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 26, 2019 Pediatric Advisory Committee Meeting

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 2018 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 467 devices were sold in the U.S., and 268 devices were implanted. At least 248 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 145 MDRs regarding Contegra identified in the FDA's MDR database between June 1st, 2018 and May 31st, 2019, including 106 identified as unique MDRs. The remaining 39 MDRs are excluded from the MDR data analysis for this year's review since these MDRs described events reported in literature that were either presented to the PAC previously (prior years), or are discussed in the Literature Review section of this document. Therefore, the MDR analysis is based on the review of 106 unique MDRs, all submitted by the manufacturer.

<u>**Patient Demographic Data**</u>

Of the 106 MDRs, 104 (98%) were received from the United States (US). Patient gender information is included in 104 MDRs; 60 involved males and 44 involved females. Patient age is included in 102 MDRs; 98 are pediatric patients and 4 are adults. TABLE 1 summarizes this information.

TABLE 1: Patient Demographic Data (Total 106 MDRs; involve 98 pediatric patients)

Demographic Data		Percentage	Number of MDRs containing the demographic
Reporting Country	US : OUS	98% : 2%	104 : 2 (106 Total)
Patient Gender	Male : Female	58% : 42%	60 : 44 (104 Total)
Patient Age	Pediatric : Adult	96% : 4%	98 : 4 (102 Total)
Pediatric Only Age Range: 11 days – 21 years Average Age: 10.6 ± 5.5 years			

<u>**Primary Reported Events**</u>

The 106 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, as well as the associated TTEO ranges and means are outlined in TABLE 2 below.

TABLE 2: Primary Reported Event by Patient Age and TTEO for 2019 PAC Review

Primary Reported Event	Total MDR Count	Patient Age (year)			*TTEO (month)	
		Pediatric (<22)	Adult (≥22)	Age not reported	Range	Mean
Stenosis	**51**	50	1	0	0 - 165	87
Device replaced (reason not provided)	**38**	32	4	2	9 - 163	76
Valve regurgitation/insufficiency	**6**	5	1	0	14 -114	54
Inadequate size for patient	**4**	4	0	0	0 -109	56
Arrhythmia	**2**	2	0	0	0.3 -3.9	2
Increased pressure gradient	**2**	2	0	0	88 -155	121
Infection/endocarditis/sepsis	**2**	**2	0	0	0.1 - 2	1
Aneurysm	**1**	**1	0	0	65	65
Grand Total	**106**	98	6	2		

* TTEO: "Time to event occurrence" was obtained from MDR event text or calculated as the period between the Date of Implant and the Date of Event.

** There were 3 deaths reported in this period involving pediatric patients. The remaining 103 MDRs represent injury events.

A comparison of the primary events reported in the MDRs for the current analysis period with those from 2017's and 2018's PAC MDR analysis are shown in TABLE 3 below. The total number of MDRs increased from 84 and 52 for the 2017 and 2018 PACs, respectively, to 106 for the 2019 PAC. The types of primary reported events are similar, with "Stenosis", "Device replacement" and "Valve regurgitation/insufficiency" remaining as the most frequently reported events for the past 3 years. Although "Inadequate size for patient" was not reported as a primary reported event in 2017 and 2018, the event appeared to be related to patient or procedural factors which are discussed in the section below.

TABLE 3: Comparison of Primary Reported Event for Contegra MDRs in 2017, 2018 and 2019

Primary Reported Event	2017 PAC MDR Count (%)	2018 PAC MDR Count (%)	2019 PAC MDR Count (%)
Stenosis	37 (44%)	33 (63%)	51 (48%)
Device replaced (reason not provided)	35 (42%)	12 (23%)	38 (36%)
Valve regurgitation/insufficiency	5 (6%)	2 (4%)	6 (6%)
Inadequate size for patient	0	0	4 (4%)
Arrhythmia	2 (2.3%)	0	2 (2%)
Increased pressure gradient	1 (1.2%)	2 (4%)	2 (2%)
Infection/endocarditis/sepsis	1 (1.2%)	1 (2%)	2 (2%)
Conduit dilation/aneurysm	2 (2.3%)	1 (2%)	1 (1%)
Pulmonary edema/hemorrhage	0	1 (2%)	0
Thrombus	1 (1.2%)	0	0
Total	**84**	**52**	**106**

The primary events reported in the 106 MDRs involving 3 deaths and 103 injuries are summarized below.

Stenosis (n=51 MDRs, including 50 pediatric patients)

Stenosis of conduit or pulmonary artery continued to be the most frequently reported event. In these 51 reports, stenosis (in conjunction with calcification, obstruction, pulmonary regurgitation or insufficiency and/or elevated pressure gradients) was identified in patients between 0 and 165 months post implant.

Of the 51 stenosis reports, 3 reflect early and mid-term events (within one year post Contegra implant) in pediatric patients. Two of these 3 pediatric events involved infants who required a transcatheter valve-in-valve implantation 2 months post implant due to stenosis of pulmonary arteries. In the 3rd pediatric patient, the Contegra device was explanted surgically one day post implant due to pulmonary artery stenosis with a pressure gradient of 50 mmHg. The patient was discharged without additional complication reported. The other 48 reports (involving 47 pediatric and 1 adult patients) reflect late events of stenosis (greater than one year post implant) and the patients required interventions between 2 to 14 years post implant without additional adverse effects reported.

Overall, the interventions required for the 51 patients with stenosis included surgical replacement of pulmonary valve (19) and transcatheter pulmonary valve-in-valve (TPV) implantation (32).

Device replacement[1] – reason for replacement not reported (n=38 MDRs; 32 pediatric patients)

Thirty-eight MDRs indicate that Contegra was replaced, including 32 MDRs involving pediatric patients. Although the reasons for the device replacement were not reported in the MDRs, 23 of the 32 pediatric reports described that the valved conduit was replaced with a different or a larger size of device between 9 and 163 months post Contegra implant. In the remaining 9 MDRs, no information was available regarding the reason of device replacement and the device was not returned to the manufacturer for analysis. There were no device defects nor other adverse patient effects reported in the MDRs.

Valve regurgitation/insufficiency (n=6 MDRs; 5 pediatric patients)

Six MDRs reported valve regurgitation or insufficiency between 14 and 114 months post Contegra implant. All 6 patients, including 1 adult and 5 pediatric patients, required a TPV valve-in-valve implantation. Contegra valved conduits remained in the patients and were not explanted. No additional adverse patient effects were reported.

Inadequate size for the patient (n=4 MDRs; 4 pediatric patients)

Four reports noted inadequate size of valved conduit for the pediatric patients. In one of the 4 patients, Contegra valved conduit (size 12mm) was explanted immediately post implant since the surgeon felt a larger size was necessary and replaced the conduit with a 16mm Contegra device. The other 3 pediatric patients received the Contegra device during infancy and required a surgical replacement with a larger valved conduit between 45 and 109 months post implant due to patient outgrowth.

---

[1] "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.

Arrhythmia (n=2; 2 pediatric patients)

Both pediatric patients developed complete heart block which necessitated permanent pacemaker implantation between 9 days and 4 months post implant of the Contegra valved conduit. No additional adverse patient effects were reported. The manufacturer noted that conduction disturbances are known potential adverse effects associated with cardiac or thorarcic procedures and can be resolved with medical treatment(s) or a permanent pacemaker.

Increased pressure gradients (n=2 MDR; 2 pediatric patients)

Two MDRs described increased pressure gradients in pediatric patients. Both patients required a TPV valve-in-valve implantation between 7.2 and 12.8 years post implant due to moderate or high pressure gradients. The Contegra devices remained implanted in the patients and were not returned for manufacture's analysis. There were no other additional adverse patient effects reported.

Infection/endocarditis/sepsis (n=2 MDRs; 2 pediatric deaths)

One of the 2 infection MDRs involved a newborn who previously underwent a Ross-Konno procedure plus closure of a ventricular septal defect (VSD) and aortic arch augmentation for critical aortic stenosis with a unicuspid aortic valve, aortic arch hypoplasia, as well as a large posterior malalignment type VSD. One day post implant of the pulmonary valved conduit in the mitral position (off-label use), the patient had positive blood cultures for sepsis. The cause of sepsis was unknown as the patient was very sick with an open chest. The pulmonary conduit was implanted inside of a 14mm Dacron tube due to severe mitral regurgitation. Post implant day 3, the patient also experienced complete atrio-ventricular (AV) block and persistent hypotension and necessitated extracorporeal membrane oxygenation (ECMO). The case was further complicated by right sided seizure and there was progressive acidosis. Three days later, the patient's family requested to discontinue all life support measures and the patient expired after ECMO and ventilator support were discontinued. The manufacturer indicated that no autopsy was performed and the device remained in the patient. Without the return of the device, no definitive conclusion can be made regarding the clinical observation.

The other MDR of infection reported that the Contegra device was explanted from a 3-year-old patient 1.8 months post implant due to a possible fungal infection and the patient expired. The manufacturer indicated that pathology confirmed fungal vegetation on the cusps of the conduit. White pannus was seen on the outer wall and soft thrombotic tissue (vegetation) appeared to infiltrate the leaflet. Vegetation was also observed on the adjacent aortic wall. The cause of death was reported as mediastinal abscess with fungal pulmonary artery graft endocarditis and sepsis. The manufacturer's review of the device history record showed that the product met all manufacturing specifications for product released for distribution. The main source of infection is unknown. The reported mediastinal abscess and sepsis are possible pre-disposing factors. There is no indication that endocarditis originated from the device.

Aneurysm (n=1 MDR; one pediatric death)

A 7-year-old patient had a history of pulmonary atresia, VSD, multiple aortopulmonary collateral

arteries, hypoplastic right and left pulmonary artery stenosis, right ventricle to pulmonary artery conduit failure, DiGeorge syndrome, pulmonary hypertension, secundum atrial septal device, ascending thoracic aortic aneurysm, bicuspid aortic valve and severe vasoplegia coagulopathy. The patient underwent multiple previous surgical procedures including an implantation of a Contegra pulmonary valved conduit at age 2. The conduit was explanted 5.4 years post implant due to an aneurysm and was replaced with a 23 mm valve. The patient expired 1 day post valve implant and the cause of death was cardiac arrest. The physician reported that the device did not cause or contribute to the death and there were multiple concurrent procedures performed, including ascending aortic graft, repair of pulmonary artery stenosis by reconstruction with a patch and repair of an atrial septal defect.

Conclusions Based on the MDR Review

1. The MDRs received in this reporting period reflect peri-operative or late term events which are known complications. These events were likely associated with the procedure or patient underlying conditions and have been addressed in the device IFU.

2. No new safety issues were identified based on the MDR review for this reporting period.

CONTEGRA LITERATURE REVIEW

Purpose

The objective of this systematic literature review is to provide an update on the safety of the Contegra device when used in pediatric patients.

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 2018 literature review. The search was limited to articles published in English from 06/01/2018 through 05/31/2019.

Figure 1 depicts the article retrieval and selection process including the criteria for exclusion. A total of 87 (21 PubMed and 66 EMBASE) articles were retrieved. Eighteen articles were duplicates. The remaining 69 articles were subjected to review of titles and abstracts. Fifty-three articles were excluded from full-text review for reasons listed below:

Two articles on animal study**,** 2 articles on *in-vitro* study/biomarkers, 9 conference abstracts, 3 letters to the Editor/Editorials, 16 articles on Melody valve/percutaneous pulmonary valve implantation (PPVI), 6 articles on other xenografts/devices, 7 articles on surgical procedures/techniques, 4 articles reviewed in past PAC meetings, 1 article in a foreign language, and 3 articles were not relevant to Contegra (other studies) were excluded.

A total of 16 articles were retained for full text review. Of these 16 articles, the following articles were excluded from further review:

Two articles were non-relevant to Contegra bovine jugular vein (non-Contegra), and 3 articles presented combined data (e.g., pediatric and adult population, or other devices).

A total of 11 articles were included in this systematic literature review.

Of note, in addition to the articles retrieved from PubMed and EMBASE databases, there were 39 publications identified through the review of the device manufacturer's adverse event reports submitted through the MedWatch system (MDR reports). Twenty-eight articles were out of search date, and the remaining 11 articles did not meet the criteria for inclusion for analysis in the systematic literature review (e.g., absence of Contegra data, other devices or combination of devices).
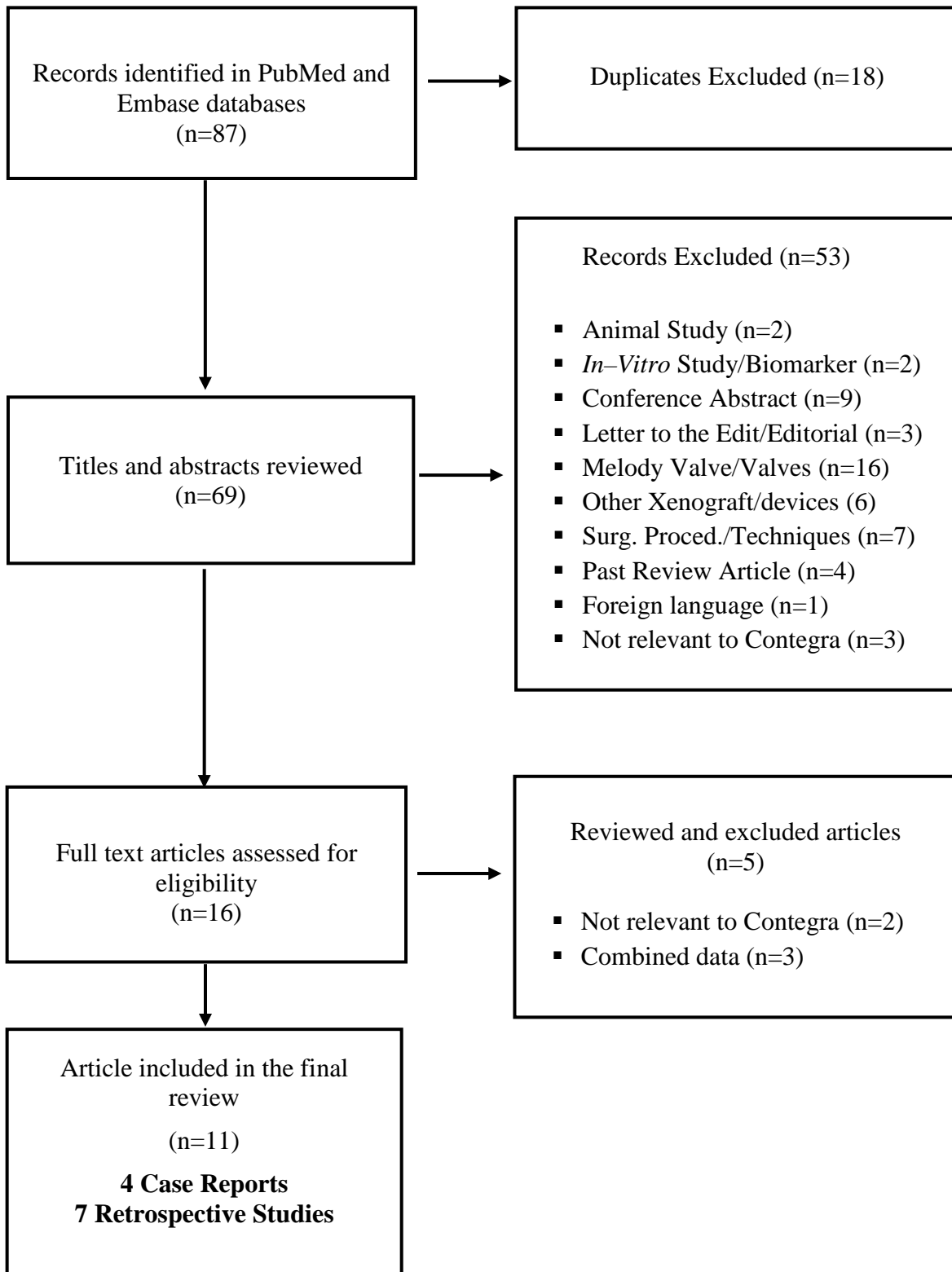
Records identified in PubMed and Embase databases (n=87)	→	Duplicates Excluded (n=18)

Titles and abstracts reviewed (n=69)	→	Records Excluded (n=53) ▪ Animal Study (n=2) ▪ *In–Vitro* Study/Biomarker (n=2) ▪ Conference Abstract (n=9) ▪ Letter to the Edit/Editorial (n=3) ▪ Melody Valve/Valves (n=16) ▪ Other Xenograft/devices (6) ▪ Surg. Proced./Techniques (n=7) ▪ Past Review Article (n=4) ▪ Foreign language (n=1) ▪ Not relevant to Contegra (n=3)

Full text articles assessed for eligibility (n=16)	→	Reviewed and excluded articles (n=5) ▪ Not relevant to Contegra (n=2) ▪ Combined data (n=3)

Article included in the final review

(n=11)

4 Case Reports
7 Retrospective Studies

Figure 1. Article retrieval and selection process

Characteristics of Publications Included in Evidence Assessment

There were 7 retrospective studies[1-7] and 4 case reports[8-11] identified in this literature review. Three of them were conducted in the USA[1,6,7], 1 in Belgium[2], 1 in Denmark[3], and 2 in Germany[4,5]. The 4 case reports were from: Spain (2)[9,10], Japan (1)[8], and Romania (1)[11].

A total of 1,254 patients including 924 pediatric patients, were involved in the 7 retrospective studies and case reports. Among pediatric patients, 711 were treated with the Contegra valved conduit. The sample sizes for Contegra conduits in the articles ranged from 1 (case reports) to 276 pediatric patients (retrospective studies). Articles reporting Contegra implants in pediatric population were: Buckley et al.[1] (n=55), Falchetti et al.[2] (n=53), Groning et al.[3] (n=109), Haas et al.[4] (n=106), Jewgenow et al.[5] (n=7), Lueth et al.[6] (n=101), and Patel et al.[7] (n=276). An additional 4 articles reported on 4 pediatric patients. There were 330 adults included in these studies. Patient enrollment date in the studies ranged from 1977 to 2017

The median age at implantation for Contegra patients in the Buckley et al.[1] and Groning et al.[3] studies was 10 days (interquartile range (IQR):16) and 7 years (IQR:13), respectively. In the Jewgenow et al.[5], Falchetti et al.[2], and Haas et al.[4] studies, the mean age of patients implanted with Contegra was 3.2 years (Min-Max: 0.5-6.0), 15±8 days, and 8.1±5.8 years, respectively. Patel et al.[7] grouped patients by age at implant: Group 1: 0 to 1 years (n=65), Group 2: 1 to 10 years (n=132), and Group 3: older than 10 years (n=118). Lueth et al.[6] studied 2 groups of pediatric patients: (a) undergoing supported Bovine Jugular Vein (sBJV) and (b) unsupported (uBJV) versions of Contegra. Median age at implant did not differ significantly between these two groups (uBJV 3.9 years (IQR: 9.7) vs. sBJV 4.3 years (IQR: 6.7). Demographic details for patient population, including adult patients and range in the subgroups, were not disclosed in 3 studies[3,4]. The patients' age in case reports ranged from 1 to 14 years.

The ages in articles with mixed pediatric and adult populations ranged from newborn to 56.1 years. The age at implant for Contegra patients ranged from 3 days to 18 years across the studies. The follow-up duration for Contegra conduits in the pediatric retrospective studies ranged from 1 year to 8.8 years.

Safety Results Discussion

Endocarditis
Retrospective Studies (n=6), Case Reports (n=2)

Endocarditis was the most commonly reported safety event in the current literature review.

Groning et al.[3] report the incidence of infective endocarditis (IE) in the right ventricle-to-pulmonary artery (RV-PA) conduits in a retrospective single site study in Denmark, that involved 311 patients with 1 or more RVOT reconstructions. Patients were treated between May 1977 and September 2016.

The incidence and risk of IE in homograft, Contegra, and Melody valve groups, were individually calculated at 1 and 5 years by Cox-regression (right sensoring) with time-dependent covariates to model the impact of conduit type. Follow-up ended when grafts were either infected or explanted, upon patient death, or on the date of the latest follow-up. Cases of mitral or aortic valve evidence of IE were excluded. The remaining cases of endocarditis were scored according to the Duke modified criteria as

"*definitive*" or "*possible*." Assessment of endocarditis in the grafts groups was conducted independently.

A total of 432 RV-PA devices were implanted in 300 patients: 259 homografts in 225 patients, 109 Contegra conduits in 97 patients, and 64 Melody valves in 61 patients. Eleven patients were excluded, 10 patients were lost to follow-up, and 1 patient underwent TPVR twice with the Melody valve stented. Median follow-up in the homograft group, Contegra, and Melody valve were 8.3, 6.0, and 3.9 years, respectively.

Ten patients were treated for IE in the homograft group (4.44 %, 10/225), and 5 cases, including 3 patients with evidence of left side endocarditis, were excluded. One case was classified as rejected due to bacteremia without endocarditis per Duke criteria, and 1 case had insufficient data. The remaining 5 patients were determined as "*definitive*" endocarditis. The Contegra group included 6 patients (6.18 %, 6/97) who were treated with endocarditis. One patient was rejected, and the remaining 5 cases were classified as "*definitive or possible*" endocarditis. The Melody valve group resulted in 7 endocarditis cases, 3 cases classified as "*possible*", and none excluded.
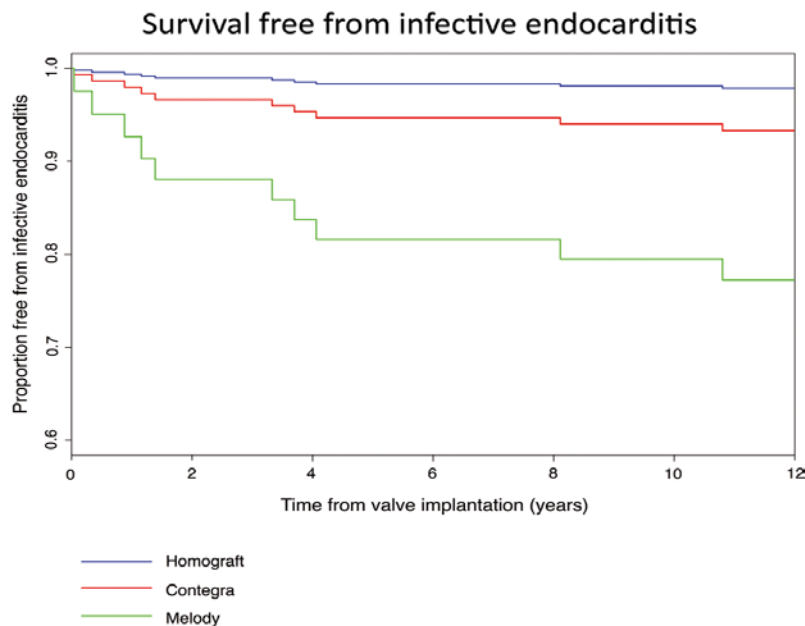

Figure 1: Survival free from infective endocarditis. Cumulative survival plot derived from the time-dependent Cox regression illustrating survival free from infective endocarditis for homografts (blue), Contegra (red), and Melody valves (green). Time from the index procedure (valve implantation) in years is depicted on the X-axis and cumulative survival on the Y-axis.

A sub-analysis comparing the incidence of IE in the Melody subgroups (i.e., homograft or Contegra plus Melody) was also presented in the article. Forty-nine Melody valves were implanted in homografts and 15 valves in Contegra. Survival-free from IE at 1 year after valve implantation was 100 % for homografts, 99 % for Contegra, and 93 % for the Melody valves. After 5 years the survival-free from IE was 99 %, 94 %, and 86 % for homografts, Contegra, and Melody valves, respectively. (Figure 1).

The authors also describe that the annualized incidence rates of IE in the Contegra group were 0.97 % and 1.12 % at 1 year and 5 years post-implant, respectively. The annualized IE incidence rates in the

homograft group was 0.40 % and 0.27 %, respectively. Sub-analysis of other cohorts in this study displayed the highest statistically significant incidence of IE in the Melody valve group (6.97 % and 2.89 %, p<0.001) compared with homografts and Contegra conduits. These authors note the lower IE incidence rates for homograft and Melody valves at 5 years post-implant, which was not observed in the Contegra group.

The only covariant identified with significant effect on the risk for IE was the number of previous conduits (>2 previous RV-PA conduits). The authors propose that this event may relate with the preponderance of patients implanted with Melody valves. The authors also propose that the endothelial lesions caused by motions of the Melody stent at the implantation area, may have caused tissue degeneration and need of valve replacement.

Similar higher incidence in IE was reported in the Melody and Contegra groups compared with the homograft group in a previous report of Van Dijck et al[12] although there were differences in study design, number of study patients, and criteria for IE assessment.

Jewgenow et al.[5] also evaluated the incidence and risk of IE as the source of life-threatening infections. A total of 47 explanted bio-prosthesis pulmonary valved-conduits from 46 patients were analyzed: 23 Hancock, 7 homografts, 7 Contegra, 7 Melody, and 3 Other valved implants for the RV-PA position. One patient initially received a 12 mm Hancock for correction of a truncus arteriosus (TA) that was replaced by a 20 mm Hancock at the age of 5.5-years old. The second Hancock graft was also explanted and replaced by a homograft 6 months later due to endocarditis unresponsive to antibiotics, and progressive stenosis.

Histopathological analysis of the 47 mentioned explants, and additional 5 healthy porcine pulmonary valves, used as control, was conducted by using standard laboratory procedures. Clinical data from the patients were obtained from medical records. Median age at implant was 1.7 years (0-7.1) in the Hancock group, 10.4 years (2.0-22.9) in the homograft group, 3.2 years (0.5-6.0) in the Contegra group, 17.9 years (12.4-23.5) in the Melody group, and 29.7 years (3.2-56.6) in the Other grafts group. The average time of implantation was 63 months (6-342 months). Mean implantation time was 51.2 months for Hancock, 91.8 months for homografts, 66.9 months for Contegra, 40.2 months for Melody, and 40.9 months for the Other group.

The main reason for device explant was obstruction (n=45) followed by regurgitation (n=7) and IE (n=6). The incidence of IE in the study was 12.8 % (6/47 specimens). The IE incidence was 4.35 % (1/23) in Hancock, 0 % (0/7) in homografts, 14.3 % (1/7) in Contegra, 57.4 % (4/7) in Melody valves, and 0 % (0/3) in Other specimens. Presence of thrombus material in the basis of the semilunar valve sinus was observed in 91.3 % (21/23) in Hancock, 100 % (7/7) in homografts, 100 % (7/7) in Contegra, 100 % (7/7) in Melody valves, and 66.6 % (2/3) in Other specimens. There was no clinical or echocardiographic suspicion of valve thrombus formation in any of these patients prior to implant explant and histopathological examination.

Despite existence of thrombus material in most valve cusps, only specimens from IE patients presented additional thrombus material as vegetations at the conduit wall and valve cusps. All IE (6/47, 12.7 %) specimens, displayed the typical thickening features of endocarditis. No evidence of thrombus was observed in the 5 porcine pulmonary valves used as control. All valve specimens from patients with no history of endocarditis were thin and intact with no thrombus material apposition.

Graft stenosis was the leading cause for conduit explant (44/47, 93.6 %), followed by valve insufficiency (11/47, 23.4 %). The authors conclude that given the high incidence of thrombus and its potential impact on IE, preventive anti-platelet and anti-coagulation therapy seen to be reasonable in patients with implanted conduits.

Haas et al.[4] report a retrospective single-site study that compared the risk of bacterial endocarditis (BE) after surgical- and percutaneous pulmonary implantation of different types of valves in 246 patients between January 2010 and December 2015. The study sample comprised *166 surgical patients* (67.58 %) implanted with 55 homografts (22.4 %, mean diameter 27.4 mm), 106 Contegra conduits (43.1 %, mean diameter 17.4 mm), and 5 Hancock valves (2.0 %, mean diameter 25.6 mm) vs. *80 percutaneous pulmonary valve implants* (PPVI, 32.5 %) that included 51 Sapien valves (20.7 %, mean diameter 25.2 mm), and 29 Melody valves (11.8 %, mean diameter 21.9 mm).

Patients who underwent surgical procedures as well as those with PPVI received similar antibiotic therapy (a minimum of 5 days IV Cephalosporine at the valve implantation), and low dose of Aspirin (3-5 mg/Kg or 100 mg max for at least 1 year after surgical procedures). The mean follow-up was 3.1±1.8 years and consisted of outpatient clinical visits and echocardiographic assessments every 6 months. Patients' mean age was 15.9 years (SD 12.7, Median 13.3). Mean patient weight was 47.1 kg (SD 25.8, Median 47 kg), and the mean height was 145 cm (33, Median 153 cm). The majority of patients presented with Tetralogy of Fallot (TOF, 59.3 %) followed by TA (12.6 %), and PA with Ventricular Septal Disease (PA-VSD, 8.9 %). Other CHD represented ~ 20 % of the total number of cases in the study.

The Contegra conduits were implanted in younger patients (8.1 years age ± 5.8) and had smaller diameter (17.4 mm ± 3.4 mm) compared to the homograft group that were implanted in older patients (age 26.2-years ± 15.6) and had the largest diameter (27.4 mm ± 2.6). Likewise, Contegra graft patients implanted with Melody valves were younger (13.0-years ± 4.0) and the valve diameters were smaller (21.9 mm ± 2.2) compared to Sapien valves implanted at median 20.1 years age ± 9.5, and valve diameter 25.2 mm ± 2.1. The authors estimate that differences in valve size diameter and patient age did not have any significance or correlation with BE except in the case of TA that displayed low incidence based on univariate and multivariate analyses.

A total of 11 patients developed BE (4.7 % (5/106) and 20.7 % (6/29) in the Contegra and Melody groups, respectively). The mean time to BE was 33 months (range 23-46 months) for Contegra, and 20.1 months (range 4-50 months) for the Melody valve group. *Staphylococcus aureus* was identified in 1 deceased patient, and *Streptococci* in 1 patient with subsequent positive blood cultures. Three patients developed severe right heart failure due to outflow tract obstruction that required balloon dilatation. No BE was detected in other patient groups. Significant risk factors for BE occurrence in the study included Melody valve (hazard rate: 5.0) and TA (hazard rate: 4.2).

In summary, the authors report that biological (bio-prosthesis (Melody valves and Contegra)) substrates were associated with an increased risk of BE. The Melody valves displayed the highest risk for BE (6/29 patients, 20.7 %) compared with other valves. The Contegra group had 5/106 (4.7 %) endocarditis cases, which is consistent with published results in the literature. The authors refer to the Jalal et al.[13] *in-vitro* study that similarly shows an increased susceptibility of BJV to bacterial infection due to increased bacterial adhesion compared to other bovine or porcine biological substratum. Of note, it was observed

that the Contegra and Melody groups included only pediatric patients (8.1 ±5.8 years) while the homografts, Hancock conduits, and Sapien valve cohorts included adult patients. Therefore, comparison of the results across the treatment groups was limited, however the analysis results within the Contegra group (106 patients) was seen as adequate for assessment of Contegra performance in pediatric patients. The 4.7 % incidence for BE in the Contegra group is consistent with published results in the literature.

Patel et al.[7] conducted a retrospective analysis in 276 children who received 315 Contegra implants between 1999 and 2016 at one institution. Patients were grouped by age at implant: Group 1: 0 to 1 years (n=65), Group 2: 1 to 10 years (n=132), and Group 3: older than 10 years (n=118). The mean (SD) follow-up time for groups 1, 2, and 3 was 4.0 (4.2), 4.9 (4.2), and 5.9 (4.1) years, respectively. Long-term follow-up was available for 84% of patients.

A total of 21 (6.6 %, 21/315 conduits) patients developed endocarditis, 113 (5 %) required re-operation, and 10 (n=3.2 %) received antibiotic therapy alone. Groups 1, 2, and, 3 had an incidence of endocarditis of 3%, 4%, and 11%, respectively. Freedom from conduit endocarditis by age group at ten years postoperatively was 72%, 83%, and 81% for Groups 1, 2, and 3, respectively (P<.004). Indications for re-operation in these patients included conduit stenosis (2), conduit regurgitation (2), a combination of stenosis and regurgitation (3), and persistent systemic manifestations of bacteremia (4).

Lueth et al.[6] conducted a retrospective, single-center, chart review of 101 patients aged 0 to 18 years undergoing 109 BJV conduits implantations with supported (sBJV, n=39) or unsupported (uBJV, n=70) device versions, between January 1, 2009 to December 31, 2017. The purpose of the study was to compare clinical and echocardiographic performance and outcomes in both BJV versions. Blinded cardiologists reviewed postoperative at 6, 12, 24, and 36 months clinical data and the most recent echocardiogram prior to any valve related event or death. Median duration of conduit follow-up was not different between groups (3.6 years). Patients in both groups had a similar median age at conduit implant: uBJV 3.9 years (IQR: 0.6 to 10.3 years) and sBJV 4.3 years (IQR: 1.5 to 8.2 years). Other patients' demographics and conduit size did not differ between cohorts.

The authors report 9% (n=10) incidence of endocarditis at a median age of 6.7 years and median follow-up 2.4 years. Seventy percent of cases with endocarditis were managed medically. There was no statistically significant difference between the groups in the incidence of endocarditis. Five episodes occurred in 4 patients with uBJV conduit (6%), and 6 episodes occurred in 6 patients with sBJV conduit (15%). Three conduits were replaced surgically either due to persistently positive blood cultures or valve degradation in the setting of endocarditis. All infective endocarditis were confined to the implanted conduits and did not involve other cardiac structures.

Buckley et al.[1] report an endocarditis incidence of 1.3 % (1 (1.8%) in Contegra and 2 (2.4 %) in homografts) from a total of 138 patients (83 Pulmonary homographs, and 55 Contegra conduits) in a median follow-up of 2.9 years. A similar endocarditis rate of 1.2 % (2/162) in the Contegra group with same median follow-up was reported by Nichay et al.[14]. Beckerman et al.[15] also observed a higher incidence rate (10 %) of late endocarditis at 7.5-years post-conduit implantation. Both studies were presented in the last PAC literature review.

Olivella et al.[9] report a case referred to the center with fever, chills, and sudden aphasia. He had been diagnosed at birth with Pulmonary atresia, ventricular septal defect (VSD), and hypoplastic pulmonary arteries. The patient was initially palliated with systemic to pulmonary shunts (modified right and left

Blalock-Taussig), and later with a central shunt. Eventually the intraventricular defects were repaired with a fenestrated patch, right ventricle (RV) to pulmonary artery Contegra conduit, and pulmonary arterioplasty/closure at 14-year of age.

At admission, it was suspected an IE, and confirmed positive *Streptococcus parasanguinis* by blood culture. Transesophageal echocardiography showed a thickened Contegra valve and 10 x 14 mm vegetation. Ultimately cardiac PET/CTA detected pulmonary emboli. The patient was treated with Penicillin G sodium and Gentamicin, and additional anticoagulation therapy (Enoxaparin) due to the high thrombotic component of the vegetations. Blood cultures were negative 3 weeks after completion of the antibiotic therapy. The authors report that the patient remained asymptomatic at 13 months.

In a second case report, Hirose et al.[8] reported a pediatric case of *Staphylococcus lugdunensis*-induced IE from mediastinitis in the Contegra BJV graft after RV outflow reconstruction (RVOTR). The patient was a 2-year-old boy diagnosed with moderate-to-severe pulmonary stenosis and mild pulmonary regurgitation. His original diagnosis was TA with multiple VSDs at birth. Total correction was performed with a handmade monocusp in an expanded polytetrafluoroethylene (ePTFE) conduit on day 3. His pulmonary stenosis and regurgitation deteriorated over time as the monocusp in the ePTFE stiffened conduit. He underwent re-RVOTR under cardiopulmonary bypass at 2 years and 11 months. The former ePTFE conduit was resected and a 16 mm BJV graft (Contegra) was inserted between the RV and PA. The patient presented with high fever on postoperative day 6. Blood and drainage effusion cultures were all positive for *S. lugdunensis* and prescribed with Vancomycin. Echocardiography showed vegetation at the BJV. Re-re-RVOTR was performed 51 days after re-RVOTR. In the operation, vegetation was adhered to the right-sided leaflet and three leaflets were degenerated. After complete BJV graft resection, an ePTFE conduit with tri-leaflets was implanted. The patient did not show signs of recurrent infection 8 months after the surgery.

Therefore, the overall endocarditis findings including incidence rate and risk factors reported in this series of literature reviews are not newly identified or unexpectedly high safety events, particularly considering the previously reported increased risk of endocarditis over time.

Thrombosis, Dissection, and Pseudo-aneurysm
(Case Report (n=1) and Retrospective studies (n=3))

Ortega-Loubon et al.[10] report a ten-year old female with TA type 2 who presented acute symptoms of asthenia, tachypnea, diaphoresis, systolic and diastolic murmur, hepatomegaly, and pedal edema. The patient had been implanted with a 12 mm Contegra conduit at neonatal age, and the implant was replaced by a 16 mm implant at 2 years of age due to growth. The patient remained asymptomatic for 8 years until an echocardiography indicated the conduit 20 mm Hg stenosis and regurgitation, dilated right ventricle, severe dysfunction (TAPSE 7 mm), and image compatible with mural thrombus (3x2 cm) in the RVOT confirmed by angio-computed tomography. An emergency surgery under cardiopulmonary bypass was conducted. The conduit showed intimal disruption with intramural thrombus and endothelial calcification and was replaced by an 18-mm Hancock conduit. Microscopic analysis of the specimen revealed structured thrombotic material with calcifications and neo-vascularization. The post-operative was uneventful, and the patient was discharged with a slightly hypertrophic right ventricle, better systolic function (TAPSE 12 mm), and acceptable gradient in the Hancock conduit.

The authors conclude that valve thrombosis is likely very rare and may have resulted from neointimal

proliferation causing occlusion of the conduit and dissection of the distal anastomosis.

The Jewgenow et al.[5] also investigated the development of thrombus as a potential source of life-threatening IE in a series of 47 bio-prosthetic implants. Presence of thrombus material at the basis of semilunar valve sinuses was observed in 91.3 % (21/23) in Hancock, 100 % (7/7) in homografts, 100 % (7/7) in Contegra, 100 % (7/7) in Melody valves, and 66.6 % (2/3) in Other specimens. Antiplatelet and anticoagulant treatment was conducted in 13 patients. Forty-four of the 47 specimens presented superficial apposition of thrombotic material. However, there was no clinical or echocardiographic suspicion of valve thrombus formation in any of these patients prior to implant explant and histopathological examination.

The study reports high prevalence (44/47, 93.6 %) of *subclinical* thrombus formation at the sinus of the valve cusps diagnosed by histopathological analysis of explanted valved pulmonary conduits. Despite the mentioned thrombus material at the valve cusps, only specimens from patients with endocarditis presented additional vegetation material at the conduit. These data are consistent with earlier reports from Schoen[16] and Makkar et al.[17] in the literature.

In a retrospective study, Falchetti et al.[2] report 3/30 (10 %) Contegra patients with valve thrombosis at 5.9 years follow-up, and none were observed in the homograft cohort (p=0.11), without the need for early re-operation (and no case of proximal dilatation). In another retrospective study reported in the past PAC literature review, the thrombosis rate in Contegra patients was reported 3.3 % (2/60) at a mean follow-up of 29 days, compared to 0 % (mean follow-up: 14 days) in the homograft group (Poinot et al.[18] 2018). Also, Nichay et al.[14] previously reported a range of 0 % (Contegra) to 4.3 % (other xenograft types) at a median follow-up of 4.2 years.

Only a case (1/55, 1.8 %) of pseudo-aneurysm treated with a vascular plug in a Contegra conduit was reported by Buckley et al.[1] No additional details about this case were provided. None of the patients treated with the other devices (n=161) in this study developed pseudo-aneurysm. No other cases of pseudo-aneurysm were reported in this literature review comprising 711 pediatric patients implanted with Contegra.

Importantly, factors affecting the results for thrombus formation occurrence across literature may be differences of diagnosis criteria for thrombosis (i.e., clinical vs. histopathological) and follow-up time (i.e., days vs. years).

Mortality and Perioperative Complications
Retrospective Studies (n=4)

Buckley et al.[1] conducted a retrospective 15-center analysis in 216 patients with TA between 2009 and 2016 to determine risk factors for late mortality and RV-PA conduit re-intervention.

Patients excluded from the analysis were those who had undergone pulmonary artery banding, but died before repair, those with hemi- or pseudo-truncus, and patients who had concomitant repair of TA and interrupted or obstructed aortic arch. Patient population median age at surgery was 10 days (25 % to 75 % percentile, 7 to 23 days), and the median follow-up was 2.9 years (range 0.1 to 8.8). Ninety-six percent (207 patients) were diagnosed with 22q.11 deletion, and (29 %, 61 patients) were diagnosed with DiGeorge syndrome. The RV-PA conduit type included Aortic Allograft, Pulmonary allograft, Contegra conduit, and Other/none of which 102 (53 %) underwent re-intervention. RV-PA conduit types in patients

with Pulmonary, Aortic, and Contegra, were compared by using X^2, Fisher's exact test, or Kruskal-Wallis tests for conduit characteristics, follow-up duration, and performance timing for re-operation.

Most patients (191, 88 %) in the study received pulmonary allografts, aortic homografts, and Contegra conduits. Thirty-seven patients (17 %) underwent concomitant truncal valve surgery. Ten percent of the post-operative cohort received extra-corporeal membrane oxygenation (ECMO).

When including treatment methods (allografts, aortic homografts, and Contegra conduits), there were 201/216 (93 %) patients who survived the surgical procedures, and 29 expired in the study. Fifteen (7 %) patients died perioperatively and 14 (6.5 %) patients were late deaths (median of 8.3 months, range 2.5 to 77.9 months). Late mortality was defined as death that occurred after hospital discharge and is greater than 30 days after surgery. The Kaplan-Meier survival curve indicated that 71 % (10 patients) of late deaths occurred within 12 months after surgery including but not limited to those using Contegra conduits (Figure 1).

Number at risk

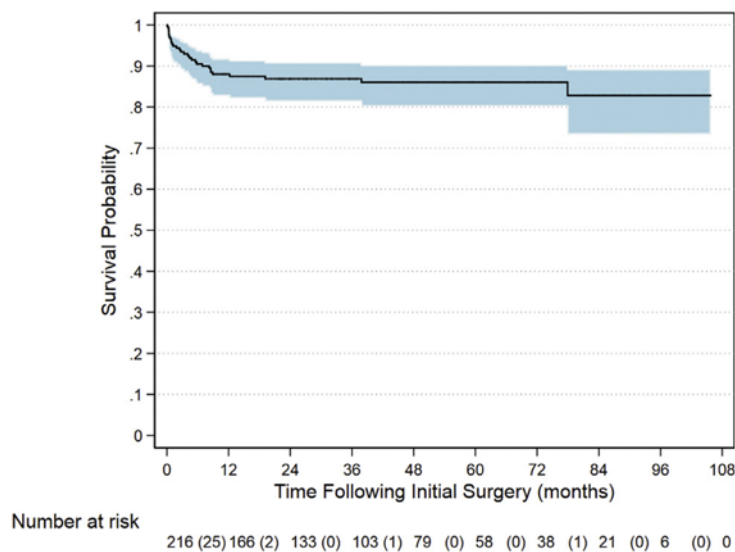216 (25) 166 (2) 133 (0) 103 (1) 79 (0) 58 (0) 38 (1) 21 (0) 6   (0) 0

Fig 1. Kaplan-Meier survival curve after repair of truncus arteriosus (including but not limited to patients receiving Contegra conduits). Number at risk are provided at each 12-month time point, with number of mortalities during each time interval provided in parentheses. There were 29 deaths, 14 of which were late deaths. Most late mortality (n ¼ 10 [71%]) occurred within the first 12 months after surgical repair.

Comparative analysis of patients who died after discharge with those who survived, indicated that DiGeorge syndrome, pre-operative mechanical ventilation, un-planned re-operation, and tracheotomy were significantly more common in the late mortality group of patients. Late mortality rates in the study were 17% and 50% for patients with DiGeorge syndrome and tracheostomy, respectively. Cox regression analysis indicated that DiGeorge syndrome (hazard ratio (HR): 5.4 (95 % CI: 1.6–17.8)) and tracheotomy at discharge (HR: 5.9 (95 % CI 1.8–19.4)) were risk factors for late mortality (p-value: 0.006 and 0.003, respectively). In contrast, center volume, concomitant valve operation at the initial repair, and residual valve insufficiency were not associated with late mortality.

Falchetti et al.[2] consists in a retrospective, single-site study conducted between 1992 and 2014 that compared outcomes of 12 mm diameter Contegra conduits with those from 9-14 mm homografts for reconstruction of the RVOT. Freedom from event (death or re-intervention) was calculated by Kaplan-Meier, and for intergroup comparisons, log-rank test was conducted.

A total of 53 newborns (Contegra: 30, homograft: 23) participated in the study. CHD distribution for Contegra and homograft implantation was balanced. Patient mean age at the surgery was 15 ± 8 days (range 3-30 days) in the Contegra, and 10 ± 7 days (range 1-30 days) in the homograft group. Median weight was 3.3 ± 0.6 kg in Contegra, and 2.8 ± 0.5 kg in the homograft group. Z-score was for the implants was 2.9 and 2.5 for Contegra and homografts, respectively. Mean follow-up was 121 months ±74 months. Only two (6.7 %) patients in the Contegra group were lost of follow-up in the study.

Nakata index was calculated for each patient to manage over the threshold of 170 mm/m^2 if observed correlation between the indexed surface area of pulmonary arteries and degradation of the conduit. Low Nakata index was determined in 47 % in Contegra and 39 % in homograft groups. In the Contegra group proximal anastomosis was completed without the use of any additional prosthetic material while in the pulmonary homograft group, glutaraldehyde autologous pericardial patch was concomitantly used. Z-score mismatch between conduit size and valve size was considered ideal between +1 and +3. Oversized conduits (z-score > +3) was determined in 11 Contegra (37 %) and 10 (43 %) homograft conduits. Conduit gradient was considered significant if >50 mm Hg, moderate if between 50-15 mm Hg, and negligible if <15 mm Hg. Conduit failure and early replacement were defined as the need of graft replacement within 24 months surgery. Indications for replacement were severe stenosis or regurgitation associated with conduit functional degradation, right ventricular enlargement, or arrhythmias.

Overall mortality was 16.6 % and 17.4 % in Contegra and homograft groups, respectively. All deaths occurred within 6 months after intervention. Survival free from re-operation of homograft and Contegra, (Figure 1).
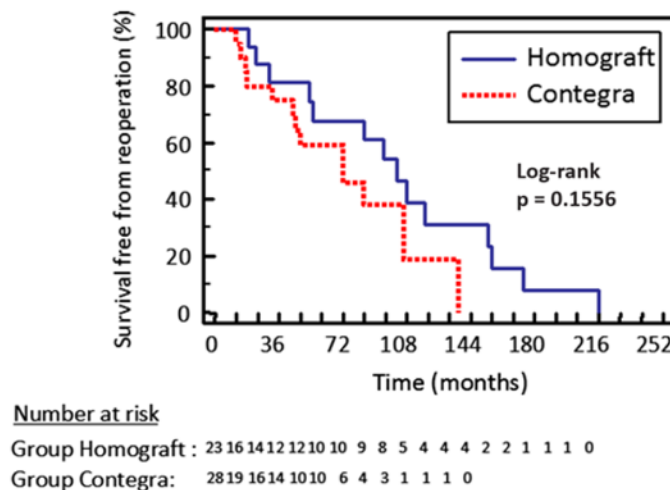

Figure 3. (Colour online) Actuarial Kaplan–Meier curve for survival free from reoperation of pulmonary homograft (blue line) compared with Contegra (red line).

Early conduit failure requiring re-operation was observed in 13 % Contegra and 14 % homografts patients within 24 months post-device implantation.

Early and late morbidity were similar between both cohorts. Some degree of regurgitation was also observed in 19 (63 %) Contegra patients, and 17 (73 %) in the homograft group.

The authors conclude that Contegra 12 mm is an alternative to small pulmonary homografts (commonly

unavailable) in newborn patient population. The presence of severe early gradient did not increase the rate of early re-operations. Interestingly, multivariate analysis showed a significant association between early severe gradient and survival-free from re-operation. Reasons for graft failure in the Contegra group were: distal stenoses at 14 and 17 months after surgery (2 cases), proximal stenosis at 18 months after surgery (1 case), and stenosis at the pulmonary artery bifurcation with regurgitation at 12 months post-operatively (1 case).

Patel et al.[7] also report 7/276 (2.5 %) early postoperative deaths. The proportion of early mortality was highest in the youngest group (9 %, 0 %, and 1% for Groups 1, 2, and 3, respectively, p < .001). Of the 6 patients in group 1, 3 died early and required extracorporeal membranous oxygenation (ECMO) for post-cardiotomy low cardiac output syndrome. These early deaths in group 1 were due to sepsis. The sole early death in group 3 was due to postoperative coagulopathy. An additional 7 (2.8 %) patients expired after hospital discharge at a median interval of one year postoperatively. Late mortality was 5 %, 2 %, and 2 % for Groups 1, 2, 3, respectively. Ten-year survival by age-group was 85 %, 97 %, and 98% for Groups 1, 2, and 3, respectively (p < .001). Pneumonia was the leading cause of late death. Other causes included meningitis, cardiac arrest, and postoperative complications after mitral valve operation.

Postoperative complications were more common in Group 1 (28 %) compared to Groups 2 (11 %) and 3 (4 %). Requirement of ECMO (11) and mediastinal exploration (5) were the two most common early complications for Group 1. Four patients required mediastinal exploration for hemorrhage while on ECMO. Complications for group 2 patients included re-exploration for bleeding (2 %), chylothorax (3 %), and heart block requiring a permanent pacemaker insertion (2%). In Group 3, one patient required re-exploration for bleeding.

The authors evaluate the mid- to long-term outcomes and experience of BJVC for RVOT reconstruction in their institution. The highest early mortality (9 %) as well as late mortality (5 %) were observed in the youngest group of patients (0-1 year old).

Lueth et al.[6] conducted a single-center retrospective chart review of 101 patients aged 0 to 18 years undergoing BJV (supported or unsupported) placement. The purpose of the study was to compare the clinical outcomes and echocardiographic valve performance between the sBJV and uBJV versions of the BJV. The median time from implant to most recent echocardiogram, last study prior to valve intervention, valve replacement, or patient death was 3.8 years for the uBJV group and 4.0 years for the sBJV group (p = 0.50). Four patients (4/101, 3.9 %) in the study died at 0.1, 0.3, 0.4, and 3.8 years follow-up. No deaths were conduit-related. Valve type was not associated with mortality.

Explantation, Reintervention, Stenosis, and Calcification
Retrospective Studies (n=3)

In Patel et al.[7]'s study, 49/276 (18 %) Contegra patients required BJVC replacement once, and one patient required BJVC replacement twice. Five-year survival without conduit explantation was higher in the older age group (53 %, 89 %, and 94 % for Groups 1, 2, and 3, respectively). Ten-year survival without conduit explant was 15 %, 62 %, and 77 % for Groups 1, 2, and 3, respectively. Indications for conduit replacement included endocarditis, conduit stenosis and/or regurgitation (as combined cause of reoperation), distal conduit stenosis, branch PA stenosis, and cardiac transplantation. Time between catheter-based intervention and conduit explant ranged from 10 days to 10 years (median: 7 months (IQR range: 3-17 months)). Twenty-two patients required only a catheter-based procedure on their

conduit (2, 10, and 10 for Groups 1, 2, and 3, respectively).

The authors also conducted histopathologic examinations of 29 of 51 (57 %) explanted conduits. The most common pathological findings were fibrosis (10/29, 34.4 %), diffuse calcification (10/29, 34.4 %), chronic inflammation (5/29, 17.2 %), and focal calcification (5/29, 17.2 %). Only 2 of the 29 explants had actual leaflet calcification (both in Group 2).
Patel and colleagues report conduit dysfunction commonly requiring re-intervention. Mean time for occurrence by age-group was 4.8, 9.0, and 11 years for Groups 1, 2, and 3, respectively (P < .001). The mean time to conduit failure by age-group was 5.2, 9.9, and 11 years for Groups 1, 2, and 3, respectively (P < .001).

Buckley et al.[1] report 109 (~50 %) patients experienced RV-PA catheterization or surgical re-intervention (median time of 23 months, range 0.3 to 9.3) after repair. Follow-up of patients implanted with the different conduit types was reported as statistically similar, but Contegra conduit resulted in fewer re-interventions. Conduit intervention was balloon angioplasty in 19 patients, balloon angioplasty with stent in 30 patients, placement of vascular plug for conduit aneurysm in 1 patient, conduit patch in 1 patient, and replacement in 58 patients. Contegra bovine jugular vein conduits reported significant lower probability of re-intervention than pulmonary (38 % vs. 58 %, p=0.02) independently of conduit diameter. Relationship between conduit size and need for conduit re-intervention was also analyzed. Probability of smaller conduit diameters (<45 mm/m^2) at the initial repair compared with larger conduit diameters correlated with higher risk for early re-intervention during the follow-up period (Figure 2).
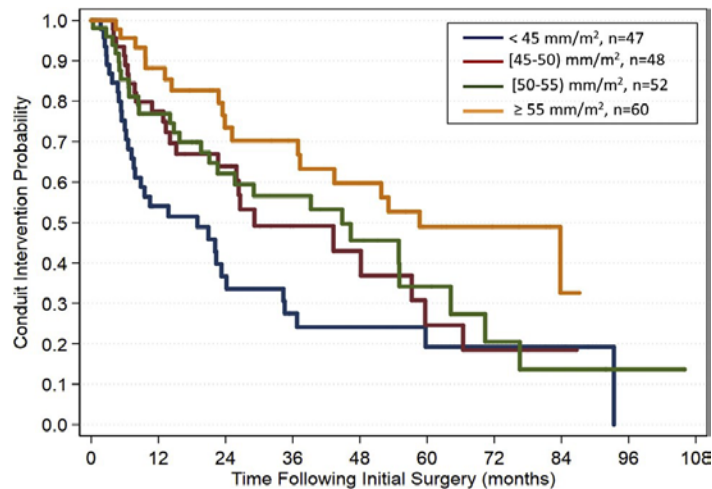

Figure 2. Probability of RV-PA conduit intervention. Contegra bovine jugular vein conduits (green) had a lower probability of intervention compared with pulmonary (blue) and aortic (red) homografts, accounting for the competing risk of mortality over time (p < 0.02).

In Lueth et al.[6]'s study, 11/101 (10.8 %) patients underwent catheter-based interventions, and 25/101 (24.8 %) patients experienced conduit replacement. The most common indication for conduit replacement were stenosis alone (n=8) and a combination of stenosis and regurgitation (n=8). There were no differences in valve intervention or replacement rates between valve type (median follow-up 3.6 years). At 6- and 12-month follow-up, the sBJV group exhibited a slightly higher gradient of stenosis than the uBJV group (33 % vs. 31 %). There were no other differences in stenosis at any other follow-up

time.

As part of the findings, Jewgenow et al.[5] report the presence of histopathological neo-stenosis and new-endothelization in the totality of the conduit walls and valve cusps of the 47 specimens studied (23 Hancock, 7 homografts, 7 Contegra, 7 Melody, and 3 Other valved implants) for the RV-PA position. Graft stenosis/obstruction was the leading cause for conduit explant (44/47, 93.6 %) and valve insufficiency was displayed in 11/47 (23.4 %) conduits. Pulmonary stenosis was the indication for explantation in 85.7 % (6/7) of the Contegra conduits.

Truncus Arteriosus Correction
(Case Report (n=1)

Toma et al.[11] report a 12-month-old male diagnosed with TA Type-I by echocardiography. The patient was admitted with respiratory distress, cyanosis, difficulty in breathing, tachypnea, poor feeding, and failure to thrive. Clinical examination revealed 90/48 mm Hg blood pressure, loud and single second sound heart and systolic murmur (3/6) at the lower left sternal border, hepatomegaly (~ 2 cm below the right costal margin), 6.5 kg (80% of the expected weight), 94% peripheral oxygen saturation, 70 respirations/min, and 150 beats/min. The hemoglobin was 12.2g/dL and the hematocrit 34%. The electrocardiogram showed peaked P wave and bi-ventricular hypertrophy. A chest X-ray showed cardiomegaly with enlarged right cardiac cavities and increased pulmonary vascular markings. The echocardiography exhibited characteristic features of TA with a single arterial stem resulting in a pulmonary trunk and normal-size pulmonary arteries, and a large ventricular septal defect with R/L shunt. In addition, it was observed quadricuspid truncal valve with mild regurgitation. The coronary arteries and aortic arch were normal. The CT scan confirmed TA Type-I diagnosis. Cardiac catheterization demonstrated a mean pulmonary artery pressure of 47 mm Hg, reactive PVR (3.82 UW/m^2-atmospheric air and 2.25 W/m^2 after administration of nitric oxide), which indicated the need of surgical correction. TA repair consisted in correction of the ventricular septal defect, restoration of the right ventricle and pulmonary artery continuity with a 15 mm Contegra conduit, and separation of the pulmonary arteries from the primitive TA. The surgery was uneventful. Post-operatively, the patient presented symptoms of low cardiac output due to bi-ventricular dysfunction that required the use of inotrope agents, nitric oxide, and a phosphodiester type 5 inhibitor for the pulmonary artery hypertension (PAH). The patient was discharged 20 days after surgery with a 12 mm Hg gradient in the pulmonary bio-prosthesis, mild aortic regurgitation, a small residual interventricular septal shunt, and mild tricuspid valve regurgitation (gradient 40 mm Hg). Echocardiography conducted at 1 year after cardiac surgery showed good bi-ventricular function, and no signs of PAH.

Evidence Assessment

Overall, there were no new safety events identified, and/or change in their incidence or severity. The current systematic literature review reflects the post-market reported safety data of the Contegra device for use in pediatric patients.

The evidence derived from this systematic literature review has some limitations that need to be considered when interpreting the findings. The literature search identified 4 case reports and 7 retrospective studies. The evidence provided is not of the highest scientific quality compared to controlled clinical trials and may be subject to potential biases and confounding. Examples of this are:

retrospective nature of the studies, single site studies, insufficient/incomplete patient demographic data, combined use of device types and mixed patient populations (pediatric and adults), and differences in the length of follow-up. Lack or insufficient balance for differences in covariates can introduce biases on the assessment of device performance and/or safety outcomes.

In addition, changes in the standard of care, technological advances, and complexity of medical therapies and procedures over time (1977 to 2017) may impact the conclusions from retrospective studies.

Finally, the same search terms as in previous searches were used for consistency and reproducibility. There is the possibility that other descriptive search terms for the device may have resulted in different publications, which could cause unintended missed articles.

Conclusions Based on the Literature Review

Review of the literature published between 06/01/18 and 05/31/19 revealed the following observations:

☐ Published literature reported comparable risk of post-operative mortality for patients undergoing replacement with Contegra or pulmonary homograft to be (16.6 % vs. 17.4 % within 6 months post-intervention). The incidence of late mortality was 17 % (Contegra and homografts) and reached 50 % in DiGeorge pediatric patients and tracheostomy after congenital heart surgery. The post-operative mortality was greater in younger Contegra patients. Late mortality remains high in the first year after surgical repair although it remains considerably lower than the absence of intervention and comparable alternative treatments of congenital cardiovascular conditions.

☐ There were no significant differences in the incidence of early conduit failure requiring re-operation/explant comparing Contegra with homografts (13 % in Contegra and 14 % in homografts). Device failure incidence may depend on the root cause of the adverse event (e.g., stenosis, thrombosis, etc.). Contegra bovine jugular vein conduits demonstrate significant lower probability of re-intervention than pulmonary homografts (38 % vs. 58 %, p=0.02) independent of conduit diameter in one article.

☐ The rate of endocarditis in the Contegra group in the retrospective studies ranged from 1.8 % (1/55, median follow-up: 2.9 years) to 14.3 % (1/7, mean implantation time: 5.6 years) and was seen associated with the length of conduit implantation. These results are consistent with previously reviewed studies in the literature (1.2 % (2/162) at median follow-up of 2.9 years[19]; 10 % (25/253) at a median follow-up of 7.5 years[15]).

The 4.7 % (5/106) bacterial endocarditis rate in Contegra grafts at a mean follow-up of 3.1 years was lower compared to 20.6 % (6/29) for Melody valve, suggesting that biological materials might be associated with an increased risk for bacterial endocarditis. Most commonly observed bacteria associated with endocarditis were *Streptococcus parasanguinis, Streptococcus lugdunensis,*

Staphylococcus aureus, and *Lactobacillus*, and A*biotrophia.*

Survival-free from IE for Contegra and homograft were similar at both, 1 year and 5 years after implant.

☐ Significantly higher incidence of subclinical thrombosis (44/47, 93.6 %, mean implantation time: 5.6 years) compared with control native pulmonary valves from pigs (0/5, 0 %) was detected by histopathological analysis in explanted conduits with no clinical and echocardiographic signs of valve thrombosis observed in the patients.

SUMMARY

The FDA did not identify any new unexpected risks during this review of the MDRs received and the literature published since our last report to the PAC. The FDA believes that the HDE for this device remains appropriate for the pediatric population for which it was granted.

The FDA recommends continued routine surveillance and will report the following to the PAC in 2020:

☐ Annual distribution number
☐ MDR review and
☐ Literature review

REFERENCES

1. Buckley JR, Amula V, Sassalos P, et al. Multicenter Analysis of Early Childhood Outcomes After Repair of Truncus Arteriosus. *The Annals of thoracic surgery.* 2019;107(2):553-559.

2. Falchetti A, Demanet H, Dessy H, Melot C, Pierrakos C, Wauthy P. Contegra versus pulmonary homograft for right ventricular outflow tract reconstruction in newborns. *Cardiology in the young.* 2019;29(4):505-510.

3. Groning M, Tahri NB, Sondergaard L, Helvind M, Ersboll MK, Orbaek Andersen H. Infective endocarditis in right ventricular outflow tract conduits: a register-based comparison of homografts, Contegra grafts and Melody transcatheter valves. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2019.

4. Haas NA, Bach S, Vcasna R, et al. The risk of bacterial endocarditis after percutaneous and surgical biological pulmonary valve implantation. *International journal of cardiology.* 2018;268:55-60.

5. Jewgenow P, Schneider H, Bokenkamp R, et al. Subclinical thrombus formation in bioprosthetic pulmonary valve conduits. *International journal of cardiology.* 2019;281:113-118.

6.   Lueth ET, Gist KM, Burkett DA, et al. A Retrospective Comparison of the Supported and Unsupported Bovine Jugular Vein Conduit in Children. *The Annals of thoracic surgery.* 2019.

7.   Patel PM, Tan C, Srivastava N, et al. Bovine Jugular Vein Conduit: A Mid- to Long-Term Institutional Review. *World journal for pediatric & congenital heart surgery.* 2018;9(5):489-495.

8.   Hirose K, Ikai A, Nagato H, et al. A pediatric case of Staphylococcus lugdunensis-induced infective endocarditis at bovine jugular vein. *The Annals of thoracic surgery.* 2019.

9.   Olivella A, Pizzi MN, Dos-Subira L, et al. Right-sided endocarditis on Contegra tube in a complex cianotic congenital heart disease. *Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology.* 2019.

10.   Ortega-Loubon C, Fernandez-Doblas J, Perez-Andreu J, Fernandez-Molina M, Siliato MS, Abella RF. Late Dissection of a Contegra Conduit: A Rare Complication. *World journal for pediatric & congenital heart surgery.* 2019;10(2):239-241.

11.   Toma D, Șuteu CC, Togănel R. Favorable postoperative evolution after late surgical repair of truncus arteriosus type 1: A case report. *Journal of Interdisciplinary Medicine.* 2018;3(2):110-113.

12.   Van Dijck I, Budts W, Cools B, et al. Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants. *Heart.* 2015;101(10):788-793.

13.   Jalal Z, Galmiche L, Lebeaux D, et al. Selective propensity of bovine jugular vein material to bacterial adhesions: An in-vitro study. *International journal of cardiology.* 2015;198:201-205.

14.   Nichay NR, Zhuravleva IY, Kulyabin YY, et al. In search of the best xenogeneic material for a paediatric conduit: an analysis of clinical data. *Interactive cardiovascular and thoracic surgery.* 2018;27(1):34-41.

15.   Beckerman Z, De Leon LE, Zea-Vera R, Mery CM, Fraser CD, Jr. High incidence of late infective endocarditis in bovine jugular vein valved conduits. *The Journal of thoracic and cardiovascular surgery.* 2018;156(2):728-734.e722.

16.   Schoen FJ. Approach to the analysis of cardiac valve prostheses as surgical pathology or autopsy specimens. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology.* 1995;4(4):241-255.

17.   Makkar RR, Fontana G, Jilaihawi H, et al. Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves. *The New England journal of medicine.* 2015;373(21):2015-2024.

18.   Poinot N, Fils JF, Demanet H, Dessy H, Biarent D, Wauthy P. Pulmonary valve replacement after right ventricular outflow tract reconstruction with homograft vs Contegra®: a case control comparison of mortality and morbidity. *Journal of cardiothoracic surgery.* 2018;13(1):8.

19.   Nichay NR, Zhuravleva IY, Kulyabin YY, et al. In search of the best xenogeneic material for a paediatric conduit: An analysis of clinical data. *Interactive cardiovascular and thoracic surgery.* 2018;27(1):34-41.