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 20, 2018, Pediatric Advisory Committee Meeting

INTRODUCTION

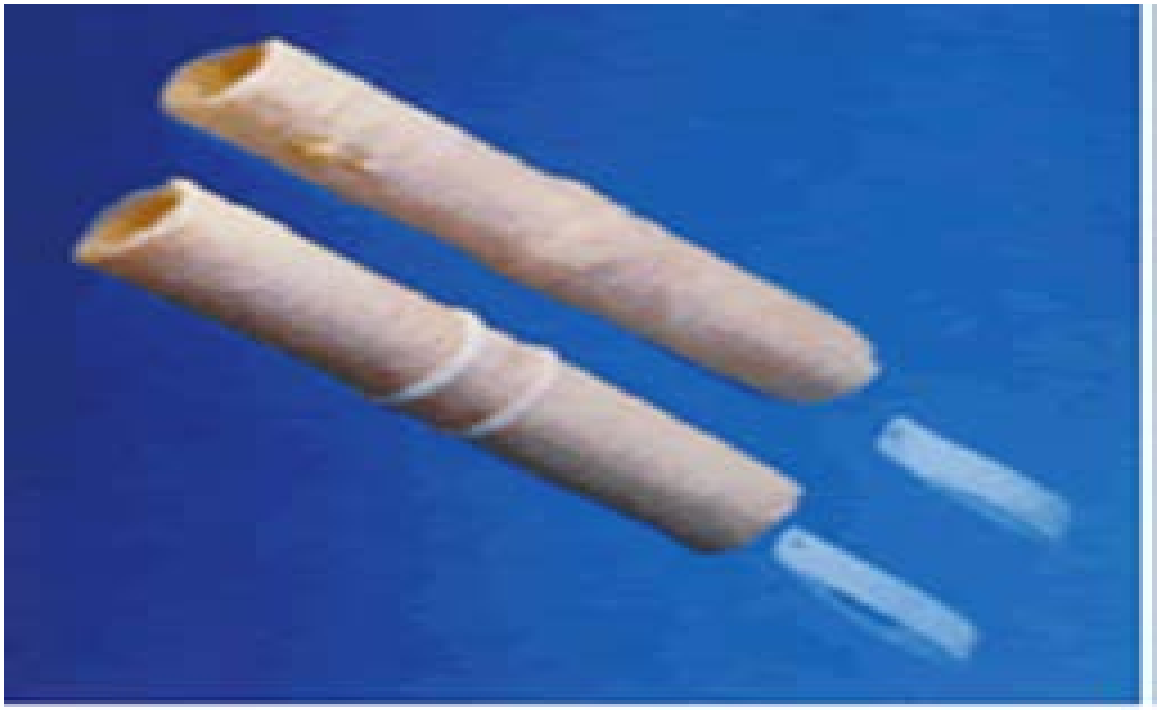
In accordance with the Pediatric Medical Device Safety and Improvement Act, this document provides the Pediatric Advisory Committee (PAC) with post-marketing safety information to support its annual review of the Contegra® Pulmonary Valved Conduit ("Contegra"). The purpose of this annual review is to (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 2015 report to the PAC. It includes data from the manufacturer's annual report, post-market medical device reports (MDR) of adverse events, and peer-reviewed literature.

BRIEF DEVICE DESCRIPTION

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

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



INDICATIONS FOR USE

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

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

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

REGULATORY HISTORY

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

DEVICE DISTRIBUTION DATA

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. However, it is to be noted that unless the sponsor requests to update their ADN based on the 21st Century Cures Act, the ADN will still be based on the previously approved ADN of 4,000. The approved ADN for Contegra is 4000 tests total per year. Since the last PAC review, a total of 459 devices were sold in the U.S., and 284 devices were implanted. At least 269 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 71 MDRs regarding Contegra identified in the FDA's MDR database between June 1st, 2017 and May 31st, 2018. Of these, 52 were identified as unique MDRs, and the remaining 19 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 52 unique MDRs, all submitted by the manufacturer.

Patient Demographic Data

All 52 MDRs were received from the United States (US). Patient gender information is included in 49 MDRs; 25 involved males and 24 involved females. Patient age is included in 50 MDRs; 47 are pediatric patients and 3 are adults. TABLE 1 summarizes this information.

TABLE 1: Patient Demographic Data (Total 52 MDRs; 47 involve pediatric patients)

Demographic Data		**Percentage**	**Number of MDRs containing the demographic**
Reporting Country	US	100%	52 (52 Total)
Patient Gender	Male : Female	51% : 49%	25 : 24 (49 Total)
Patient Age	Pediatric : Adult	94% : 6%	47 : 3 (50 Total)
Pediatric Only Age Range: 1 month to 21 years Average Age: 10.2 ± 5 years			

Reported Events

The 52 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 2018 PAC Review

Primary Reported Event	Total MDR Count	Patient Age (year)			TTEO (month)	
		Pediatric (<22)	Adult (≥22)	Age not reported	Range	Mean
Stenosis	**33**	29	2	2	3 - 159	74
Device replaced (reason not provided)	**12**	12			0 - 78	44
Regurgitation	**2**	2			79 - 129	104
Increased pressure gradient	**2**	1	1		0.3	0.3
Pulmonary edema/hemorrhage*	**1**	1			2	2
Infection/Endocarditis	**1**	1			117	117
Conduit dilation	**1**	1			0.6	0.6
Grand Total	**52**	47	3	2		

***** There was a death reported in this period involving a pediatric patient. The remaining 51 MDRs represent injury events.

A comparison of the primary reported events in the MDRs for the current analysis period with those from 2017's PAC MDR analysis are shown in TABLE 3 below. The total number of MDRs decreased from 84 for the 2017 PAC to 52 for the 2018 PAC. The types of primary reported events are similar, with "Stenosis", "Device replacement" and "Regurgitation" remaining as the most frequently reported events for both years. Although "Pulmonary edema/hemorrhage" was not reported in 2017, the event was deemed to be related to ongoing respiratory support and there were no allegations related to the device.

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

Primary Reported Event	2017 PAC	2018 PAC
	MDR Count (%)	MDR Count (%)
Stenosis	37 (44 %)	33 (63%)
Device replacement (reason not provided)	35 (42 %)	12 (23%)
Valve regurgitation	5 (6 %)	2 (4 %)
Increased pressure gradient	1 (1.2%)	2 (4 %)
Pulmonary edema/hemorrhage	0	1 (2 %)
Infection/Endocarditis	1 (1.2%)	1 (2 %)
Conduit dilation/aneurysm	2 (2.3 %)	1 (2 %)
Arrhythmia	2 (2.3 %)	0
Thrombus	1 (1.2%)	0
Total	**84**	**52**

The primary events reported in the 52 MDRs involving one death and 51 injuries are summarized below.

Stenosis (n=33 MDRs, including 29 pediatric patients)

Stenosis continued to be the most frequently reported event. In these 33 reports, stenosis (in conjunction with calcification, obstruction, pulmonary regurgitation or insufficiency and/or elevated pressure gradients) was identified in patients between 3 and 159 months post implant.

Of the 33 stenosis reports, 3 reflect early and mid-term events (within one year post Contegra implant) in pediatric patients. Two of these 3 events involved infants and both required a surgical replacement with a larger size of pulmonary valved conduit or homograft. For the 3rd pediatric patient, a transcatheter pulmonary valve (TPV) was implanted valve-in-valve due to stenosis. The manufacturer indicated that no conclusion can be made for these 3 events, as the Contegra devices were not returned for evaluations. The other 30 reports (including 26 pediatric patient events) citing stenosis involved late events (greater than one year post Contegra Implant). These reports indicated that the patients required interventions due to stenosis between 1.1 to 13.3 years post implant without additional adverse effect reported.

Overall, the interventions required for the 33 patients with stenosis included TPV implant (19) and surgical replacement of pulmonary valve (14).

Device replacement[1] – reason not reported (n=12 MDRs; 12 pediatric patients)

Twelve MDRs involving pediatric patients indicate that Contegra was replaced within 6.5 years post implant. Although the exact reasons for the device replacement were not provided in the MDRs, in 3 reports, Contegra was explanted and replaced with a different size of the device peri-operatively (1 MDR) or 3 months post implant (2 MDRs). In the remaining 9 MDRs, limited information was provided despite the manufacturer's attempts to obtain more information. There were no failure mechanism nor other adverse effects reported in the MDRs.

Valve regurgitation (n=2 MDRs, 2 pediatric patients)

Both MDRs involved pediatric patients who required a TPV valve-in-valve implantation to replace the Contegra device between 6.5 and 10.8 years post implant due to pulmonary regurgitation secondary to Tetralogy of Fallot. No additional adverse patient effects were reported.

Increased pressure gradients (n=2 MDR; including 1 pediatric patient)

Two MDRs noted increased pressure gradients (one pediatric and one adult patient). The pediatric patient presented with progressive fatigue and exercise intolerance after an unspecified period post Contegra implant. Echocardiogram showed a peak pressure gradient of 90 mmHg. The patient was

[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.

treated with conduit dilations, stent implants and a TPV valve-in-valve implantation and no adverse patient effects were reported. In the adult patient, the Contegra device was explanted 10 days post implant due to high pressure gradients and a residual ventricular septal defect. The Contegra device was replaced with another valved conduit and there were no allegations against the valve or its function.

Pulmonary edema/hemorrhage (n=1 MDR; involving a pediatric death)

A 10-month old patient had pulmonary edema and hemorrhage 9 weeks post Contegra implant and subsequently expired due to ongoing issues with respiratory support and pulmonary edema/hemorrhage. According to the manufacturer, no allegations were made relating the valve or its function to the death. Neither autopsy results nor explant information was provided despite multiple attempts by the manufacturer to gather additional information. No definitive conclusion could be drawn regarding the event.

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

A 21-year old patient developed endocarditis about 9.8 years post Contegra implant. Bacteremia was identified by blood cultures and the patient was treated with long term oral antibiotics. The Contegra device remained implanted. No additional adverse patient effects were reported.

Conduit dilation (n=1 MDR; involving a pediatric patient)

An infant was implanted with a Contegra valved conduit as part of a truncus repair. An echocardiogram showed the device was dilated and was impacting flow to the pulmonary arteries. The device was explanted and replaced with an aortic homograft, in conjunction with a patch angioplasty of the left pulmonary artery. No other adverse effects were reported. The manufacturer reported that despite multiple attempts, the product was not returned and no additional information was provided, hence no definitive conclusions could be drawn regarding the event.

Conclusions Based on the MDR Review

1. Most of the MDRs received in this reporting period reflect peri-operative and mid- to long-term events which are known complications or associated with 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 pediatrics.

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 2017 literature review. The search was limited to articles published in English from 06/01/2017 through 05/31/2018.

Figure 1 depicts the article retrieval and selection process including the criteria for exclusion. A total of sixty-nine (69) (twenty (20) Pubmed and forty-nine (49) Embase) articles were retrieved. Seventeen (17) articles were duplicates. The remaining fifty-two (52) articles were subjected to review of titles and abstracts. Thirty-one (31) articles were excluded from full-text review for reasons listed below:

Four (4) articles on animal study**,** five (5) articles on *in-vitro* study/biomarker, six (6) articles on conference abstract/poster, six (6) letters to the Editor, one (1) article previously reviewed and presented, and nine (9) articles on the Melody valve/percutaneous pulmonary valve implantation (PPVI).

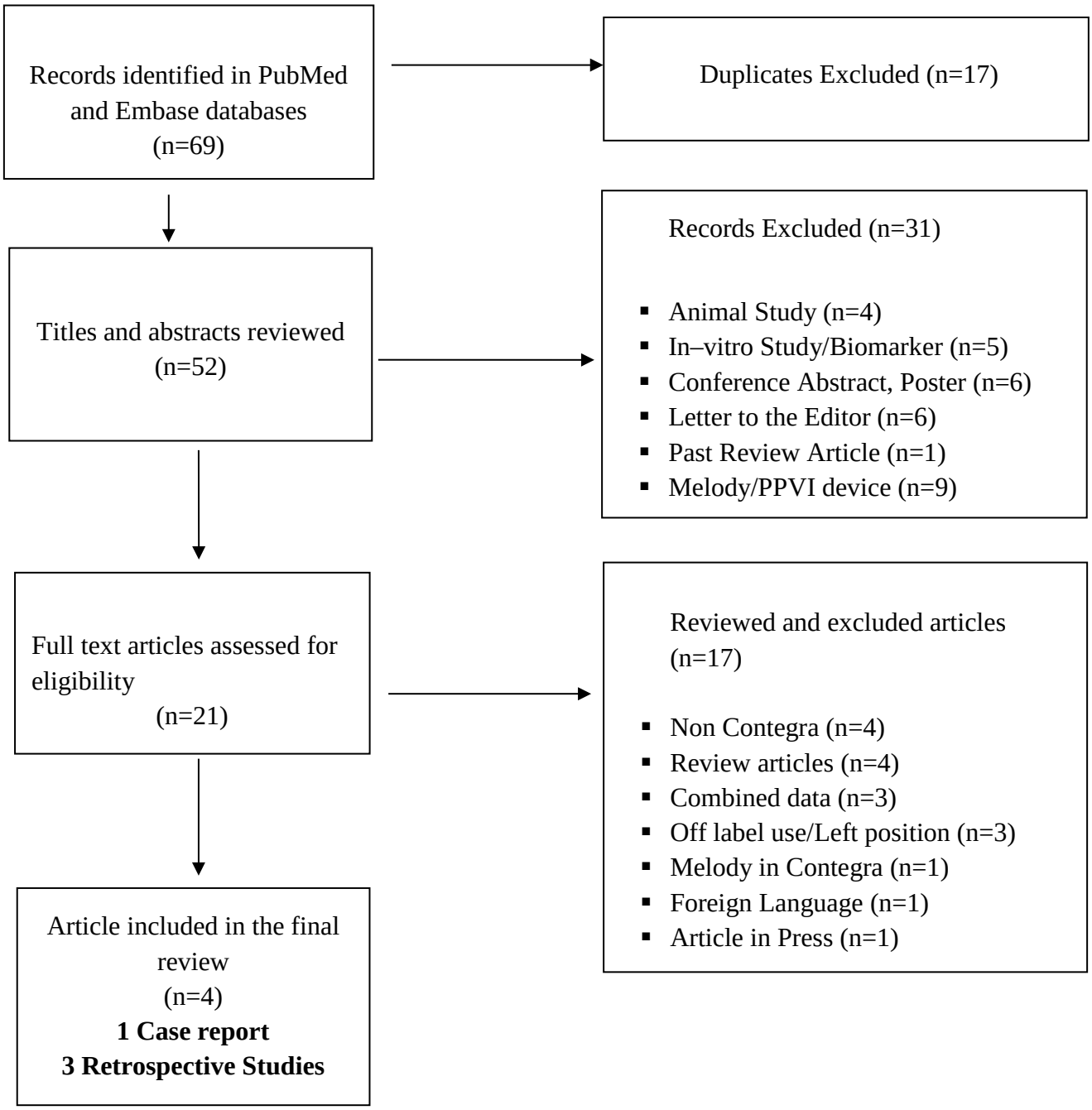
A total of twenty-one (21) articles were retained for full text review. Of these 21 articles, the following additional 17 articles were excluded from further review:

Four (4) articles were on other bovine jugular vein (non-Contegra) devices, four (4) articles were review papers, three (3) articles did not report data specific for Contegra (i.e., Contegra was evaluated with other xenografts but no separate data reported for Contegra), three (3) articles involved off-label use of the device (“left heart” position), one (1) article was about the replacement of Contegra with another device, one (1) article was in press and unavailable for review, and one (1) article in a foreign language. Thus, a total of four (4) articles were retained for the final review and qualitative synthesis**.**

Of note, in addition to the articles retrieved from PubMed and Embase databases, there were nineteen (19) publications identified through the review of the device manufacturer’s adverse event reports submitted through the MedWatch system (MDR reports). Six (6) articles were out of search date, and the remaining 13 articles did not meet the criteria for inclusion and analysis (e.g., absence of Contegra

data, other devices or combination of devices, and citation duplicate). Thus, the articles did not meet the inclusion criteria for this systematic literature review.

Figure 1: Article Retrieval and Selection



Characteristics of Publications Included in Evidence Assessment

There were three (3) retrospective studies and one case report. Of the three retrospective studies one (1) was from the United States (Beckerman et al.), one (1) from Belgium (Poinot et al.) and one (1) from Russia (Nichay et al.). The one (1) case report was from United States (Rao et al.,).

Two (2) retrospective studies (Poinot et al.[2], and Nichay et al.[3]) reported data involving pediatric patients only (n=383). The third study (Beckerman et al.)[4] included predominantly pediatric population and only 6 of 228 patients (2.6%) were above 18 years of age. The mean age at implant for Contegra patients in Poinot et al., study was 7.2 years and the median age at implant in Nichay et al., and Beckerman et al., studies were 1 year (range: 0.5- 2.3 years) and 2 years (range: 15 days to 45 years), respectively.

The sample sizes for Contegra conduits assessed in the articles ranged from 1 (case report) to 484 (retrospective studies). The follow-up duration for Contegra conduits in the three retrospective studies ranged from 3 days to 14 years.

Safety Results Discussion

Case Report (n=1)

Hemolysis

Rao S., et al.[1] reported a case of hemolytic anemia due to calcification and stenosis of a Contegra conduit that was placed in the right ventricular (RV) to pulmonary artery (PA) position. The authors state that although hemolysis is a well-recognized potentially serious complication of left-sided mechanical or bio-prosthetic heart valves, hemolytic anemia in patients with a bio-prosthetic RV to PA-valved conduit has been rarely reported.

The patient was a 4-year old female with a history of truncus arteriosus type 1A who underwent repair at 2 months of age that included atrial and ventricular septal defect closure, and implantation of a 12mm Contegra conduit to the RV- PA. She was well for 4 years after the surgery with no cardiovascular symptoms. A few weeks prior to the current presentation, she started getting tired more easily. There was no history of shortness of breath, syncope, diaphoresis, fever, or dark urine.

On physical examination, there were no significant findings other than a grade IV/VI harsh systolic murmur, best heard at the left upper sternal border, and a palpable liver just below the right costal margin.

Her laboratory tests revealed decreased hemoglobin (from 111 to 75 g/L over a period of 3 months), increased reticulocyte count of 21.9%, increased mean corpuscular volume of 98fl and an increased serum lactic acid dehydrogenase of 1575 IU/L. Peripheral smear showed 5% burr cells and 5% schistocytes, with significant polychromatophilia. The direct antiglobulin test was negative, and total bilirubin was mildly elevated to 1.2 mg/dL, with direct bilirubin at <0.2 mg/dl.

An echocardiogram revealed RV to PA conduit stenosis, and turbulent flow with a peak velocity of at least 3.9 m/s (peak gradient, 61mm Hg). A cardiac computed tomographic angiogram revealed significant conduit calcification with irregularity of the lumen (severely narrowed proximal conduit), and intimal hyperplasia.

In view of the clinical findings (i.e., severe conduit stenosis, calcified conduit, RV hypertension, and hemolysis) the 12mm Contegra conduit was replaced with a 18mm Contegra.
Histology of the stenotic explanted conduit confirmed intimal hyperplasia and calcification. The patient's laboratory results returned to normal three months after the conduit replacement.

Retrospective Studies (n=3)

Mortality and Peri-operative Complications

Poinot et al[2] conducted a retrospective analysis of 82 children (43 boys, 39 girls) who received 87 RV - PA implants (60 Contegra and 27 Homografts) (five patients had multiple procedures) between January 1999 and December 2016. A propensity score was used to match the two groups on covariates: age to replace the conduit, duration of implantation, weight, gender, extra-anatomic and anatomic position of the conduit, post-Ross procedure, and concomitant procedures.

The authors reported low surgical mortality in the two groups. Post-operative death rate was not significantly different between Contegra (2 deaths, 2.37%) and homograft (0 deaths, 0.00%), adjusted p-value = 0.301. The two deaths in the Contegra patients were determined to be not device-related.

Perioperative complications during Contegra or homograft replacement was reported as 13.47% and 15.36%, respectively (p-value = 0.758). Re-entry injuries were reported as the most common complication (n=2 Contegra and n=2 homograft), three of which required emergency conversion to cardiopulmonary bypass. Other reported complications included air embolism (n=2 Contegra), perioperative ventricular fibrillation (n=2 Contegra), allergic reaction to protamine (n=1 homograft), pneumothorax (n=1 Contegra).

Perioperative complications and mortality rates in Contegra and homograft groups were found to be similar by Poinot et al., suggesting that the choice between homograft or Contegra for RVOT reconstruction should not be influenced by the surgical risk during procedure. However, these findings need to be interpreted in the context of the study strengths and limitations. One of the strengths of this study is the fact that propensity scores were used to match the study groups on potential confounders.

However, an important limitation is the retrospective nature of the study design and the small sample size. Retrospective studies may be subject to biases (e.g. patient selection, assessment of exposure and/or outcomes), and due to the small sample size, the study is not powered to assess rare outcomes. Despite these limitations, the findings reported by Poinot et. al. are consistent with findings from published literature, per systematic literature reviews presented at previous PAC annual meetings.

Endocarditis

Beckerman et al[4] evaluated the incidence of late endocarditis in patients implanted with Contegra in the RV-PA position. A retrospective analysis was performed on 228 patients (median age at implant 4 years, range 3 days to 54 years, six patients > 18 years) implanted with 253 Contegra conduits between 2001 and 2017 at a single institution. A sub-analysis comparing the risk of endocarditis between conduits, homografts (pulmonary and aortic), and porcine heterograft (Hancock bio-prosthetic valved conduit) were also included.

After a median follow-up of 7.5 years, 25 Contegra grafts (10%, 25/253) in 25 patients developed endocarditis. Of the 25 patients with endocarditis, 1 patient had a dental procedure prior to the endocarditis diagnosis. Endocarditis was classified as definite in 22 (88%) and possible in 3 (12%) patients, per the Duke modified criteria for endocarditis. The most common infectious agent was streptococci viridans (n=13, 59%). Twenty-three (23, 92%) of the infected Contegra conduit required surgical replacement.

Ten percent (10%, 25/253) of Contegra grafts developed endocarditis compared to 0.8% (4/507) for homografts and 2.9% (5/69) for the porcine heterografts with a median follow-up of 7.5 years. The incidence of endocarditis in Contegra conduit rapidly increased after 7.5 years post implant, whereas no endocarditis was developed in homograft or porcine heterograft conduits. The 10-year rate of freedom from endocarditis for Contegra grafts was 77%, which was significantly lower than homografts or porcine heterografts, as depicted by the graphs below (p-value < 0.001, Kaplan Meier analysis). During the additional follow-up time from 7.5 to 10 years there were no homograft or porcine heterograft conduits that developed endocarditis **(Figure 2**).

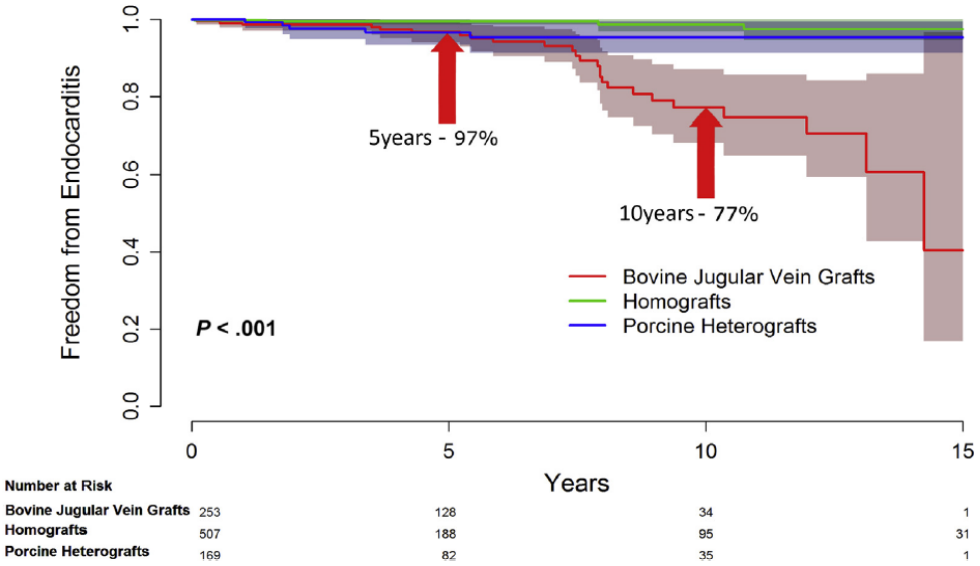


FIGURE 2. Kaplan–Meier curves depicting freedom from endocarditis according to conduit type. Bovine jugular vein grafts had a significantly higher incidence of endocarditis than homograft and porcine heterografts (P<.001). The number of infected bovine jugular vein grafts drastically increase after 7 years of conduit implantation.

Beckerman et al. / The Journal of Thoracic and Cardiovascular Surgery 2018

In a multivariable analysis, Contegra grafts had significant higher risk for developing endocarditis (HR:15.7, 95% CI 4.9 - 50.7) compared to homograft, adjusting for covariates including age, conduit size, syndrome type, and diagnosis (truncus arteriosus, Ross procedure etc.) and initial conduit (yes, no, z-score).

In contrast, Nichay et al[3] reported endocarditis rate of 1.2% (2/162) in Contegra grafts (GA-BJV) during a median follow-up of 2.9 years, which was comparable to the rates for other xenograft types (GA-PVC: glutaraldehyde-treated bovine pericardial valved conduit (2.9%), DE-PAC: diepoxy-treated porcine aortic conduit (0%); and DE-PVC: diepoxy-treated bovine pericardial valved conduit) (3.2%), (p-value=0.43).

The reported endocarditis rate of 10.0% among subjects treated with Contegra grafts, at a median follow-up of 7.5 years is, consistent with other published studies. Albanesi et al.[6] have reported endocarditis rate of 11.3% in Contegra over a median follow-up of 7.6 years, and Ugaki et al[7] also reported 9.4% Contegra infected conduits during a median follow-up of 3.4 years in previous studies. Mery et al.[5] estimated that as many as 17% of patients would develop endocarditis at 10-years post-implantation, and the risk seems to increase with time. Although the incidence of endocarditis in the current literature (Beckerman et al.) is estimated to be 23% at 10 years, it is important to note that the publication by Beckerman et al. included a combined study population of pediatric and adults. Although the number of adult patients was low (6 patients, 2%), these patients may have been implanted over a long period and therefore, longer durability of Contegra conduit in patients could be a predisposing factor for developing endocarditis.

Despite the inherit limitations of the three retrospective studies, similar endocarditis rates have been reported in the published literature, as discussed above. This finding is not a newly identified safety event, and the rate is not unexpected considering the risk of endocarditis increases with time.

Reintervention, Calcification and Stenosis

Nichay et al[3] conducted a retrospective analysis of pediatric patients who underwent RVOT placement with the bovine jugular vein (Contegra), porcine aortic root conduit, and bovine pericardial valved conduit to determine the rate of re-intervention and xenograft calcification. The study was conducted with patients implanted at a single center from August 2000 to August 2016.

A total of 301 patients (age 1 day to 18 years) underwent placement with 337 xenografts including 171 GA-BJV or Contegra grafts, 75 GA-PVC, 58 DE-PAC, and 33 DE-PVC for RVOT reconstruction. The median follow-up for the groups were 2.9, 5.3, 5.7 and 4.4 years for Contegra, GA-PVC, DE-PAC, and DE-PVC, respectively.

A total of 37.2% (116/312) xenografts required 1 or more reinterventions. The most common factor reported as the cause of first reintervention was xenograft stenosis (88%, 103/116). At first reintervention, stenosis was present in 17.3% (28/162) Contegra, which was significantly lower than in GA-PVC (52.2% (36/69)), DE-PAC (64% (32/50)), and DE-PVC (22.6% (7/31)) groups (p-value < 0.001). The rate of freedom from first reintervention was not statistically significant different between the groups, **(Figure 3A)**, below.

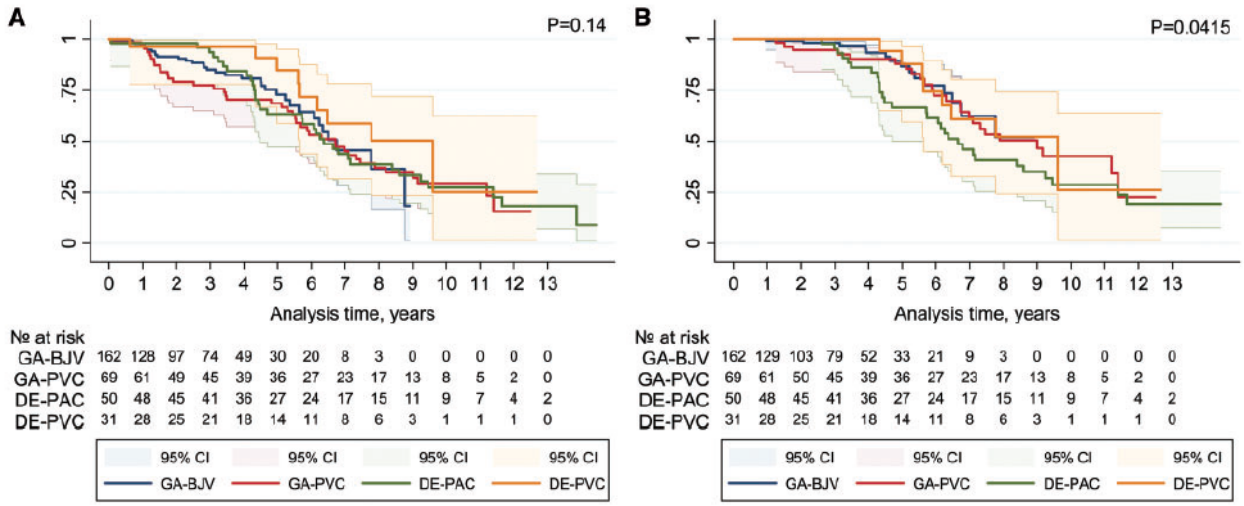


Figure 3: Freedom from xenograft reintervention. **(A)** Freedom from first reintervention by xenoconduit type. **(B)** Freedom from reintervention caused by xenograft calcification. CI: confidence interval; DE-PAC: diepoxy-treated porcine aortic conduit; DE-PVC: diepoxy-treated bovine pericardial valved conduit; GA-BJV: glutaraldehyde- treated bovine jugular vein; GA-PVC: glutaraldehyde-treated bovine pericardial valved conduit.

N.R. Nichay et al. / Interactive CardioVascular and Thoracic Surgery

Further, multivariate regression analysis showed that the type of xenograft was not significantly associated with first reintervention (HR: 1.03, 95% CI: 0.83 - 1.28).

Calcification of the xenograft was identified as the most frequent cause of stenosis (74.8%, 77/103) in this study. The least number of calcified conduits was found in the Contegra group (9.3%, 15/162). The DE-PAC group had the highest proportion of xenograft calcification (60% (30/50). The proportion of calcified conduits for the other xenografts were GA-PVC 34.8% (24/69), and DE-PVC 25.8% (8/31).

The DE-PAC group had the lowest rate of freedom from intervention of 83.7% and 58.8% at 4- and 6-years, respectively. The Contegra group had freedom from reintervention rate of 93.3% and 73.5% at 4- and 6-years, respectively, comparable to the rates in GA-PVC group 90.5% and 73.0%, and in DE-PVC group 94.1% and 67.6% at 4- and 6-year, respectively, **(Figure 3B)**.

Multivariate proportional hazard model also showed the DE-PAC group had risk of calcification 3 times higher than the GA-BJV Contegra group, (HR: 3.20, $p < 0.001$). The Contegra group had risk of calcification comparable to GA-PVC and DE-PVC groups (HR= 1.32, p= 0.36 and HR: 1.16, p = 0.59), respectively.

In the study by Poinot at al[2] described above, calcifications were observed in 48% (29 of 60) of the explanted Contegra, and 52% (14 of 27) of explanted homografts. Stenosis of the conduit with associated valvular insufficiency was identified as the main cause of replacement in the two groups of patients (i.e., 45%, 27 of 60 in the Contegra, and 40.7%, 11 of 27 in the homograft).

The study by Beckerman et al[4] (n=253) reported 5- and 10-year freedom from replacement rate of 84% and 49%, respectively, for the Contegra conduit.

The study by Nichay et al.[3] did not find association between time of first reintervention and the type of xenograft. The risk of calcification in the Contegra group was found comparable to other xenografts such as GA-PVC and DE-PVC. However, the study by Nichay et al. also had limitations including lack of adjustment for potential confounding factors and differences in length of the follow-up period for Contegra, GA-PVC, DE-PAC and DE-PVC groups.

Thrombosis

In the retrospective analysis conducted by Poinot and colleagues of 87 RVOT implants (60 Contegra and 27 homograft), the reported thrombosis rate was 3.3% (2/60) in the Contegra conduit group (mean follow-up of 29 days), and 0% rate in the homograft group (mean follow up 14 days). The Nichay and colleagues' study reported thrombosis rate of 0% in the Contegra xenograft group (n=162, median follow-up of 2.9 years), 4.3% in the GA-PVC xenograft group (n=69, median follow-up of 5.3 years), 0% in the DE-PAC xenograft group (n= 50, median follow-up of 5.7 years), and 0% in the DE-PVC xenograft group (n=31, median follow-up of 4.4 years).

Pseudo-aneurysm

One case of pseudo-aneurysm of the right ventricle was reported by Poinot and colleagues,[2] which led to removal and replacement of the Contegra. There was no pseudo-aneurysm case (0%) reported by Nichay and colleagues[3] in the retrospective analysis of Contegra conduit (n=162) during a median follow-up of 2.9 years.

Evidence Assessment

Overall, the current systematic literature review reflects the safety profile of the Contegra device, when used in pediatric patients, has not changed from that of previous reviews. There were no new safety events identified.

The evidence derived from this systematic literature review has some limitations that need to be considered when interpreting the findings. First, our systematic search of the literature resulted in identification of a case report and three retrospective studies. Such evidence is not of the highest quality as compared to evidence from controlled trials and may be subject to potential biases and confounding. For example, the retrospective nature of the study designs can introduce biases on the assessment of exposure to the device and/or outcomes, there is also potential for bias introduced by loss to follow-up. We reviewed three publications reporting on retrospective data analyses. The studies were not randomized to balance for differences in covariates, with exception of one study that used propensity score.

Studies based on a single center may have limited generalizability to the general patient population. Inclusion of adult subjects can also limit the generalizability of results to the pediatric population. Furthermore, some reported comparisons were performed without appropriate control for potential confounding factors, and there were differences in the length of follow-up for subjects treated with Contegra versus the alternative treatments. Differences in length of follow-up by treatment could have influenced the observed safety outcomes.

Additionally, the publications based retrospective analyses do not report on important outcomes such as hemolysis. We only found one publication based on a case report. It seems, hemolysis is a rare endpoint among subjects treated with Contegra, but the evidence is limited.

The three retrospective studies reported on subjects who were implanted over a wide time-period (1999 to 2017). Patient management or standard of care could have changed over time.

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 been used in different publications, which could result in unintended missed articles.
The exclusion of an unavailable full text publication in a foreign language could also have led to missed information.

Conclusions

Review of the literature published from 06/01/17 through 05/31/18 revealed the following observations:

- Published literature reported comparable low risk of post-operative morbidity and mortality for patients undergoing replacement with Contegra or pulmonary homograft.

- The 10% endocarditis rate in Contegra grafts at a median follow-up of 7.5 years was high compared to 0.8% for homografts and 2.9% for the porcine heterografts. However, endocarditis rate of up to 11.3% at a median follow up of 7.6 years has previously been reported in the literature.

  After 7.5 years, the rate of endocarditis increased rapidly in Contegra conduits compared to homograft or porcine heterografts. The 10-year freedom from endocarditis for Contegra grafts of 77%, was demonstrated to be significantly lower than that of homografts or porcine heterografts (Kaplan Meier analysis, $p< 0.001$).

- There were no significant differences in the freedom from first reintervention among xenograft groups including Contegra.

- Calcification of xenografts was reported as the main cause of conduit dysfunction. Among the xenograft groups studied, (DE-PAC, DE-PVC, GA-BJV or Contegra, and GA-PVC), the Contegra group had the least percentage of calcified conduits (9.3%,15/162). The freedom from reintervention due to calcification in the Contegra group was 93% and 74% at 4 and 6 years, respectively.

- Thrombosis rate due to Contegra conduit reported in the studies were in the range of 0-3.3%, comparable to the rates (0.0% to 4.3%) reported by Nichay et al. for other xenograft types.

- One case of hemolysis due to calcified, stenosed Contegra treated by conduit replacement, was reported in a 4-year old child. The absence of hemolytic event in the 484 Contegra conduits assessed in the three (3) retrospective studies is in favor of Rao et al. report that this safety event infrequently occurs in Contegra conduits placed in the RVOT position.

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 2019:

- Annual distribution number
- MDR review and
- Literature review

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