reports, 3 were from the United States, 1 from the Netherlands, 1 from Germany and 1 from Oman. Of the 4 retrospective studies, 2 were conducted in the United States, 1 in Germany and 1 in Japan. The one (1) study with prospective and retrospective data collection was conducted in Germany[8].

The sample sizes for Contegra-treated patients ranged from 1 to 245 (case reports and articles) and up to 444 Contegra conduits. The mean age at implant for Contegra patients in two pediatric studies were 25 months and 15.6 years, and in one study the median age was 8 months (range 4 days to 4 years). The ages in articles with mixed pediatric/adult population ranged 3 days to 65 years. The mean follow-up time ranged from 4.3 to 6.4 years.

Case Reports

Buelow et al. 2016[2]. This was on a 10- month old male with a history of D- transposition of the great arteries, ventricular septal defect, pulmonary stenosis and a single coronary artery who presented with acute heart failure (progressive diaphoresis and tachypnea of 7 days duration, hepatomegaly, elevated B-type natriuretic peptide of 3,040 pg/mL and an elevated troponin I of 0.824 ng/mL). Four (4) months before presentation, patient had undergone surgery with placement 12 mm Contegra between right ventricle (RV) and pulmonary artery (PA). On presentation transthoracic echocardiography (TTE) revealed severe RV dysfunction, RV and atrial dilation, tricuspid valve insufficiency, pulmonary insufficiency, and severe RV to PA conduit obstruction. Transesophageal echocardiography and intraoperative inspection revealed a conduit dissection 5 mm proximal to the distal anastomosis. The conduit was excised and replaced with a pulmonary homograft. The patient's recovery was uneventful and was discharged home 8 days postoperative.

Maddali et al. 2016[4]. The authors described an unconventional technique used to increase the anteroposterior diameter of the chest of an infant implanted with Contegra. A 1 month old male was admitted in heart failure. TTE revealed a pulmonary-dominant common arterial trunk (truncus arteriosus, TA), type B interrupted aortic arch and bilateral pulmonary artery origin stenosis. Repair of the TA and the interrupted aortic arch with pulmonary arterioplasty was done. During the repair, a size 12 Contegra conduit was implanted. There was a mismatch between the conduit size and the patient's needs which resulted in protrusion of the conduit between the sternal edges. An attempt was made to approximate the sternal edges but this resulted in compression of the Contegra graft. The sternum was approximated by stitches from above and below. When the mid part of the sternum was reached, the suture was pulled up to move the sternum away from the Contegra to increase the anterior posterior diameter of the chest wall and constant traction was applied on the sternum for 10 days. The authors reported that the constant traction induced a pectus carinatum deformity in the child which accommodated the conduit without external compression. The pectus deformity decreased by seven

weeks post- surgery. A follow-up computed tomography angiography (CT angiogram) showed no conduit compression by the sternum. Thus there were no plans to revise the pectus.

Reeves et al. 2016[7]. The authors described the first successful biventricular repair in a patient with (S,D,L) transposition of the great arteries (TGA), a rare form of TGA, ventricular septal defect, pulmonary stenosis and ventricular malpostioning by the use of aortic translocation. The patient was diagnosed at 2 days old. At 15 months the patient underwent a series of surgical procedures including right ventricular outflow tract (RVOT) reconstruction with an unsupported 14-mm Contegra valved conduit. Follow-up echocardiography at 38 month showed mild RVOT stenosis with no insufficiency.

Tunks et al. 2016[10] A 7-day old infant underwent complete surgical repair of a rare case of congenital heart defects, including double-outlet right ventricle, ventricular septal defect, malpositioning of the great arteries and a large aortopulmonary window with pulmonary obstruction in the neonatal period. Per the authors, complete surgical repair of this type of combination of anomalies in the neonatal period has not been previously reported. The surgical repair included transection of the main pulmonary artery. Right ventricular to pulmonary artery continuity was established by placement of a 12 mm Contegra conduit. At 6 months old, the patient underwent elective uncomplicated conduit replacement due to progressive distal conduit stenosis.

Ziesenitz et al. 2016[11] The authors reported of a case of a female infant patient with tetralogy of Fallot, absent pulmonary valve, and familial Alagille syndrome (a genetic disorder with multiple system disorder including the heart associated with mutations of *JAG 1* gene) who successfully underwent cardiac repair. The patients underwent corrective heart surgery at 9 months of age. Complete agenesis of the pulmonary valve and pulmonary stenosis were confirmed intraoperatively. A valved Contegra conduit was implanted between the right ventricle and the pulmonary artery. Post-operative course was uneventful.

Mauritz et al. 2015[5] The authors reported on a 21 year old male who was born with complex cardiac anomaly including pulmonary atresia. The patient underwent RVOT reconstruction at the age of 5, followed by re-reconstuction of the RVOT with a Contegra conduit at10 years old. The patient presented with 1 month history of diarrhea, nausea and shortness of breath for 7 days. Chest X-ray showed cardiomegaly. Laboratory tests done revealed an elevated D-dimer of 2283 mg/L and a C-reactive protein of 39 mg/L. Positron emission tomography/computed tomography (PET/CT) performed showed a focal area of increased uptake of fluorodesoxyglucose (FDG) around the Contegra bovine leaflet, strongly suggestive of endocarditis. Blood cultures were positive for Staphylococcus mitis. The authors described the incremental role of PET/CT in diagnosing infective endocarditis, particularly in a case of an inconclusive echocardiogram of a prosthetic valve or cardiac device.

Retrospective/Prospective Studies

Of the 4 retrospective studies, 3 studies included patients exclusively in the pediatric age group[1,3,9] and 1 study population was a mixture of pediatric and adult patients[6]. The study with prospective/retrospective data included a mixture of pediatric and adult patients[8].

Pediatric-Only Studies (3 publications)

Study Outcomes

Re-intervention/Reoperation

One study reported data on re-intervention or reoperation[3]. Kido and collegues[3] analyzed pediatric patients (n=13, median age 8 months, age range 4 days-4 years, median weight 5.5 kg) implanted with small caliber Contegra (12-16 mm sizes and bicuspidized downsized 9 and 10 mm conduits) and reported freedom from re-intervention/reoperation of 53 % during a mean follow-up period of 10 months. The patient population included patients who exhibited persistent pulmonary hypertension with post-operative pressure gradient > 60 mm Hg. The authors concluded that low body weight at operation and pulmonary hypertension may have contributed to early graft failure and reoperation in these patients. In another study, Sarikouch and colleagues[9] reported freedom from explantation and intervention of 65.2% for Contegra versus 79.1% for patients implanted with cryopreserved pulmonary homograft at 10 years.

Explantation

The rate of freedom from explantation for Contegra at 5 and 10 years was reported as 90.1% and 84.3% respectively[9]. Sarikouch and colleagues evaluated the performance of decellularized fresh pulmonary homografts (DPHs,) in 93 patients (mean age15.8 years, mean follow-up 4.6 years) matched to 93 patients implanted with cryopreserved pulmonary homografts (CHs, mean age 15.9 years, mean follow-up 7.4 years) and 93 patients implanted with Contegra (mean age 15.6 years, mean follow-up 6.4 years) and reported the following rates of freedom from explantation and freedom from explantation and peak pressure gradient ≥ 50 mm Hg:

TABLE 4: Rate of Freedom from Explantation and Freedom from Explantation and Gradient ≥ 50 mm Hg for Contegra and Homografts

	Explantation		**Explantation + gradient ≥ 50 mm Hg**	
	5-year Freedom Rate (%)	10-year Freedom Rate (%)	5-year Freedom Rate (%)	10-year Freedom Rate (%)
CONTEGRA	90.1	84.3	60.4	48.5
DPH	100	100	85.9	85.9
CH	90.0	84.2	79.9	63.5
Log rank test				
DPH vs. Contegra	P= 0.010		P< 0.001	
DPH vs. CH	P= 0.011			

CH vs. Contegra		P= 0.009

Endocarditis

The rate of freedom from endocarditis reported by one paper for bovine jugular vein (BJV) conduit or Contegra was 94.4% at both 5 and 10 years[9] time points. In the Sarikouch et al. study that compared DPH implants to matched (age, diagnosis, number of previous heart operations and number of previous pulmonary valve replacement) Cryopreserved homograft (CH) and Contegra implanted patients, there was no significant differences in the rate of freedom from endocarditis between pairs. At 10 years the rate of freedom from endocarditis was 100% for DPH versus 97.1 % for CH patients (P= 0.2) and 94.3% for Contegra patients (P =0.06, Contegra vs. DPH). No significant differences were found in the rate of freedom from endocarditis between the pairs at 5 and 10 years. The rates at 5 and 10 years were the same.

Pulmonary insufficiency and/stenosis

A significant pulmonary insufficiency and stenosis was observed in 5 of 13 patients (38.5%) during a mean follow up of 10 months[3]. Distal stenosis was observed in 15.4% (2/13) of the patients[3].

Sarikouch and colleagues[9] reported similar rates of freedom from moderate insufficiency at 5 years for Contegra 76.7%, decellularized PH 81.4% and cryopreserved homograft (CH) 74.6%. At 10 years the freedom from moderate insufficiency for Contegra and CH were 51.8% and 50.5% respectively.

Thrombosis

Thrombosis was reported in one study[1]. In 16 pediatric patients with congenitally corrected transposition of the great arteries, (mean age 25 months, range 4 to 72 months), three patients had concomitant pulmonary stenosis. The three patients were implanted with extracardiac conduits (Dacron, freestyle Bioprosthesis and Contegra) to provide right ventricular to pulmonary continuity. Thrombosis of the right ventricle to the pulmonary valved conduit developed one month after operation in the patient implanted with Contegra which required thromboembolectomy.

Coronary Artery Compression

One study reported coronary artery compression in one patient[3]. This female patient was implanted with a 12 mm ring-supported Contegra conduit at age 1yr and developed coronary artery stenosis, caused by compression between the ring of the Contegra and the annulus of a mechanical valve. Post Contegra implantation, the patient's left ventricular function gradually deteriorated after discharge but suddenly developed cardiogenic shock 6 months after implantation which required extracorporeal life support. Catheterization revealed obstruction of the left main coronary caused by the Contegra ring and the mechanical valve. The implanted devices were removed and left coronary patch plasty was performed. Coronary angiography performed 2 months after the surgery showed patent left coronary artery and improved left ventricular ejection fraction from 30% preoperatively to 45 % post-operative.

Death

The rate of survival for Contegra was reported as 96.0% at 5 and 10 years in one study[9].Two deaths (2/13) were reported in the Kido et al. study, one death was due to severe right ventricular failure and the other, necrotic enterocolitis related septic shock[3].

Studies with Mixed Pediatric Adult Population (2 publications)

There were 2 studies with mixed pediatric and adult populations[6,8].

Study Outcomes

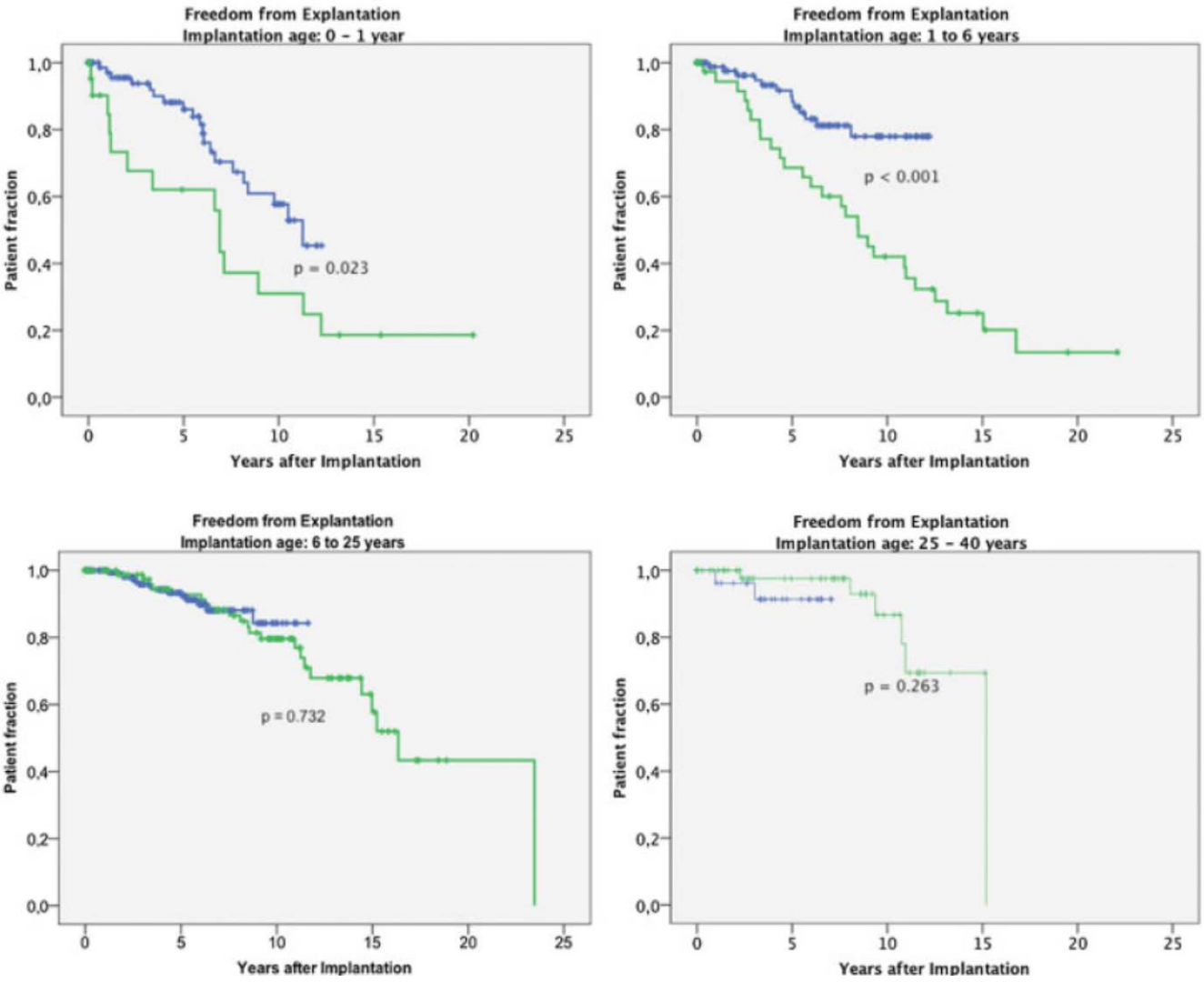
Re-intervention/Replacement

In one study, Mery and colleagues analyzed 586 patients (age range 3 days to 47 years, median age 4 years) who underwent placement with a total 792 valved conduits including 245 Contegra grafts, 289 pulmonary homografts, 121 aortic homografts and 137 porcine heterografts or Hancock. After a median follow-up of 7 years, the Contegra was the only graft observed to be associated with a lower risk of conduit re-intervention hazard ratio (HR) of 0.54 (95% CI: 0.4-0.73, p< 0.0001) and conduit replacement HR of 0.51 (95% CI 0.36-0.73, p = 0.0002) when compared to pulmonary homografts[6]. The risk of conduit re-intervention and conduit replacement in aortic homografts and porcine heterografts were similar when compared to pulmonary homografts.

Explantation

Sandica and colleagues[8] assessed a total 633 patients who received 711 conduits (between 1985 and 2012) including 444 consecutive Contegra implantations (mean patient age: 10.4 years, median 9.4 years, and interquartile range of 1.6 to 15.8 years) and 267 homografts (mean patient age: 20.9 years, median 17.6 years, and interquartile range 5.3 to 32.5 years) stratified according to age group categories: < 1 year; 1–6 years, 6–25 years, 25–40 years, > 40 years. The mean follow-up was 4.3 years for Contegra patients and 6.6 years for homograft patients. The authors reported that Kaplan–Meier analyses indicated that freedom from explantation was better for Contegra in patients younger than 1 year (p = 0.023) and in patients aged between 1 and 6 years (p < 0.001) (Figure 3). No conduit explantation was required in patients who received their conduit beyond the age of 40 years.

Figure 3: Freedom from Explantation by Conduit Type and Age Group



Regression analysis indicated a larger conduit diameter as a protective factor against earlier explantation ($p < 0.001$, HR = 0.84), and the use of a Contegra reduced the risk for earlier explantation: $p = 0.022$, HR = 0.52)[8].

Insufficiency/Stenosis

Sandica and colleagues determined the risk for events in their study and reported that female patients were less prone to developing insufficiency (HR = 0.6, $p = 0.001$), and that younger patients had higher risk for insufficiency compared to patients > 40 years (1 year: HR = 30.1, $p < 0.001$; 1–6 years: HR = 13.7, $p= 0.001$; 6–25 years: HR = 5.5, $p= 0.003$,) in a combined cohort of 486 Contegra and homograft

patients. But stenosis occurred earlier in females (HR=1.4, p = 0.019), later in patients treated with Ross procedure for aortic valve dysfunction (HR= 0.30, p< 0.001), and later with larger conduits (HR= 0.85, p < 0.001) in a cohort of 219 Contegra and homograft patients[8].

Degeneration

Cox regression analysis performed in the Sandica et al. study (described above) also indicated that patients age less than 1 year old (HR= 5.8, p= 0.003), 1 to 6 years of age (HR= 5.2, p = 0.003,) and 6 to 25 years of age (HR= 4.0, p= 0.009,) as significant risk factors for conduit degeneration. The study observed that larger conduits degenerated later (HR = 0.9, p < 0.001), and the conduits of patients with a double outlet right ventricle (DORV) had a significantly higher risk for degeneration (HR =1.6, p= 0.021).

Endocarditis

Endocarditis was reported in both studies[6,8]. In the study by Mery and colleagues[6] that evaluated 586 patients who underwent placement of 792 valved conduits, including Contegra (n=245), pulmonary homograft (n=289), aortic homograft (n= 121) and porcine heterograft (n= 137) with a median follow-up of 7 years, 6% of Contegra grafts developed endocarditis during the study period. The 10-year rate of freedom from endocarditis was 83% for Contegra grafts, versus 100% for aortic homografts, 98% for pulmonary homografts, and 95% for porcine heterografts. The use of Contegra was associated a 9 times greater risk of endocarditis compared to homografts (HR 9.05, 95% CI: 2.57-31.83, P= .0006). The HR for Contegra was higher than that for the other conduit types and increased with time.

Sandica and colleagues also reported that the Contegra grafts were significantly more prone to endocarditis (HR 22.9, p < 0.001) compared to pulmonary homografts[8].

Discussion of the literature

The Contegra device was reported to be associated with a lower risk of re-intervention and replacement compared to pulmonary homograft (HR: 0.54, p< 0.0001 for re-intervention and HR: 0.51, p = 0.0002 for replacement)[6] while in another study the rate of freedom from re-intervention or reoperation of 53% was reported at 10 months[3]. Prior studies have reported comparable rates of freedom from reoperation or conduit exchange between the Contegra and pulmonary homografts (Contegra 59-79% vs. homograft 69-85% at 5 years)[12-14].

The rate of freedom from explantation for Contegra was found to be significantly lower than decellularized pulmonary homograft at 5 years (DPH 100%, vs. Contegra 90.1%, P= 0.01) and 10 years (DPH 100% vs. Contegra 84.3%, P = 0.01). Compared with decellularized pulmonary homograft or cryopreserved pulmonary homograft, the rate of freedom from explantation and peak trans-conduit gradient ≥50 mmHg for Contegra was found also to be significantly lower (5-year rates: DPH 85.9% vs. 60.4%; 10 year rates: DPH 85.9% vs. 48.5%, p<0.001; 5 year rates: CH 79.9% vs. Contegra 60.4%; 10 year rate: CH 63.5% vs. Contegra 48.5%, p= 0.009)[9].

However, in the Sandica study which comprises of 633 patients implanted with a total of 711 conduit (444 Contegra conduits and 267 homografts) stratified by age group, the authors reported that freedom from explantation was significantly better for Contegra patients in the younger age groups, ages less than 1 year ($p = 0.023$) and 1 to 6 years ($p < 0.001$) compared to homograft patients[8]. This 5-year rate of freedom from explantation reported in the literature (90.1%)[9] is numerically higher than the rate reported at 5 years for the Contegra humanitarian device exemption (HDE) patients 80.7%.

The freedom from moderate insufficiency was found to be similar in patients implanted with Contegra, decellularized pulmonary homograft and cryopreserved homograft 76.7%, 81.4% and 74.6% respectively at 5 years. At 10 years the freedom from moderate insufficiency for Contegra and cryopreserved homograft were similar, 51.8% vs. 50.5% respectively[9]. Sandica and colleagues however observed that younger patients implanted with conduits (Contegra or homograft) tended to have higher risk of insufficiency (< 1 year old: HR, 30.1, $p < 0.001$; 1–6 year old: HR, 13.7, $p= 0.001$, 6–25 year old: HR = 5.5, $p= 0.003$,) than older patients above 40 years [8].

In a prior study, Vitanova and colleagues[13], found that freedom from moderate insufficiency developed faster in Contegra than in homograft in patients less than 1 year old (freedom from moderate insufficiency of 74.6% and 44% at 5 and 10 years respectively for Contegra versus 92% and 65%, respectively for homograft).

The use of Contegra was found to be associated with a 9 times greater risk of endocarditis than pulmonary homograft (HR: 9.05, P= .0006) after median follow up 7 years (range 6 days to 20 years) in the study by Mery and colleagues[6]. Sandica and colleagues[8] also reported that Contegra grafts were significantly more prone to endocarditis (HR 22.9, $p < 0.001$) compared to pulmonary homografts after mean follow up 5.2 years. Both study populations included pediatric and adult patients. In the study with only pediatric patients matched for age (mean ages 15.6, 15.8 and 15.9 years in 3 cohorts), diagnosis, number of previous heart operations and number of previous pulmonary valve replacements, Sarikouch and colleagues did not find significant differences in the rate of freedom from endocarditis between Contegra conduit patients and patients implanted with decellularized PH or cryopreserved homografts at 5 and 10 years (5 year rates were 94.4%, 100%, and 97.1%; 10 year rates were 94.4%, 100% and 97.1% for Contegra, decellularized PH and cryopreserved homografts respectively)[9].

The rate of freedom from endocarditis of 94.4% at both 5 and 10 years reported in the literature is comparable to the Kaplan Meier estimated rate of 93.7% for the HDE patients at both 5 and 7 year time points.

One study reported freedom death rate of 96% at both 5-year and 10-year follow-up in Contegra patients [9]. The studies that reported deaths did not specify whether or not a death was related to the Contegra [3,9].

Thrombosis of the Contegra conduit was not commonly reported in this literature search[1]. Contegra conduit dissection was reported in one patient who presented in acute heart failure[2]. The Contegra conduit was excised and replaced with pulmonary homograft with uneventful outcomes. Although dissection of the Contegra conduit and compression on the left main coronary artery[3] have rarely been reported, these are potential complications associated with the Contegra conduit.

Conclusion on the Literature Review

Review of literature published from 05/31/15 through 05/31/16 revealed the following observations.

- Published literature reported a lower risk of re-intervention and replacement for patients implanted with Contegra compared to pulmonary homograft implants.
- The rate of freedom from explantation and pressure gradient ≥ 50 mmHg was reported to be significantly lower for Contegra patients than patients implanted with decellularized or cryopreserved pulmonary homografts. In one study the freedom from explantation was found to be significantly better for Contegra patients in younger age groups (less than 1 year and 1 to 6 years) compared to homograft patients.
- The freedom from moderate insufficiency was similar in Contegra patients, and patients implanted with decellularized or cryopreserved homograft.
- Contegra was associated with a greater risk of endocarditis compared to pulmonary homograft in studies with mixed pediatric and adult populations. One study that evaluated matched pediatric population found no significant difference in the rate of freedom from endocarditis in Contegra patients and patients implanted with decellularized or cryopreserved homograft.
- The rate of freedom from endocarditis of 94.4% at both time points 5 and 10 years reported in the literature is similar to the Kaplan Meier estimated rate of 93.7% at both time points 5 and 7 years for the HDE patients.
- One case of Contegra conduit dissection was reported. In another case report, compression of the coronary artery by ring-supported Contegra conduit occurred in a patient. One case of a mismatch between the conduit size and the patient which resulted in protrusion of the conduit between the sternal edges was reported.
- The role of PET/CT in diagnosing endocarditis was reported in one case.

The ability to draw conclusions from this literature review is limited by the following factors:

1. Majority of the studies reviewed were retrospective. Thus, the studies were not randomized to balance for differences in covariates, especially for studies that compared Contegra to homograft conduit. Therefore the study results may not be as robust as for randomized controlled trials (RCT).

2. In studies that compared Contegra to other conduit(s), the follow-up times tended to vary for the different treatment arms, which could influence observed rates.
3. The Contegra conduits studied were implanted over a wide time period (1999 to 2014) and patient management or standards of care could have changed over this period of time.

SUMMARY

The FDA did not identify any new unexpected events during this review. The number of MDRs with device sizing issues declined in this reporting period. The literature review identified variable rates with respect to device explantation and endocarditis whencomparing Contegra to homograft conduits.The types and rates of adverse events noted in the literature review were were comparable to those reported in the Contegra HDE studies. The rare but serious events identified in the case reports (e.g. conduit dissection, coronary artery compression and patient-conduit size mismatch issue) are similar to the events reported in the MDRs which were reviewed by the PACs in 2014 and 2015 and addressed in the IFU update in 2015. 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 safety and distribution information for this device.

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